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1,3-DIPOLAR CYCLOADDITION OF DIAZOMETHANE TO 1,1-DIFLUOROALLYLPHOSPHONATES: APPLICATION TO SYNTHESIS OF CYCLOPROPANE DERIVATIVES HAVING A DIETHOXYPHOSPHORYLDIFLUOROMETHYLENE UNIT[¶]

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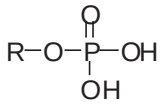
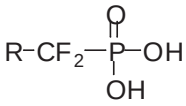
Abstract—1,3-Dipolar cycloaddition of diazomethane to (1,1-difluoroallyl)phosphonates was examined to give pyrazolines functionalized by a diethoxyphosphoryldifluoromethylene unit. The pyrazolines were transformed to the cyclopropane derivatives possessing a diethoxyphosphoryl-difluoromethylene functionality by photolysis.

The ubiquitous presence of a phosphate group in a vast array of biologically active molecules has stimulated intense research efforts in the search for structural analogues where different constitution and chemical reactivity allow them to be used as either useful biochemical probes or potent inhibitors in enzymatic reactions.[1] Blackburn's postulate[2] that 1,1-difluoromethylenephosphonic acids (DFMPA) (**2**) are a hydrolytically stable mimic of the corresponding phosphate esters (**1**) has gained wide experimental support in recent years. As a result, many enzyme inhibitors with significant activity have been identified.[3] Despite the growing development of new and efficient methods for the synthesis of DFMPA-functionalized molecules, few methods are available for stereoselective introduction of a DFMPA-functionality to a secondary carbon within a cyclic array.[4] We have been particularly interested in introducing a DFMPA-functionality to cyclopropane rings; the resulting rigid molucules would be useful as a probe for studying 3D-structural activity relationships of biologically active DFMPA-derivatives.[3i] Recent reports from these laboratories described the sulfur-ylide-induced cyclopropanation of the DFMPA-functionalized enoates.[5] The reaction has been applied to stereoselective synthesis of novel cyclopropane nucleotide analogue (**3**) with significant inhibitory activity aganist purine nucleoside phosphorylase.[3i,5b] In this paper, we describe an alternative synthesis of DFMPA-functionalized cyclopropane derivatives on the basis of photolysis of Δ^1-pyrazoline derivatives readily available from (1,1-difluoroallyl)phosphonates through 1,3-diploar cycloaddition with diazomethane.[6]

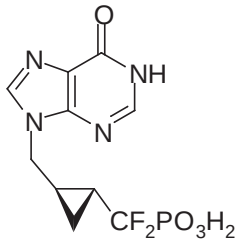
[¶] This paper is dedicated to Professor James P. Kutney on the occasion of his 70th birthday.



1

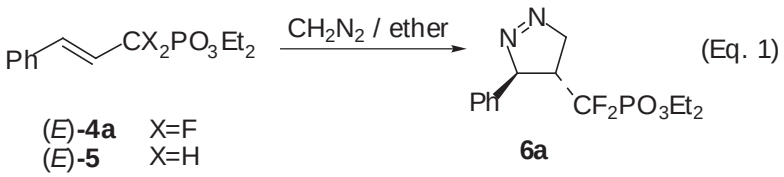


2 (DFMPA)



3

While 1,3-dipolar cycloaddition of electron-deficient olefins with diazomethane has been well established,[6] it was not clear how the DFMPA-ester functionality affects the 1,3-dipolar cycloaddition of (1,1-difluoroallyl)phosphonates. We first examined 1,3-dipolar cycloaddition of diazomethane with (*E*)-styryl-1,1-difluoromethylphosphonate ((*E*)-**4a**)[7] and the analogous non-fluorinated phosphonate ((*E*)-**5**)[8] to verify effects of the fluorine atom and phosphonate functionality on the reactivity of the 1,3-dipolar cycloaddition (Eq. 1).



(*E*)-**4a** X=F
(*E*)-**5** X=H

6a

(Eq. 1)

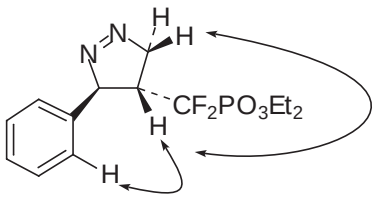


Figure 1. NOESY correlations of **6a**

Treatment of (*E*)-**4a** with a large excess of an ethereal solution of diazomethane at room temperature for 15 h gave the corresponding Δ^1-pyrazoline (**6a**) in 72% yield without detectable formation of the regioisomer. The stereo- and regio-chemistry of **6a** were confirmed on the basis of the diagnostic NOESY-correlations (500 MHz, $CDCl_3$) depicted in Figure 1. The non-fluorinated analogue ((*E*)-**5**) was found to be inert to diazomethane under the same conditions, and no adduct was obtained from the reaction. The results suggest the fluorine atoms of (*E*)-**4a** contribute toward lowering the LUMO-energy to interact favorably with HOMO of diazomethane.[6] The direction of cycloaddition of diazomethane to (*E*)-**4a** is consistent with the prediction from the calculated density of LUMO and HOMO of (*E*)-**4a** and diazomethane, respectively (Figure 2). The calculation (MOPAC 2000 / PM 3) reveals the density of LUMO (f_r) at the α- and β-carbon atoms of (*E*)-**4a** to be 0.143 and 0.121; density of HOMO (f_r) at the carbon and nitrogen atoms of diazomethane to be 0.618 and 0.363, respectively.

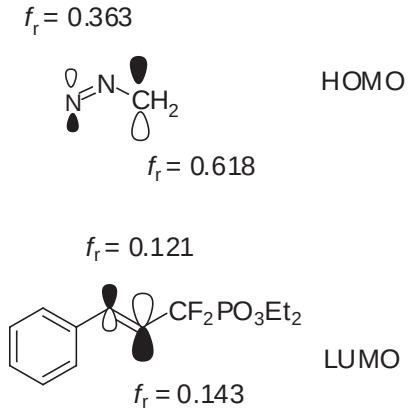


Figure 2. Density HOMO and LUMO of diazomethane and (*E*)-**4a**

To explore the scope and applicability of the reaction, we further examined 1,3-dipolar cycloaddition of (1,1-difluoroallyl)phosphonates ((*E*)-**4b-j**) with varying electronic nature of the β-substituents. The results of this exploratory study are summarized in Table 1. As expected, (1,1-difluoroallyl)phosphonates ((*E*)-**4b**) and ((*E*)-**4c**) having an electron-withdrawing substituent such as fluorine and carbomethoxy functionality in the phenyl reacted with diazomethane to give Δ^1-pyrazolines (**6b**) and (**6c**) in reasonable yield, respectively (Entries 1 and 2). 3-Pyridinyl derivative ((*E*)-**4d**) was found to be a good substrate for this reaction to give **6d** in modest yield (Entry 3). However, 4-methoxyphenyl derivative ((*E*)-**4e**)[7] and *n*-butyl derivative ((*E*)-**4f**)[7] were totally inert to diazomethane under the same conditions (Entries 4 and 5). These results clearly demonstrated that the 1,3-dipolar cycloaddition was significantly affected by the electronic nature of the substituents. The reaction of enoate ((*E*)-**4g**)[5] and enones ((*E*)-**4h**)[5] and ((*E*)-**4i,j**) with diazomethane proceeded with concomitant tautomerization of the adducts to give Δ^2-pyrazolines (**7g-j**) in modest to good yield (Entries 6-9).

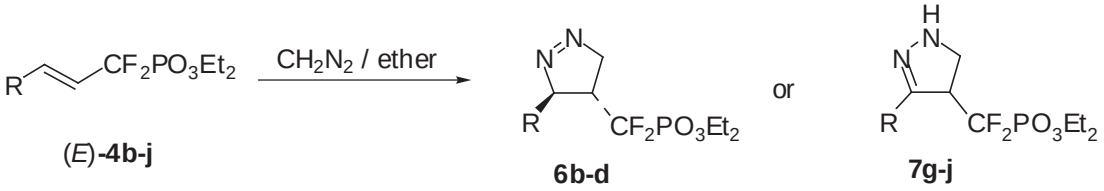


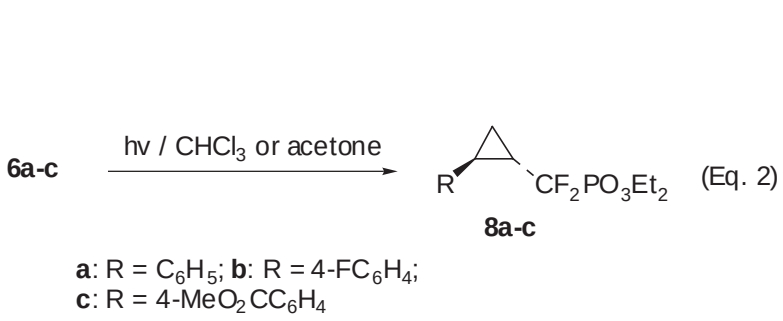
Table 1. 1,3-dipolar cycloaddition of (*E*)-**4b-j** with diazomethane[a]

Entry	Substrate R		Yield (%)	
			6b-d	**7g-i**
1	(*E*)-**4b**	4-FC_6H_4	83	—
2	(*E*)-**4c**	4-$MeO_2CC_6H_4$	64	—
3	(*E*)-**4d**	3-pyridinyl	60	—
4	(*E*)-**4e**	4-$MeOC_6H_4$	n.r.[b]	—
5	(*E*)-**4f**	*n*-Bu	n.r.[b]	—
6	(*E*)-**4g**	EtO_2C	—	79
7	(*E*)-**4h**	MeCO	—	59
8	(*E*)-**4i**	EtCO	—	80
9	(*E*)-**4j**	*i*-PrCO	—	81

[a] All reactions were carried out at room temperature for 15 h. [b] Not reacted.

Photolysis of the Δ^1-pyrazolidines (**6a-c**) was carried out by irradiation with a high-pressure mercury-lamp (500 W) in acetone or chloroform to yield the corresponding cyclopropanes (**8a-c**) in nearly quantitative yield[9] (Eq. 2). The configuration of the stereogenic centers of the Δ^1-pyrazolidines retains through the photolysis; this was proved by NOE experiments (400 MHz, $CDCl_3$) on the cyclopropane

derivative (**8a**) (Figure 3).



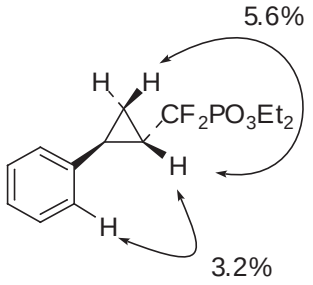
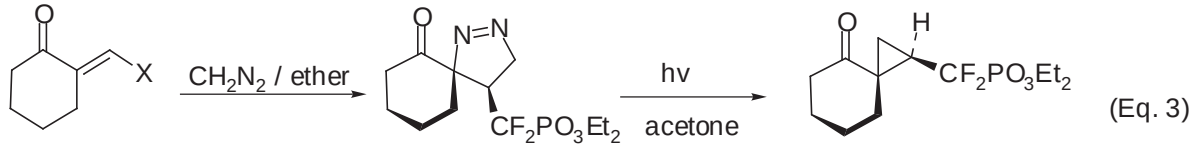


Figure 3 Revalent % NOE values for stereochemical assignment of **8a**

Finally, the sequence was applied to stereoselective synthesis of novel spiro-cyclopropane derivative (**8k**) (Eq. 3). (*E*)-2-Iodomethylenecyclohexanone (**9**)[10] was transformed to the phosphonate (**4k**) in 63% yield through cross-coupling reaction with $BrZnCF_2PO_3Et_2$ in the presence of CuBr in DMF.[7] Treatment of (*E*)-**4k** with a large excess of diazomethane in ether gave the adduct (**6k**) in 65% yield. Photolysis of **6k** in acetone by irradiation with a high-pressure mercury-lamp (500 W) gave **8k** in 91% yield. Transformation of (*E*)-**4k** to **8k** through cyclopropanation with dimethyloxosulfonium methylide in DMSO according to the previous method[5] results in very low yield (24%) due to unfavorable side reactions at the carbonyl.[5a] Therefore, the present method complements our previous approach to DFMPA-functionalized cyclopropanes based on sulfur-ylide-induced cyclopropanation of (1,1-difluoroallyl)phosphonates.[5]



9 X = I
(*E*)-**4k** X = $CF_2PO_3Et_2$

6k

8k

EXPERIMENTAL

All reactions were carried out under nitrogen atmosphere. ^1H NMR spectra were recorded at 400 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ (7.26 ppm) as internal references. ^{13}C NMR(100 MHz) and ^{31}P NMR (162 MHz) were taken in $CDCl_3$ using $CDCl_3$ (77.0 ppm) as 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 internal standard. The density of LUMO for (*E*)-**4a** and density of HOMO for diazomethane were calculated by MOPAC 2000 (PM 3) implemented in CAChe Worksystems (Fujitsu Corporation).

Preparation of (1,1-difluoroallyl)phosphonates ((*E*)-4a-k). All (1,1-difluoroallyl)phosphonates used in this study were synthesized through cross-coupling reaction between the corresponding iodoalkenes and $BrZnCF_2PO_3Et_2$ according to the general procedure described previously.[7] The required iodoalkenes were

prepared by the literature procedure.[11] Yield and physical data of new (1,1-difluoroallyl)phosphonates ((*E*)-**4b-d**) and ((*E*)-**4i-k**) are as follows:

Diethyl (2*E*)-1,1-difluoro-3-(4-fluorophenyl)prop-2-enylphosphonate ((*E*)-4b). Yield: 45%; an oil; ^{1}H NMR δ 7.49-7.40 (2H, m), 7.11-6.98 (3H, m) 6.23 (1H, ddt, J_{HH}=16.0 Hz, J_{HF} = 12.8 Hz, J_{HP}=2.9 Hz), 4.37-4.18 (4H, m), 1.38 (6H, t, J = 7.0 Hz); ^{13}C NMR δ 163.4 (d, J_{CF} = 250.0 Hz), 135.8 (dt, J_{CP} = 6.1 Hz, J_{CF} = 10.7 Hz), 130.5, 128.2 (d, J_{HF} = 8.4 Hz), 118.5 (dt, J_{CP} = 13.3 Hz, J_{CF} = 22.0 Hz), 117.3 (dt, J_{CP} = 221.1 Hz, J_{CF} = 259.5 Hz), 115.8 (d, J_{CF} = 21.9 Hz), 64.7 (d, J_{CP} = 6.7 Hz), 16.3 (d, J_{CP} = 5.2 Hz); ^{19}F NMR δ –45.7 (2F, dd, J_{HF} = 12.8 Hz, J_{PF} = –48.4 (1F, m); ^{31}P NMR δ 6.89 (t, J_{PF} = 114.4 Hz); 171 (M^+–P(O)(OEt)$_2$); IR (neat) 2987, 1653, 1603, 1511, 1269, 1038 cm^{-1}; MS (EI) *m/z* 308 (M^+); Anal. Calcd for $C_{13}H_{16}O_3F_3P$: C, 50.66; H, 5.23. Found: C, 50.49; H, 5.17.

Methyl 4-[(1*E*)-3-diethoxyphosphoryl]-3,3-difluoroprop-1-enyl]benzoate ((*E*)-4c). Yield: 42%; an oil; ^{1}H NMR δ 8.04 (2H, d, J = 8.3 Hz), 7.52 (2H, d, J = 8.3 Hz), 7.11 (1H, ddt, J_{HH} = 16.2 Hz, J_{HP} = 2.8 Hz, J_{HF} = 2.3 Hz), 6.40 (1H, ddt, J_{HH} = 16.2 Hz, J_{HP} = 2.7 Hz, J_{HF} = 12.6 Hz), 4.40-4.21 (4H, m), 3.92 (3H, s), 1.38 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 166.3, 138.4, 135.8 (dt, J_{CP} = 6.2 Hz, J_{CF} = 10.5 Hz), 130.7, 129.9, 127.2, 121.2 (dt, J_{CP} = 12.9 Hz, J_{CF} = 21.3 Hz), 52.0, 16.3 (d, J_{CP} = 5.2 Hz); ^{19}F NMR δ –46.2 (2F, ddd, J_{HF} = 2.3, 12.6 Hz, J_{PF} = 113.3 Hz); ^{31}P NMR δ 6.56 (t, J_{PF} = 113.3 Hz); IR (neat) 2986, 1723, 1282, 1181, 1110, 1037 cm^{-1}; MS (EI) *m/z* 348 (M^+), 211 (M^+–P(O)(OEt)$_2$); HREIMS calcd for $C_{15}H_{19}O_5F_2P$ (M^+): 348.0938. Found: 348.0944.

Diethyl (2*E*)-1,1-difluoro-3-(pyridin-2-yl)prop-2-enylphosphonate ((*E*)-4d). Yied: 35%; an oil; ^{1}H NMR δ 8.61 (1H, d, J = 4.7 Hz), 7.69 (1H, dt, J = 1.8, 7.8 Hz), 7.36 (1H, d, J = 7.7 Hz), 7.24 (1H, dd, J = 4.7, 7.7 Hz), 7.13 (1H, ddt, J_{HH} = 15.6 Hz, J_{HP} = 2.8 Hz, J_{HF} = 2.8 Hz), 6.87 (1H, ddt, J_{HH} = 15.6 Hz, J_{HP} = 2.7 Hz, J_{HF} = 13.1 Hz), 4.41-4.20 (4H, m), 1.38 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 152.6, 149.8, 136.8, 136.2 (dt, J_{CP} = 6.2 Hz, J_{CF} = 10.2 Hz), 123.7, 123.4, 123.1 (dt, J_{CP} = 13.0 Hz, J_{CF} = 21.3 Hz), 117.4 (dt, J_{CP} = 226.0 Hz, J_{CF} = 259.4 Hz), 64.8 (d, J_{CP} = 6.7 Hz), 16.3 (d, J_{CP} = 5.3 Hz); ^{19}F NMR δ –46.2 (1F, dd, J_{PF} = 113.4 Hz, J_{HF} = 13.1 Hz); ^{31}P NMR δ 6.67 (t, J_{PF} = 113.4 Hz); IR (neat) 2986, 1585, 1472, 1435, 1270, 1037 cm^{-1}; MS (EI) *m/z* 292 (M^++1), 154 (M^+–P(O)(OEt)$_2$); HREIMS calcd for $C_{12}H_{16}NO_3F_2P$ (M^+): 291.0836. Found: 291.0849.

Diethyl (2*E*)-1,1-difluoro-4-oxohex-2-enylphosphonate ((*E*)-4i). Yield: 42%; an oil; ^{1}H NMR δ 6.78-6.58 (2H, m), 4.36-4.19 (4H, m), 2.65 (2H, t, J = 7.2 Hz), 1.38 (6H, t, J = 7.1 Hz), 1.13 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 198.8, 133.6 (dt, J_{CP} = 5.6 Hz, J_{CF} = 8.3 Hz), 132.2 (dt, J_{CP} = 13.1 Hz, J_{CF} = 21.8 Hz), 116.4 (dt, J_{CP} = 217.1 Hz, J_{CF} = 259.8 Hz), 65.0 (d, J_{CP} = 6.8 Hz), 34.7, 16.2 (d, J_{CP} = 4.8 Hz), 7.4; ^{19}F NMR δ –48.6 (2F, dd, J_{HF} = 10.9 Hz, J_{PF} = 108.6 Hz); ^{31}P NMR δ 5.54 (t, J_{PF} = 108.6 Hz); IR (neat) 2985, 1710, 1269, 1171, 1038 cm^{-1}; MS (EI) *m/z* 271 (M^++1); HREIMS calcd for $C_{10}H_{17}O_4F_2P$ (M^+): 270.0833. Found: 270.0856.

Diethyl (2*E*)-1,1-difluoro-5-methyl-4-oxohex-2-enylphosphonate ((*E*)-4j). Yield: 67%; an oil; ^{1}H NMR δ 6.83-6.68 (2H, m), 4.36-4.20 (4H, m), 2.82 (1H, septet, J = 6.9 Hz), 1.38 (6H, t, J = 7.1 Hz), 1.15 (6H, d, J = 6.9 Hz); ^{13}C NMR δ ; 201.4, 132.5 (dt, J_{CP} = 12.9 Hz, J_{CF} = 21.8 Hz), 132.2 (dt, J_{CP} = 5.8 Hz, J_{CF} = 8.0 Hz), 116.4 (dt, J_{CP} = 217.1 Hz, J_{CF} = 259.8 Hz), 64.9 (d, J_{CP} = 6.7 Hz), 39.7, 17.5, 16.1 (d, J_{CP} = 5.3 Hz); ^{19}F NMR δ –48.4 (2F, dd, J_{HF} = 9.0 Hz, J_{PF} = 108.8 Hz); ^{31}P NMR δ 5.59 (t, J_{PF} = 108.8 Hz); IR

(neat) 2978, 1705, 1273, 1019 cm^{-1}; MS (EI) *m/z* 569 ($2M^+$+1), 285 (M^++1); HREIMS calcd for $C_{11}H_{19}O_4F_2P$ (M^+): 284.0959. Found: 284.0996.

Diethyl (2*E*)-1,1-difluoro-2-(2-oxocyclohexylidene)ethylphosphonate ((*E*)-4k). Yield: 63%; an oil; ^{1}H NMR δ 6.39-6.26 (1H, m), 4.36-4.18 (4H, m), 2.89-2.78 (2H, m), 2.52 (2H, t, *J* = 6.7 Hz), 1.95-1.85 (2H, m), 1.83-1.73 (2H, m), 1.38 (6H, t, *J* = 7.1 Hz); ^{13}C NMR δ 200.1, 146.3 (dt, J_{CP} = 6.2 Hz, J_{CF} = 6.2 Hz), 124.0 (dt, J_{CP} = 12.2 Hz, J_{CF} = 22.2 Hz), 118.0 (dt, J_{CP} = 217.5 Hz, J_{CF} = 259.1 Hz), 64.7 (d, J_{CP} = 6.3 Hz), 40.6, 28.1, 23.2, 16.2; ^{19}F NMR δ –43.4 (2F, ddt, J_{HF} = 3.0, 16.3 Hz, J_{PF} = 111.2 Hz); ^{31}P NMR δ 6.50 (t, J_{FP} = 111.2 Hz); IR (neat) 2942, 1700, 1272, 1033 cm^{-1}; MS (EI) *m/z* 297 (M^++1); HREIMS calcd for $C_{12}H_{19}O_4F_2P$ (M^+): 296.0989. Found: 296.1004.

General procedure for the cycloaddition of diazomethane to (1,1-difluoroallyl)phosphonates ((*E*)-4a-k). A typical experiment is described for the synthesis of pyrazoline (**6a**). An ethereal solution (15 mL) of diazomethane was prepared from *N*-nitroso-*N*-methylurea (3.1 g, 30 mmol) and 50% KOH (15 mL) at 0 °C as usual. The solution was added to an ethereal solution (15 mL) of (*E*)-**4a** (870 mg, 3.0 mmol) at 0 °C. The light-protected solution was stirred at 25 °C for 15 h, then, excess diazomethane was eliminated by addition of acetic acid (3 drops) and the solvent was evaporated. The residue was chromatographed on silica gel (*n*-hexane: EtOAc = 3:1) to afford **6a** (717 mg, 72%) as an oil. The new pyrazolines (**6b-d**, **6k**, and **7g-j**) were prepared in a similar manner.

Diethyl difluoro[(3*S,4*S**)-3-phenyl-4,5-dihydro-3*H*-pyrazol-4-yl]methylphosphonate** (**6a**). Yield: 72%; an oil; ^{1}H NMR δ 7.48-7.24 (3H, m), 7.21-7.09 (2H, m), 6.10-5.97 (1H, m), 4.93 (1H, dd, *J* = 5.5, 18.6 Hz), 4.79 (1H, ddd, *J* = 2.5, 9.7, 18.6 Hz), 4.36-4.11 (4H, m), 2.82-2.63 (1H, m), 1.35 (3H, t, *J* = 7.0 Hz), 1.33 (3H, t, *J* = 7.0 Hz); ^{13}C NMR δ 137.1, 128.9, 128.2, 127.2, 127.1, 119.2 (dt, J_{CP} = 216.1 Hz, J_{CF} = 263.3 Hz), 90.9, 76.6, 64.9 (d, J_{CP} = 6.9 Hz), 64.7 (d, J_{CP} = 6.9 Hz), 44.3 (dt, J_{CP} = 15.4 Hz, J_{CF} = 20.7 Hz). 16.2 (d, J_{CP} = 4.8 Hz), 16.1 (d, J_{CP} = 4.9 Hz); ^{19}F NMR δ –51.0 (1F, ddd, J_{FF} = 300.8 Hz, J_{HF} = 13.1 Hz, J_{FP} = 108.9 Hz), –53.7 (1F, ddd, J_{FF} = 300.8 Hz, J_{HF} = 17.9 Hz, J_{FP} = 105.0 Hz); IR (neat) 1274, 1039, MS (EI) *m/z* 333 (M^++1). Anal. Calcd for $C_{14}H_{19}N_2O_3F_2P$: C, 50.59; H, 5.77; N, 8.43. Found: C, 50.29; H, 5.64; N, 8.40.

Diethyl difluoro[(3*S,4*S**)-3-(4-fluorophenyl)-4,5-dihydro-3*H*-pyrazol-4-yl]methylphophonate** (**6b**). Yield: 83%; an oil; ^{1}H NMR δ 7.18-7.00 (4H, m), 6.03-5.96 (1H, m), 4.91 (1H, dd, *J* = 5.6, 18.6 Hz), 4.80 (1H, ddd, *J* = 2.6, 9.7, 18.6 Hz), 4.35-4.15 (4H, m), 2.77-2.58 (1H, m), 1.36 (3H, t, *J* = 7.2 Hz), 1.33 (3H, t, *J* = 7.2 Hz); ^{13}C NMR δ 162.4 (d, J_{CF} = 247.2 Hz), 133.1 (d, J_{CF} = 3.2 Hz), 128.9 (d, J_{CF} = 8.3 Hz), 119.2 (dt, J_{CP} = 216.1 Hz, J_{CF} = 263.4 Hz), 115.8 (d, J_{CF} = 21.7 Hz), 90.2, 76.7, 64.9 (d, J_{CP} = 7.0 Hz), 64.6 (d, J_{CP} = 6.0 Hz), 44.4 (dt, J_{CP} = 15.6 Hz, J_{CF} = 20.6 Hz), 16.2 (d, J_{CP} = 4.8 Hz), 16.1 (d, J_{CP} = 5.0 Hz); ^{19}F NMR δ –50.9 (1F, m), -51.2 (1F, ddd, J_{HF} = 14.5 Hz, J_{FF} = 300.7 Hz, J_{PF} = 106.1 Hz), –53.5 (1F, ddd, J_{HF} = 19.3 Hz, J_{FF} = 300.7 Hz, J_{PF} = 106.1 Hz); ^{31}P NMR δ 6.04 (t, J_{PF} = 106.1 Hz), IR (neat) 1512, 1271, 1162, 1035 cm^{-1}; MS (EI) *m/z* 351 (M^++1); HREIMS calcd for $C_{14}H_{18}N_2O_3F_3P$ (M^+): 350.1007. Found: 350.0996.

Methyl 4-{(3*S,4*S**)-4-[(diethoxyphosphoryl)(difluoro)methyl]-4,5-dihydro-3*H*-pyrazol-3-yl}benzoate (6c)**. Yield: 64%; an oil; ^{1}H NMR δ 8.05 (2H, d, *J* =8.8 Hz), 7.25 (2H, d, *J* = 8.8 Hz), 6.09-6.02 (1H, m), 4.94 (1H, dd, *J* = 5.7, 18.7 Hz), 4.82 (1H, ddd, *J* = 2.5, 9.7, 18.7 Hz), 4.36-4.15 (4H, m),

3.92 (3H, s), 2.82-2.62 (1H, m), 1.35 (3H, t, J = 7.1 Hz), 1.33 (3H, t, J = 7.1 Hz); ^{13}C NMR δ 166.4, 142.0, 130.2, 130.0, 127.2, 119.0 (dt, J_{CP} = 215.9 Hz, J_{CF} = 263.5 Hz), 76.9, 65.0 (d, J_{CP} = 6.8 Hz), 64.8 (d, J_{CP} = 4.3 Hz), 16.2 (d, J_{CP} = 4.4 Hz); ^{19}F NMR δ –51.0 (1F, ddd, J_{HF} = 14.2 Hz, J_{FF} = 300.9 Hz, J_{PF} = 107.2 Hz), –53.8 (1F, ddd, J_{HF} = 19.6 Hz, J_{FF} = 300.9 Hz, J_{PF} = 104.6 Hz), ^{31}P NMR δ 5.93 (dd, J_{PF} = 104.6 Hz, 107.2 Hz); IR (neat) 2987, 1723, 1281, 1020 cm^{-1}; MS (EI) *m/z* 391 (M^++1). Anal. Calcd for $C_{16}H_{21}N_2O_5F_2P$: C, 49.24; H, 5.42; N, 7.18. Found: C, 48.77; H, 5.43; N, 6.85.

Diethyl difluoro[(3*S,4*S**)-3-pyridin-2-yl-4,5-dihydro-3*H*-pyrazol-4-yl]methylphosphonate (6d)**. Yield: 60%; an oil; ^{1}H NMR δ 8.55-8.48 (1H, m), 7.75 (1H, dt, J = 1.8, 7.6 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.24 (1H, ddd, J = 1.1, 4.8, 7.6 Hz), 6.15-6.06 (1H, m), 4.99 (1H, ddd, J = 0.9, 5.6, 18.4 Hz), 4.90 (1H, ddd, J = 2.5, 9.5, 18.4 Hz), 4.40-4.06 (4H, m), 3.48-3.28 (1H, m), 1.35 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR δ 154.8, 149.8, 136.9, 124.2, 123.2, 119.4 (dt, J_{CP} = 216.1 Hz, J_{CF} = 262.9 Hz), 92.9, 77.5, 64.8 (d, J_{CP} = 6.8 Hz), 64.6 (d, J_{CP} = 6.9 Hz), 41.2 (dt, J_{CP} = 15.9 Hz, J_{CF} = 20.6 Hz), 16.2 (d, J_{CP} = 6.0 Hz), 16.1 (d, J_{CP} = 6.5 Hz); ^{19}F NMR δ –51.5 (1F, ddd, J_{HF} = 17.8 Hz, J_{FF} = 300.7 Hz, J_{PF} = 106.9 Hz), –52.5 (1F, ddd, J_{HF} = 17.8 Hz, J_{FF} = 300.7 Hz, J_{PF} = 106.9 Hz). ^{31}P NMR δ 6.30 (t, J_{PF} = 106.9 Hz), MS (EI) *m/z* 334 (M^++1); HREIMS calcd for $C_{13}H_{18}N_3O_3F_2P$ (M^+): 333.1054. Found: 333.1051.

Diethyl difluoro[(4*R,5*R**)-6-oxo-1,2-diazaspiro[4,5]dec-1-en-4-yl]methylphosphonate (6k).** Yield: 63%; an oil; ^{1}H NMR δ 4.85 (1H, dd, J = 9.7, 18.5 Hz), 4.66 (1H, dd, J = 9.1, 18.5 Hz), 4.38-4.21 (4H, m), 3.66-3.47 (4H, m), 3.66-3.47 (1H, m), 3.17 (1H, dt, J = 6.2, 14.0 Hz), 2.76-2.66 (1H, m), 2.54-2.22 (3H, m), 2.14-2.03 (1H, m), 2.02-1.83 (2H, m), 1.40 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 202.8, 120.5 (dt, J_{CP} = 217.4 Hz, J_{CF} = 264.8 Hz), 104.3 (dd, J = 2.1, 6.9 Hz), 76.4, 64.9 (d, J_{CP} = 6.7 Hz), 40.8, 37.0 (dt, J_{CP} = 16.5 Hz, J_{CF} = 19.8 Hz), 34.8 (t, J_{CF} = 3.8 Hz), 27.3, 22.1, 16.3 (d, J_{CP} = 5.2 Hz); ^{19}F NMR δ –46.9 (1F, ddd, J_{HF} = 7.6 Hz, J_{FF} = 301.9 Hz, J_{PF} = 106.9 Hz), –50.8 (1F, ddd, J_{HF} = 28.6 Hz, J_{FF} = 301.9 Hz, J_{PF} = 106.9 Hz); ^{31}P NMR δ 5.70 (t, J_{CP} = 106.9 Hz); IR (neat) 2943, 1719, 1270, 1025 cm^{-1}; MS (EI) *m/z* 339 (M^++1), 311 (MH^+-N_2). Anal. Calcd for $C_{13}H_{21}N_2O_4F_2P$: C, 46.16; H, 6.26; N, 8.28. Found: C, 45,91; H, 6.21; N, 8.31.

Ethyl 4-[(diethoxyphosphoryl)(difluoro)methyl]-4,5-dihydro-1*H*-pyrazole-3-carboxylate (7g). Yield: 79%; an oil; ^{1}H NMR δ 4.42-4.18 (6H, m), 4.14-3.94 (1H, m), 3.82 (1H, t, J = 11.9 Hz), 1.39 (3H, t, J = 7.0 Hz), 1.38 (3H, t, J = 7.0 Hz), 1.35 (3H, t, J = 7.1 Hz); ^{13}C NMR δ 162.5, 136.7, 119.4 (dt, J_{CP} = 211.9 Hz, J_{CF} = 265.7 Hz), 65.4 (d, J_{CP} = 6.2 Hz), 65.4 (d, J_{CP} = 6.1 Hz), 61.4, 51.2 (t, J_{CF} = 4.7 Hz), 47.8 (dt, J_{CP} = 16.6 Hz, J_{CF} = 22.0 Hz), 16.6 (d, J_{CP} = 5.1 Hz), 16.6 (d, J_{CP} = 5.0 Hz), 14.5; ^{19}F NMR δ –47.2 (1F, ddd, J_{HF} = 7.2 Hz, J_{PF} = 104.7 Hz, J_{FF} = 304.2 Hz), -53.3 (1F, ddd, J_{HF} = 24.3 Hz, J_{PF} = 104.7 Hz, J_{FF} = 304.2 Hz); ^{31}P NMR δ (t, J_{PF} = 104.7 Hz), IR (neat) 2986, 1726, 1266, 1229 cm^{-1}; MS (EI) *m/z* 329 (M^++1), 297 (M^+-OEt), 141 (M^+–$CF_2P(O(OEt)_2)$; HREIMS calcd for $C_{11}H_{19}N_2O_5F_2P$ (M^+): 328.1000. Found: 328.1007.

Diethyl (3-acetyl-4,5-dihydro-1*H*-pyrazol-4-yl)difluoromethylphosphonate (7h). Yield: 59%; an oil; ^{1}H NMR δ 6.36 (1H, br s), 4.39-4.19 (5H, m), 4.15-3.94 (1H, m), 3.77 (1H, t, J = 12.0 Hz), 2.44 (3H, s), 1.39 (3H, t, J = 6.9 Hz), 1.38 (3H, t, J = 7.0 Hz); ^{13}C NMR δ 192.8, 144.7, 119.0 (dt, J_{CP} = 211.4 Hz, J_{CF} = 266.1 Hz), 65.0 (d, J_{CP} = 5.9 Hz), 51.1 (t, J_{CF} = 5.1 Hz), 45.7 (dt, J_{CP} = 16.6 Hz, J_{CF} = 22.1 Hz), 25.9, 16.3 (d, J_{CP} = 4.5 Hz), 16.2 (d, J_{CP} = 4.3 Hz); ^{19}F NMR δ –46.6 (1F, ddd, J_{HF} = 6.9 Hz, J_{FF} = 303.2 Hz, J_{PF} = 105.3 Hz), -53.4 (1F, ddd, J_{HF} = 25.2 Hz, J_{FF} = 303.2 Hz, J_{PF} = 105.3 Hz) ; ^{31}P NMR δ 5.81 (t, J_{PF} =

105.3 Hz); IR (neat) 3293, 2986, 1667, 1264, 1025 cm^{-1}; MS (EI) *m/z* 298 (M^+); HREIMS calcd for $C_{10}H_{17}N_2O_4F_2P$ (M^+): 298.0894. Found: 298.0890.

Diethyl difluoro(3-propionyl-4,5-dihydro-1*H*-pyrazol-4-yl)methylphosphonate (7i). Yield: 80%; an oil; ^{1}H NMR δ 6.32 (1H, br s), 4.37-4.17 (5H, m), 4.12-3.93 (1H, m), 3.75 (1H, t, *J* = 11.9 Hz), 3.00-2.72 (2H, m), 1.39 (3H, t, *J* = 6.9 Hz), 1.37 (3H, t, *J* = 7.4 Hz); ^{13}C NMR δ 196.0, 144.2, 119.1 (dt, J_{CP} = 211.1 Hz, J_{CF} = 266.1 Hz), 65.0 (d, J_{CP} = 5.5 Hz), 50.8 (t, J_{CF} = 5.0 Hz), 45.7 (dt, J_{CP} = 16.7 Hz, J_{CF} = 22.0 Hz), 31.4, 16.3, 8.3. ^{19}F NMR δ –46.6 (1F, ddd, J_{HF} = 6.4 Hz, J_{FF} = 302.6 Hz, J_{PF} = 105.4 Hz), –54.1 (1F, ddd, J_{HF} = 25.7 Hz, J_{FF} = 302.6 Hz, J_{PF} = 105.4 Hz); ^{31}P NMR δ 5.80 (t, J_{PF} = 105.4 Hz); IR (neat) 3301, 2983, 1665, 1446, 1266, 1031 cm^{-1}; MS (EI) *m/z* 313 (M^++1). Anal. Calcd for $C_{11}H_{19}N_2O_4F_2P$: C, 42.31; H, 6.13; N, 8.97. Found: C, 42.24; H, 6.10; N, 9.44.

Diethyl difluoro(3-isobutyryl-4,5-dihydro-1*H*-pyrazol-4-yl)methylphosphonate (7j). Yield: 81%; an oil; ^{1}H NMR δ 6.33 (1H, br s), 4.37-4.18 (5H, m), 4.15-3.93 (1H, m), 3.74 (1H, t, *J* = 11.8 Hz), 3.54 (1H, septet, *J* = 6.9 Hz), 1.39 (3H, t, *J* = 7.0 Hz), 1.38 (3H, t, *J* = 6.9 Hz), 1.16 (3H, d, *J* = 6.9 Hz), 1.12 (3H, d, *J* = 6.9 Hz); ^{13}C NMR δ 199.4, 143.4, 119.2 (dt, J_{CP} = 210.9 Hz, J_{CF} = 266.2 Hz), 65.0 (d, J_{CP} = 5.7 Hz), 65.0 (d, J_{CP} = 6.0 Hz), 50.8 (t, J_{CF} = 5.0 Hz), 45.5 (dt, J_{CP} = 16.5 Hz, J_{CF} = 21.9 Hz), 35.7, 19.2, 18.2, 16.3 (d, J_{CP} = 4.7 Hz); ^{19}F NMR δ –46.4 (1F, ddd, J_{HF} = 4.9 Hz, J_{FF} = 302.3 Hz, J_{PF} = 103.4 Hz), –55.9 (1F, ddd, J_{HF} = 27.9 Hz, J_{FF} = 302.6 Hz, J_{PF} = 107.4 Hz); ^{31}P NMR δ 5.84 (dd, J_{PF} = 107.0 Hz); IR (neat) 3303, 2977, 1663, 1533, 1445, 1267, 1031 cm^{-1}; MS (EI) *m/z* 327 (M^++1). Anal. Calcd for $C_{12}H_{21}N_2O_4F_2P$: C, 44.17; H, 6.49; N, 8.59. Found: C, 44.09; H, 6.30; N, 8.82.

General procedure for the photolysis of Δ^1-pyrazolines (6a-c and 6k). In a typical experiment, an acetone solution (1.5 mL) of **6c** (270 mg; 0.7 mmol) in a Pyrex reactor under nitrogen atmosphere was irradiated at 25 °C for 3 h with a 500 W high-pressure mercury lamp. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with *n*-hexane:EtOAc=5:1 gave **8c** (230 mg, 91%) as an oil. In case of photolysis of **6a**, chloroform was used as a solvent. Physical data of **8a-c** and **8k** are given below:

Diethyl difluoro[(1*S,2*S**)-2-phenylcyclopropyl]methylphosphonate (8a).** Yield: 95%; an oil;^{1}H NMR δ 7.34-7.12 (6H, m), 4.34-4.20 (4H, m), 2.38 (1H, ddd, *J* = 9.2, 5.1, 5.1 Hz), 1.87-1.68 (1H, m), 1.45-1.34 (7H, m), 1.21 –1.12 (1H, m); ^{13}C NMR δ 139.8, 128.3, 126.4, 126.3, 118.5 (dt, J_{CP} = 220.5 Hz, J_{CF} = 258.1 Hz), 64.3 (d, J_{CP} = 6.6 Hz), 23.2 (dt, J_{CP} = 18.9 Hz, J_{CF} = 24.1 Hz), 19.2, 16.3 (d, J_{CP} = 5.3 Hz), 10.4; ^{19}F NMR δ –51.6 (2F, dd, J_{HF} = 13.7 Hz, J_{FP} = 117.0 Hz), ^{31}P NMR δ 6.83 (t, J_{PF} = 117.0 Hz); IR (neat) 1273, 1039, 1029 cm^{-1}; MS (EI) *m/z* 304 (M^+). Anal. Calcd for $C_{14}H_{19}O_3F_2P$: C, 55.24; H, 6.30. Found: C, 55.02; H, 6.22.

Diethy difluoro[(1*S,2*S**)-2-(4-fluorophenyl)cyclopropyl]methylphosphonate (8b).** Yield: 91%; an oil; ^{1}H NMR δ 7.13 (2H, dd, J_{HH}=8.7 Hz, J_{HF} = 5.3 Hz), 6.97 (2H, dd, J_{HH} = 8.7 Hz, J_{HF} = 8.7 Hz), 4.35-4.16 (4H, m), 2.39-2.29 (1H, m), 1.77-1.61 (1H, m), 1.37 (6H, t, *J* = 7.0 Hz), 1.13-1.05 (1H, m); ^{13}C NMR δ 161.6 (d, J_{CF} = 244.6 Hz), 135.5 (d, J_{CF} = 2.9 Hz), 128.2 (d, J_{CF} = 7.9 Hz), 118.5 (dt, J_{CP} = 222.2 Hz, J_{CF} = 259.8 Hz), 115.2 (d, J_{CF} = 21.5 Hz), 64.4 (d, J_{CP} = 6.7 Hz), 23.2 (dt, J_{CP} = 19.0 Hz, J_{CF} = 24.3 Hz), 18.7, 16.4 (d, J_{CP} = 5.3 Hz), 10.3; ^{19}F NMR δ –51.3 (1F, ddd, J_{HF} = 13.6 Hz, J_{FF} = 295.2 Hz, J_{PF} = 2.9 Hz), –52.3 (1F, ddd, J_{HF} = 14.1 Hz, J_{HF} = 13.6 Hz, J_{FF} = 295.2 Hz, J_{PF} = 2.9 Hz), –53.7 ~ –53.8 (1F, m);

^{31}P NMR δ 7.47 (t, J_{PF} = 115.9 Hz), IR (neat) 2987, 1514, 1271, 1037 cm^{-1}; MS (EI) *m/z* 322 (M^+); HREIMS calcd for $C_{14}H_{18}O_3F_3P$(M^+): 322.0946. Found: 322.0954.

Methyl 4-{(1*S,2*S**)-2-[(diethoxyphosphoryl)(difluoro)methyl]cyclopropyl}benzoate (8c).** Yield: 96%; an oil; ^{1}H NMR δ 7.95 (2H, d, *J* = 8.3 Hz), 7.20 (2H, d, *J* = 8.3 Hz), 4.34-4.15 (4H, m), 3.90 (3H, s), 2.44-2.36 (1H, m), 1.88-1.74 (1H, m), 1.49-1.41 (1H, m), 1.36 (6H, t, *J* = 7.1 Hz), 1.25-1.15 (1H, m); ^{13}C NMR δ 166.8, 145.4, 129.7, 128.3, 126.3, 118.2 (dt, J_{CP} = 222.0 Hz, J_{CF} = 260.2 Hz), 64.4 (d, J_{CP} = 6.7 Hz), 51.9, 24.0 (dt, J_{CP} = 19.1 Hz, J_{CF} = 24.4 Hz), 19.4, 16.3 (d, J_{CP} = 5.4 Hz), 11.0; ^{19}F NMR δ –52.0 (1F, dd, J_{HF} = 13.4 Hz, J_{PF} = 115.0 Hz), –51.9 (1F, dd, J_{HF} = 13.4 Hz, J_{PF} = 115.0 Hz); ^{31}P NMR δ 7.38 (t, J_{PF} = 115.0 Hz); IR (neat) 2987, 1721, 1280, 1113, 1036 cm^{-1}; MS (EI) *m/z* 362 (M^+). Anal. Calcd for $C_{16}H_{21}O_5F_2P$: C, 53.04; H, 5.84. Found: C, 52.50; H, 5.84.

Diethyl difluoro(1*S,3*R**)-4-oxospiro[2,5]oct-1-yl]methylphosphonate (8k).** Yield: 91%; an oil; ^{1}H NMR δ 4.38-4.20 (4H, m), 2.57-2.13 (4H, m), 2.02-1.84 (4H, m), 1.83-1.69 (1H, m), 1.38 (6H, t, *J* = 7.0 Hz), 1.11-1.02 (1H, m); ^{13}C NMR δ 208.3, 119.5 (dt, J_{CP} = 221.0 Hz, J_{CF} = 260.7 Hz), 64.4 (d, J_{CP} = 6.5 Hz), 39.6, 33.7 (d, J_{CP} = 5.0 Hz), 28.1, 25.6 (dt, J_{CP} = 23.7 Hz, J_{CF} = 21.1 Hz), 24.0, 23.4, 19.2, 16.3 (d, J_{CP} = 3.1 Hz); ^{19}F NMR δ –45.1 (1F, ddd, J_{HF} = 8.8 Hz, J_{FF} = 298.0 Hz, J_{PF} = 115.5 Hz), –48.1 (1F, ddd, J_{HF} = 23.3 Hz, J_{FF} = 298.0 Hz, J_{PF} = 110.5 Hz); ^{31}P NMR δ 6.77 (dd, J_{FP} = 110.5, 115.5 Hz); IR (neat) 2940, 1701, 1271, 1031 cm^{-1}; MS (EI) *m/z* 311 (M^++1). Anal. Calcd for $C_{13}H_{21}O_4F_2P$: C, 50.32; H, 6.82. Found: C, 49.92; H, 6.76.

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