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Nucleophilic additions of [(diethoxyphosphoryl)difluoromethyl]lithium to α,β-unsaturated compounds

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ABSTRACT

The presence of HMPA leads to an increase of 1,4- versus 1,2-additions of [(diethoxyphosphoryl)difluoromethyl]lithium onto α,β-unsaturated ketones and provides products of conjugated addition in moderate to good yields. In the absence of HMPA, benzylidine or alkylidine 1,3-diones, malononitriles or malonates as well as nitroalkenes and other Michael acceptors give products of 1,4-addition in good to high yields.

1. Introduction

α-Fluorinated alkyl phosphonates have emerged as important non-hydrolyzable phosphate mimics in many aspects of bio-organic chemistry [1]. One class of such compounds is α,α-difluorophosphonates, which are isoelectronic and isosteric analogs of natural phosphates. A wide range of biologically active difluorophosphonates have been synthesized and used as enzyme inhibitors or probes for the elucidation of mechanisms of biological processes involving phosphates. The synthesis and transformations of difluoromethylphosphonates has been widely explored and recently reviewed [2]. The common method for the introduction of the difluoromethylenephosphonate moiety is by organometallic reagents such as $MCF_2P(O)(OEt)_2$, where M can be Li, CdBr, ZnBr or SiR_3. Typical electrophilic substrates for the reaction of [(diethoxyphosphoryl)difluoromethyl]lithium (**1**) are aldehydes and ketones, primary alkyl halides or triflates and activated imines (such as *N*-sulfanylimines). Modification of reactivity of **1** can be achieved by the addition of anhydrous $CeCl_3$ and the resulting reagent is able to transfer the difluoromethylenephosphonate moiety to esters and lactones [3], DMF [3a,3b,4], vinylsulfoxides [5], vinylsulfones [6], and nitroalkenes [7]. Two exceptions to this reactivity profile have been reported. *t*-Bu ester of protected 4,5-dihydroxy-2-pentenoate was reported to undergo addition of **1** at −78 °C in THF to give the Michael adduct in 81% yield [8] and 1,4-addition of **1** to 4-chloro-β-nitrostyrene under the same conditions gave the adduct in 78% yield [9]. However, the second example was later described as limited only to nitrostyrene derivatives and requiring excess of **1**, while the presence of anhydrous $CeCl_3$ allowed the reaction with aliphatic nitroalkenes (as well as with nitrostyrene) in moderate yields [7]. Michael addition of **1** to unsaturated esters or nitriles has not been described, with the exception of reported low yields of inseparable 1:1 mixtures of 1,2- and 1,4-adducts in the reaction of **1** with ethyl acrylate or 5H-furan-2-one in the presence of $CeCl_3$ [3b]. Additionally, the literature described the reaction of **1** with various α,β-unsaturated aldehydes and ketones as exclusive 1,2-addition on the carbonyl group [1,2,10].

[(Dialkoxyphosphoryl)difluoromethyl]lithium salts available by the reaction of $MeSCF_2P(O)(RO)_2$ (R = Et or *i*-Pr) with *t*-BuLi add to a wide range of elecrophiles including nitroalkenes and DMF without the need of Ce^{3+} additives. The sulfide reagent allows access to difluoromethylphosphonates avoiding the use of environmentally problematic HCFCs and CFCs [11].

Another way to introduce the difluoromethylphosphonate moiety is by free radical additions of the phosphonodifluoromethyl radical generated from $XCF_2P(O)(OR)_2$. Various precursors and free radical initiators have been used: (a) Co^{3+} (cat.)/Zn system for X = Br in addition onto both electron-rich and electron-deficient alkenes [12], (b) $Pd(PPh_3)_4$ (cat.) for X = I in addition onto electron rich alkenes [13], (c) $Na_2S_2O_4$ for X = I in addition onto electron-rich alkenes [14] and alkynes [15], (d) Et_3B for X = I in addition onto electron-deficient alkenes such as cyclohexenone, cyclopentenone and vinyl alkyl ketones (but not onto electron-deficient alkenes with substituted double bond) [14], and (e) Bu_3SnH/AIBN for X = SMe or SePh in addition onto electron-rich alkenes [16]. Although, by intuition, electrophilic electronic character of the phosphonodifluoromethyl radical can be expected, experimental

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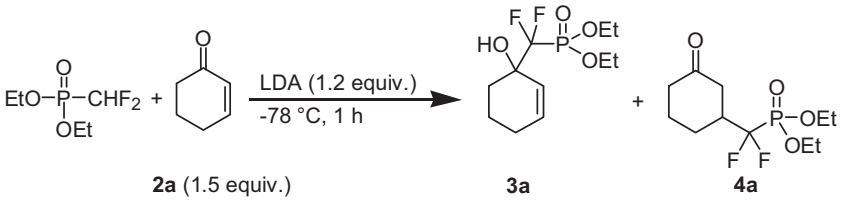
Table 1
The addition of [(diethoxyphosphoryl)difluoromethyl]lithium (**1**) to 2-cyclohexenone (**2a**).



2a (1.5 equiv.) **3a** **4a**

Entry	Solvent	Additive (equiv.)	**3a**, Yield (%)[a]	**4a**, Yield (%)[a]
1	THF	–	91[b] [17a]	0
2	THF	15-Crown-5 (2)	32	5
3	THF	12-Crown-4 (2)	78	5
4	THF	DMPU (7)	26	13
5	THF	HMPA (1.3)	73	21
6	THF	HMPA (5)	52	**47**[b]
7	THF	HMPA (8.2)	30	38
8	DME	HMPA (1.3)	70	10
9	DME	HMPA (5)	41	26
10	Diglyme	HMPA (5)	54	30

[a] ^{19}F NMR yield using $PhCF_3$ as internal standard.
[b] Isolated yield.

evidence shows that the radical can display significant nucleophilic character and reacts with both electron-rich and deficient alkenes, depending on reaction conditions (mainly nature of the free radical initiator used).

We have been interested in developing fluoroalkylation methodologies starting from fluorinated phosphonates [17] and have also described 1,4-addition of tetraethyl fluoromethylenebisphosphonate to various α,β-unsaturated ketones, esters, sulfones, sulfoxides and phosphonates [18]. This led us to investigations of nucleophilic additions of **1** to carbon–carbon double bonds of α,β-unsaturated carbonyl compounds and other Michael acceptors.

A number of factors can increase the ratio of conjugate versus 1,2-addition of an organolithium reagent to a given enone: (a) increased size and charge delocalization (softness) of the nucleophile, (b) increased solvent polarity, and (c) the addition of lithium-coordinating additives. In the absence of these additives, organolithium reagents form contact ion pairs (CIP), while solvent-separated ion pairs (SSIP) are formed in the presence of lithium-coordinating additives. CIP and SSIP rapidly interconvert and, generally, SSIP species favor conjugate addition. Lithium coordinating additives also affect the 1,4:1,2 ratio by decreasing or preventing lithium catalysis (i.e. lithium coordination to carbonyl which favors 1,2-addition by increasing its LUMO coefficient) [19]. Furthermore, alkyl lithium reagents are stabilized in solution by the formation of aggregates. Lithium coordinating additives may modify the structure of these aggregates such as break-down tetramer to dimer and thus influence reactivity of the nucleophilic reagent.

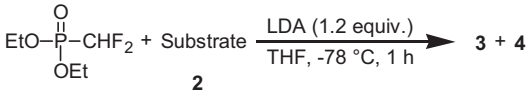
2. Results and discussion

Nucleophilic addition of **1** to 2-cyclohexenone (**2a**) as a model α,β-unsaturated ketone in THF provided the initial focus. Similar to other α,β-unsaturated aldehydes and ketones, 2-cyclohexenone is known to react exclusively in 1,2-addition fashion (attack to carbonyl group) providing alcohol **3a** in a high yield, as shown in entry 1, Table 1. Crown ethers were added to the reaction mixture to solvate the lithium ions to prevent complexation to the carbonyl group of **2a**. Indeed, the formation of small amounts of 1,4-addition product **4a** was observed (entries 2 and 3), which suggests that lithium catalysis plays only a small role in affecting chemoselectivity of this nucleophilic addition. The addition of excess 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) [20] significantly increased the product **4a**:**3a** ratio, however, the yields were only moderate (entry 4) and number of unidentified products were formed presumably coming from the reaction of **1** with DMPU. Good results were obtained in the presence of hexamethylphosphoramide (HMPA); the highest isolated yield (47%) of **4a** was achieved using 5 equiv. of HMPA in THF (entry 6). Moving from THF solvent to DME or diglyme gave similar results. In all cases, significant amounts of the product of 1,2-addition (**3a**) were present in reaction mixtures. Employment of other lithium ion-coordinating additives such as DMF or *N*-methyl-2-pyrrolidone (NMP) did not give any 1,4-addition product. It appears from these results that addition of HMPA increases the rate of conjugate addition, mainly by increasing solvent polarity and modification of aggregates of **1** in solution. It is interesting to compare our results of the addition of **1** to **2a** with the addition of the apparently softer nucleophile $PhSO_2CF_2Li$, where the presence of HMPA reverses selectivity from 1,2- to almost exclusive 1,4-addition [21]. Reaction of **1** with α,β-unsaturated aldehydes such as *trans*-cinnamaldehyde and acrolein provided only 1,2-addition products even in the presence of excess HMPA.

The scope of the 1,4-addition of **1** to various α,β-enones or Michael acceptors was explored (Table 2). In case of α,β-enones the reaction was performed in the presence of HMPA (5 equiv.). Cyclic ketone **2b** gave a good yield of the 1,4-addition product **4b**, while the acyclic 3-buten-2-one (**2c**) reacted in lower efficiency. High 1,2-addition selectivity observed with chalcone (**2d**) did not seem to be the result of steric hindrance, but rather insufficient activation of the carbon–carbon double bond. This statement was supported by the fact that 2-benzylidene-1,3-diphenylpropane-1,3-dione (**2e**) gave preferentially 1,4-addition product **4e** and 2-alkylidene derivative **2f** provided exclusively 1,4-addition product **4f** in high yield. The reactivity of **2e** was the same in the presence or the absence of HMPA suggesting that substrate electronic effects (the presence of second carbonyl group) increase the reactivity of the C=C bond to the extent that the effect of HMPA is relatively insignificant.

To our surprise, various other Michael acceptors also underwent the 1,4-addition reactions. Here, the presence of HMPA additive did not have any positive influence on the yield of Michael adducts **4** (HMPA could influence reaction rates, however, the kinetics were not investigated). On the other hand, the use of a

Table 2
The additions of [(diethoxyphosphoryl)difluoromethyl]lithium (**1**) to α,β-unsaturated compounds (**2**).



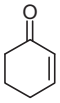
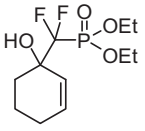
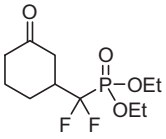
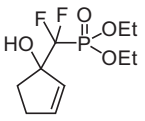
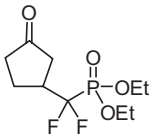
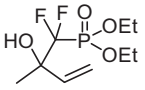
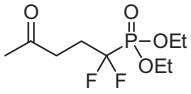
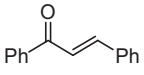
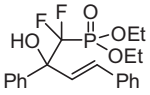
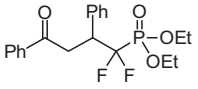
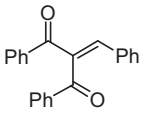
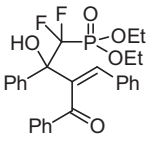
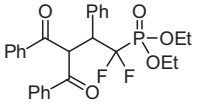
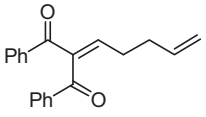
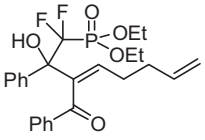
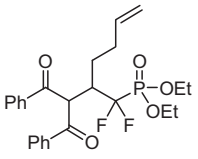
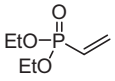
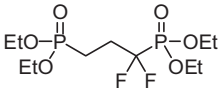
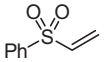
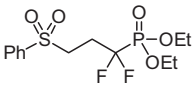
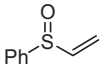
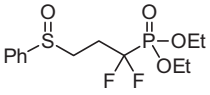
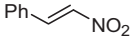
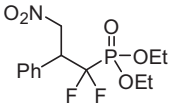
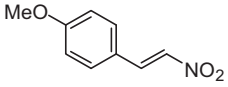
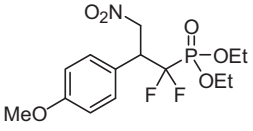
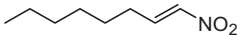
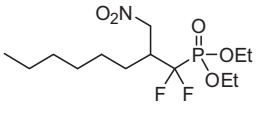
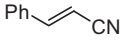
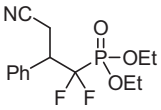
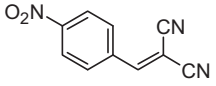
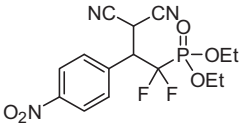
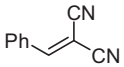
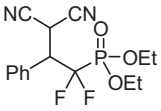
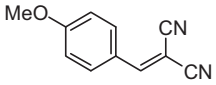
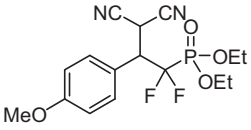
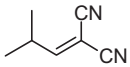
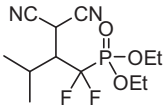
Entry	2	Substrate (equiv.)		Products and yields (%)[b]				
1[a]	**2a**		1.5 0.67	**3a**		51[c] 35[c]	**4a**		47 41
2[a]	**2b**		1.5 0.67	**3b**		40 36	**4b**		53 45
3[a]	**2c**		1.5 0.67	**3c**		21[c] 28[c]	**4c**		7[c] 27
4[a]	**2d**		1.5	**3d**		58[c]	**4d**		<2[c]
5	**2e**		0.67	**3e**		40	**4e**		57
6	**2f**		0.67	**3f**		0[c]	**4f**		85
7	**2g**		1.5 0.67	**4g**		32[d] 8[c]			
8	**2h**		1.5 0.67	**4h**		31 39			
9	**2i**		1.5 0.67	**4i**		61 62			
10	**2j**		1.5 0.67	**4j**		61 83			
11	**2k**		1.5 0.67	**4k**		70 81			
12	**2l**		0.67	**4l**		74			

Table 2 (*Continued*)

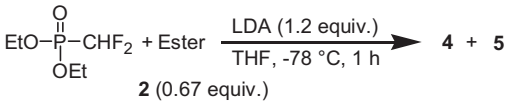
Entry	2	Substrate (equiv.)		Products and yields (%)[b]		
13	**2m**		1.5 0.67	**4m**		0[c] 0[c]
14	**2n**		1.5 0.67	**4n**		<3[c] <3[c]
15	**2o**		1.5 0.67	**4o**		78 97
16	**2p**		1.5 0.67	**4p**		74 96
17	**2q**		0.67	**4q**		97

[a] In the presence of HMPA (5 equiv.).
[b] Isolated yield calculated on deficient component.
[c] ^{19}F NMR yield using $PhCF_3$ as internal standard.
[d] GC/MS yield.

slight excess of nucleophile **1** gave generally higher yields than running reactions with excess of **2**. Vinyl phosphonate **2g** and sulfone **2h** gave products in rather low yields (no formation of any oligomeric addition product by ^{19}F NMR was observed), but sulfoxide **2i** provided the adduct **4i** in a reasonable 62% yield. In analogous Michael additions of tetraethyl fluoromethylenebisphosphonate [18] or diethyl (α-fluoro-α-phenylsulfonylmethyl)phosphonate (McCarthy's reagent) [22], the sulfone **2h** was more reactive than the sulfoxide **2i**. It should be mentioned that sulfone **2h** and sulfoxide **2i** were reported to undergo conjugate addition with **1** to give adducts **4h** and **4i** in 47% and 52% yields, respectively, but only in the presence of at least equimolar amounts of $CeCl_3$ [5,6]. Similarly, with both nitrostyrenes and nitroalkenes, we observed – in contrast to the literature [7] – that no $CeCl_3$ was needed to obtain high yields of Michael adducts. Our reactions were reproducible and no special precautions in terms of high purity and low salt content of the used *n*-BuLi (for the preparation of LDA) were needed.

Reactivities of α,β-unsaturated nitriles were also investigated. 3-Phenylacrylonitrile (**2m**) was found to be an insufficiently activated substrate; only traces of products were observed in the case of (4-nitrobenzylidine)malononitrile (**2n**) although in both cases, the formation of a deep red reaction mixture was observed upon the addition of **2m** or **2n** to the THF solution of **1** suggesting the formation of some type of resonance-stabilized carbanionic adduct. However, benzylidinemalononitrile (**2o**), its *p*-methoxy derivative **2p** as well as 2-isobutylidenemalononitrile (**2q**) showed excellent reactivities.

Table 3
The additions of [(diethoxyphosphoryl)difluoromethyl]lithium (**1**) to α,β-unsaturated esters (**2**).



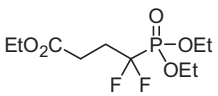
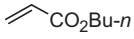
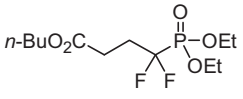
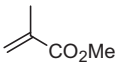
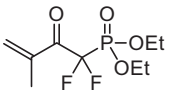
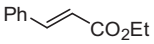
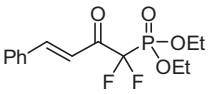
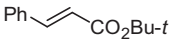
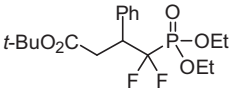
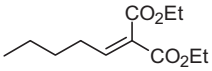
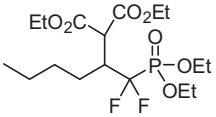
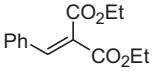
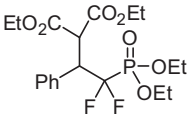
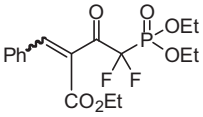
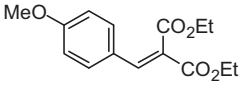
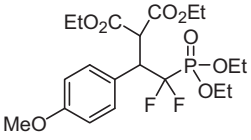
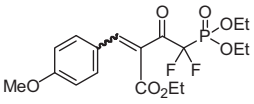
Entry	2	Ester	Products and yields (%)[a]	
1	**2r**		**4r** 	38
2	**2s**		**4s** 	40

Table 3 (*Continued*)

Entry	2	Ester	Products and yields (%)[a]	
3[b]	**2t**		**5t**	 51
4	**2u**		**5u**	 53
5	**2v**		**4v**	 17[c]
6	**2w**		**4w**	 71
7	**2x**		**4x**	 64
			5x	 13[c] + 10[c]
8	**2y**		**4y**	 56
			5y	 26[c] + 10[c]

[a] Isolated yield.
[b] In the presence of HMPA (5 equiv.).
[c] ^{19}F NMR yield using $PhCF_3$ as internal standard.

Next, attention was turned to the additions of **1** to α,β-unsaturated esters (Table 3). Alkyl acrylates **2r** and **2s** undergo 1,4-addition in moderate yields. This conjugate addition pathway is sensitive toward substitutions in α or β positions. For example, methyl methacrylate (**2t**) or ethyl cinnamate (**2u**) did not yield products of conjugate additions, but provided α,α-difluoro-β-ketophosphonates **5t** and **5u**, respectively, resulting from the attack of **1** to the oxycarbonyl group followed by the departure of the alkoxy group. A similar reactivity profile was reported for methyl or ethyl esters in reactions with **1** in the presence of $CeCl_3$ [3]. The employment of Ce^{3+} salts represents preferred conditions for the preparation of ketones **5** from esters. The presence of *tert*-butyl group in **2v** prohibited the attack of **1** to the oxycarbonyl group, probably due to steric reasons; however, the substrate was not activated enough for efficient conjugate addition and the crude product mixture contained a number of fluorinated products (all formed in low ^{19}F NMR yields), including **4v**. In contrast, the presence of the second oxycarbonyl group in alkylidine and arylidinemalonates **2w**–**2y** caused a switch of the dominant reaction pathway back to conjugate addition. In case of arylidinemalonates **2x** and **2y** the crude product mixture was accompanied by small amounts of α,α-difluoro-β-ketophosphonates **5** (mixture of *E* and *Z* isomers).

3. Conclusions

In summary, conjugate additions of [(diethoxyphosphoryl)difluoromethyl]lithium (**1**) to various α,β-unsaturated carbonyl compounds and other Michael acceptors led to number of new, structurally diverse compounds, having an α,α-difluorophosphonate moiety attached to a primary or secondary carbon center. In cyclic α,β-unsaturated ketones the reactivity can be varied from exclusive 1,2-addition in the absence of HMPA to cca 1:1 1,2/1,4-addition in the presence of excess HMPA. 1,4-Addition became the main reaction pathway (and the effect of HMPA became insignificant) for substrates containing two electron-acceptor groups on the C=C bond. Good yields of products of conjugate additions were obtained with phenyl vinyl sulfoxide, nitroalkenes,

acrylates, and alkylidene and arylidene-1,3-diphenylpropane-1,3-dione, malononitriles and malonates.

4. Experimental

4.1. General

NMR spectra were recorded at room temperature in on Bruker Avance 400 or 500 MHz instruments. Chemical shifts (δ) are reported in ppm. ^{13}C and ^{31}P NMR spectra were proton decoupled. GCMS spectra were recorded on an Agilent 7890A gas chromatograph coupled with a 5975C quadrupole mass-selective electron impact (EI) detector (70 eV). High-resolution mass spectra (HRMS) were recorded on a LTQ Orbitrap XL instrument using electrospray ionization (ESI). Infrared spectra were measured on a IR instrument. Reactions were conducted under Ar. THF and DME were dried by distillation from Na/benzophenone. Concentration of *n*-BuLi solution was determined by titration using diphenylacetic acid. All other chemicals were used as received. Purifications of products were performed by flash chromatography using silica gel 60.

4.2. General procedure for the preparation of compounds 3–5 (in the presence of 5 equiv. of HMPA and with 1.5 equiv. of α,β-unsaturated compound)

A solution of *n*-BuLi (2 M, 0.56 mL, 1.11 mmol) in cyclohexane was added dropwise to a stirred solution of *i*-Pr_2NH (0.16 mL, 1.11 mmol) in dry THF (3 mL) cooled to −78 °C. The resulting solution was stirred at 0 °C for 10 min and then cooled to −78 °C. A solution of diethyl difluoromethylphosphonate (174.3 mg, 0.93 mmol) in dry THF (1 mL) was added dropwise and the mixture was stirred at −78 °C for 45 min. HMPA (0.8 mL, 4.6 mmol) was added followed by the addition of α,β-unsaturated compound **2** (1.4 mmol) in dry THF (0.5 mL). The reaction mixture was stirred at −78 °C for 1 h and then saturated aqueous NH_4Cl (10 mL) was added. The product was extracted into diethyl ether (3× 15 mL), the combined organic phase was washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silica gel flash chromatography afforded the pure product.

4.2.1. Diethyl (difluoro(1-hydroxycyclohex-2-en-1-yl)methyl)phosphonate (3a) [16a]

Not isolated; ^{19}F NMR (470.4 MHz, $CDCl_3$): 51% yield, δ = −119.1 (dd, 1F, $^2J_{FF}$ = 302.7 Hz, $^2J_{FP}$ = 103.9 Hz), −119.8 (dd, 1F, $^2J_{FF}$ = 302.7 Hz, $^2J_{FP}$ = 105.1 Hz); MS (EI): *m*/*z* (rel. int.) = 188 (78), 161 (76), 109 (18), 132 (100), 97 (84), 79 (17), 65 (12).

4.2.2. Diethyl (difluoro(1-hydroxycyclopent-2-en-1-yl)methyl)phosphonate (3b)

Isolated as a colorless oil (104 mg, 40% yield); R_f = 0.30 (EtOAc-PE, 50:50); IR (film): ν_{max} (cm^{-1}) = 3366, 3054, 1622, 1258, 1165, 1060, 1023; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz), 1.40 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz), 1.90–1.95 (m, 1H), 2.38–2.44 (m, 1H), 2.47–2.59 (m, 2H), 3.53 (brs, 1H), 4.25–4.35 (m, 4H), 5.85–5.87 (m, 1H), 6.15–6.17 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{CP}$ = 4.9 Hz), 31.2, 32.4 (d, $^3J_{CF}$ = 1.7 Hz), 64.8 (d, $^2J_{CP}$ = 6.8 Hz), 87.4 (dt, $^2J_{CF}$ = 23.6 Hz, $^2J_{CP}$ = 13.7 Hz), 119.3 (dt, $^1J_{CF}$ = 269.0 Hz, $^1J_{CP}$ = 202.4 Hz), 129.2 (d, $^3J_{CF}$ = 2.2 Hz), 138.7; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −117.4 (dd, 1F, $^2J_{FF}$ = 302.4 Hz, $^2J_{FP}$ = 104.5 Hz), −118.4 (dd, 1F, $^2J_{FF}$ = 302.4 Hz, $^2J_{FP}$ = 104.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 7.54 (dd, $^2J_{PF}$ = 104.7 Hz, $^2J_{PF}$ = 104.5 Hz); MS (EI): *m*/*z* (rel. int.) = 188 (52), 161 (56), 132 (100), 115 (17), 83 (47), 65 (13), 55 (9), 39 (6); HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{10}H_{17}F_2NaO_4P$: 293.07247, found: 293.07248.

4.2.3. Diethyl (1,1-difluoro-2-hydroxy-2-methylbut-3-en-1-yl)phosphonate (3c) [23]

Not isolated; ^{19}F NMR (376 MHz, $CDCl_3$): 28% yield, δ = −120.7 (dd, 1F, $^2J_{FF}$ = 302.0 Hz, $^2J_{FP}$ = 107.9 Hz), −118.3 (dd, 1F, $^2J_{FF}$ = 302.0 Hz, $^2J_{FP}$ = 99.5 Hz); MS (EI): *m*/*z* (rel. int.) = 243 (3), 188 (49), 161 (55), 132 (100), 81 (12), 71 (12), 55 (6), 43 (11).

4.2.4. (E)-Diethyl (1,1-difluoro-2-hydroxy-2,4-diphenylbut-3-en-1-yl)phosphonate (3d) [10]

Not isolated; ^{19}F NMR (376 MHz, $CDCl_3$): 58% yield, δ = −116.0 (dd, 1F, $^2J_{FF}$ = 302.2 Hz, $^2J_{FP}$ = 100.6 Hz), −117.8 (dd, 1F, $^2J_{FF}$ = 302.2 Hz, $^2J_{FP}$ = 106.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 7.61 (dd, $^2J_{PF}$ = 106.0 Hz, $^2J_{PF}$ = 100.6 Hz).

4.2.5. (Z)-Diethyl (3-benzoyl-1,1-difluoro-2-hydroxy-2,4-diphenyl-3-en-1-yl)phosphonate (3e)

Isolated as a colorless oil (188 mg, 40% yield); R_f = 0.40 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3361, 3061, 3027, 1703, 1668, 1596, 1580, 1495, 1235, 1164, 1025; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz), 1.31 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz), 3.68–3.78 (m, 1H), 3.91–4.00 (m, 1H), 4.15–4.31 (m, 2H), 5.67 (brs, 1H), 7.03–7.06 (m, 3H), 7.09–7.12 (m, 2H), 7.17–7.21 (m, 2H), 7.24 (s, 1H), 7.31–7.36 (m, 2H), 7.38–7.42 (m, 2H), 7.77–7.79 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.1 (d, $^3J_{CP}$ = 5.8 Hz), 16.3 (d, $^3J_{CP}$ = 5.7 Hz), 64.6 (d, $^2J_{CP}$ = 6.8 Hz), 65.2 (d, $^2J_{CP}$ = 6.8 Hz), 80.4–80.9 (m), 119.7 (dt, $^1J_{CF}$ = 276.4 Hz, $^1J_{CP}$ = 202.8 Hz), 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 129.0, 129.7, 133.0, 134.7, 136.4, 137.0, 137.7 (d, $^3J_{CF}$ = 6.6 Hz), 199.0; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −109.6 (d, 2F, $^2J_{FP}$ = 101.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.75 (t, $^2J_{PF}$ = 101.9 Hz); MS (ESI^+): *m*/*z* (rel. int.) = 524 (30), 523 (100) $[M+Na]^+$, 483 (15), 315 (25); HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{27}F_2NaO_5P$: 523.14564, found: 523.14547.

4.2.6. Diethyl (difluoro(3-oxocyclohexyl)methyl)phosphonate (4a) [11]

Isolated as a colorless oil (127 mg, 47% yield); R_f = 0.32 (EtOAc-PE, 50:50); IR (film): ν_{max} (cm^{-1}) = 1716, 1269, 1166, 1028; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, 6H, $^3J_{HH}$ = 7.1 Hz), 1.63–1.77 (m, 2H), 2.13–2.60 (m, 6H), 2.65–2.69 (m, 1H), 4.25–4.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{CP}$ = 5.5 Hz), 23.5–23.6 (m), 24.1, 39.6–39.7 (m), 40.9, 42.7 (dt, $^2J_{CF}$ = 20.5 Hz, $^2J_{CP}$ = 15.4 Hz), 64.5 (d, $^2J_{CP}$ = 6.5 Hz), 64.6 (d, $^2J_{CP}$ = 6.5 Hz), 120.3 (dt, $^1J_{CF}$ = 263.3 Hz, $^1J_{CP}$ = 212.2 Hz), 208.5; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −115.6 (ddd, 1F, $^2J_{FF}$ = 301.5 Hz, $^2J_{FP}$ = 107.6 Hz, $^3J_{FH}$ = 13.8 Hz), −117.6 (ddd, 1F, $^2J_{FF}$ = 301.5 Hz, $^2J_{FP}$ = 108.9 Hz, $^3J_{FH}$ = 16.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.30 (dd, $^2J_{PF}$ = 108.9 Hz, $^2J_{PF}$ = 107.6 Hz); MS (EI): *m*/*z* (rel. int.) = 264 (100), 236 (16), 208 (15), 188 (36), 161 (56), 146 (84), 132 (66), 111 (47), 97 (79), 81 (31), 77 (31); HRMS (ESI^+): *m*/*z* $[M+Na]^+$ calcd for $C_{11}H_{19}F_2NaO_4P$: 307.08812, found: 307.08802.

4.2.7. Diethyl (difluoro(3-oxocyclopentyl)methyl)phosphonate (4b) [13]

Isolated as a colorless oil (134 mg, 53% yield); R_f = 0.23 (EtOAc-PE, 50:50); IR (film): ν_{max} (cm^{-1}) = 1746, 1265, 1136, 1024; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, 6H, $^3J_{HH}$ = 7.1 Hz), 2.03–2.47 (m, 6H), 2.85–3.02 (m, 1H), 4.22–4.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{CP}$ = 5.5 Hz), 21.9–22.1 (m), 37.5, 37.8–38.0 (m), 40.5 (dt, $^2J_{CF}$ = 21.2 Hz, $^2J_{CP}$ = 15.3 Hz), 64.5 (d, $^2J_{CP}$ = 6.6 Hz), 64.6 (d, $^2J_{CP}$ = 6.6 Hz), 120.3 (dt, $^1J_{CF}$ = 261.7 Hz, $^1J_{CP}$ = 214.6 Hz), 215.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −116.8 (ddd, 1F, $^2J_{FF}$ = 299.8 Hz, $^2J_{FP}$ = 107.8 Hz, $^3J_{FH}$ = 17.0 Hz), −118.7 (ddd, 1F,

$^2J_{FF}$ = 299.9 Hz, $^2J_{FP}$ = 108.7 Hz, $^3J_{FH}$ = 15.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.52 (dd, $^2J_{PF}$ = 108.7 Hz, $^2J_{PF}$ = 107.8 Hz); MS (EI): *m/z* (rel. int.) = 270 (3) $[M]^+$, 250 (74), 269 (08), 222 (09), 188 (41), 161 (69), 132 (100), 111 (30), 83 (61), 77 (33); HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{10}H_{17}F_2NaO_4P$: 293.07247, found: 293.07250.

4.2.8. Diethyl (1,1-difluoro-4-oxopentyl)phosphonate (**4c**) [11]

Isolated as a colorless oil (69 mg, 27% yield); R_f = 0.14 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 2987, 2922, 2854, 1722, 1269, 1166, 1020; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, 6H, $^3J_{HH}$ = 7.1 Hz), 2.18 (s, 3H), 2.28–2.43 (m, 2H), 2.73–2.77 (m, 2H), 4.22–4.29 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{CP}$ = 5.5 Hz), 28.0 (dt, $^2J_{CF}$ = 21.1 Hz, $^2J_{CP}$ = 15.6 Hz), 29.9, 34.8–34.9 (m), 64.5 (d, $^2J_{CP}$ = 6.8 Hz), 120.3 (dt, $^1J_{CF}$ = 259.4 Hz, $^2J_{CP}$ = 216.2 Hz), 205.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −112.4 (dt, $^2J_{FP}$ = 107.9 Hz, $^3J_{FH}$ = 19.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.82 (t, $^2J_{PF}$ = 107.9 Hz); MS (EI): *m/z* (rel. int.) = 258 (2) $[M]^+$, 216 (44), 187 (41), 161 (59), 138 (100), 132 (83), 109 (38), 120 (24), 109 (38), 93 (35), 81 (48), 65 (30), 43 (55); HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_9H_{17}F_2NaO_4P$: 281.07247, found: 281.07248.

4.2.9. Diethyl (3-benzoyl-1,1-difluoro-4-oxo-2,4-diphenylbutyl)phosphonate (**4e**)

Isolated as a colorless oil (273 mg, 57% yield); R_f = 0.21 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3064, 3036, 1701, 1670, 1596, 1581, 1497, 1265, 1162, 1044; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz), 1.12 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz), 3.73–4.06 (m, 4H), 4.95–5.04 (m, 1H), 6.56 (d, 1H, $^3J_{HH}$ = 10.5 Hz), 7.12–7.17 (m, 3H), 7.25–7.29 (m, 2H), 7.39–7.42 (m, 3H), 7.44–7.48 (m, 2H), 7.52–7.56 (m, 1H), 7.75–7.78 (m, 2H), 8.14–8.16 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.9 (d, $^3J_{CP}$ = 5.9 Hz), 16.0 (d, $^3J_{CP}$ = 5.7 Hz), 50.9–51.3 (m), 55.8–56.0 (m), 64.1 (d, $^2J_{CP}$ = 6.8 Hz), 64.4 (d, $^2J_{CP}$ = 6.8 Hz), 121.3 (ddd, $^1J_{CF}$ = 269.1 Hz, $^1J_{CF}$ = 266.1 Hz, $^1J_{CP}$ = 212.0 Hz), 127.9, 128.0, 128.4, 128.5, 128.7, 128.9, 132.9 (d, $^3J_{CF}$ = 6.9 Hz) 133.2, 133.3, 136.6, 136.8, 192.1, 192.7; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −101.7 (dd, 1F, $^2J_{FF}$ = 300.0 Hz, $^2J_{FP}$ = 105.5 Hz), −115.0 (ddd, 1F, $^2J_{FF}$ = 300.0 Hz, $^2J_{FP}$ = 102.7 Hz, $^3J_{FH}$ = 24.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 5.25 (dd, $^2J_{PF}$ = 105.4 Hz, $^2J_{PF}$ = 102.7 Hz); MS (ESI^+): *m/z* (rel. int.) = 502 (27) $[M+Na]^+$, 501 (100) $[M+Na]^+$, 479 (9) $[M+H]^+$; HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{27}F_2NaO_5P$: 523.14564, found: 523.14541.

4.2.10. Diethyl (2-(1,3-dioxo-1,3-diphenylpropan-2-yl)-1,1-difluorohex-5-en-1-yl)phosphonate (**4f**)

Isolated as a colorless oil (381 mg, 85% yield); R_f = 0.28 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3066, 1704, 1674, 1642, 1596, 1581, 1268, 1164, 1024; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, 6H, $^3J_{HH}$ = 7.1 Hz), 1.68–1.75 (m, 1H), 1.99–2.06 (m, 1H), 2.09–2.17 (m, 2H), 3.48–3.60 (m, 1H), 4.18–4.29 (m, 4H), 4.82–4.89 (m, 2H), 5.57–5.65 (m, 1H), 6.33 (d, 1H, $^3J_{HH}$ = 6.8 Hz), 7.39–7.58 (m, 6H), 8.01–8.03 (m, 2H), 8.08–8.10 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{CP}$ = 5.4 Hz), 16.3 (d, $^3J_{CP}$ = 5.3 Hz), 24.9–25.0 (m), 32.4, 43.2 (dt, $^2J_{CF}$ = 18.9 Hz, $^2J_{CP}$ = 15.9 Hz), 53.2–53.3 (m), 64.8 (d, $^2J_{CP}$ = 6.9 Hz), 64.9 (d, $^2J_{CP}$ = 7.3 Hz), 115.2, 122.1 (ddd, $^1J_{CF}$ = 267.2 Hz, $^1J_{CF}$ = 264.0 Hz, $^1J_{CP}$ = 210.2 Hz), 128.6, 128.7, 128.8, 133.3, 133.6, 136.1, 137.0, 137.5, 193.8, 194.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −106.5 (ddd, 1F, $^2J_{FF}$ = 303.2 Hz, $^2J_{FP}$ = 106.4 Hz, $^3J_{FH}$ = 18.4 Hz), −109.1 (ddd, 1F, $^2J_{FF}$ = 303.2 Hz, $^2J_{FP}$ = 108.8 Hz, $^3J_{FH}$ = 15.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.35 (dd, $^2J_{PF}$ = 108.8 Hz, $^2J_{PF}$ = 106.4 Hz); MS (ESI^+): *m/z* (rel. int.) = 524 (30) $[M+Na]^+$, 523 (100) $[M+Na]^+$, 501 (3) $[M+H]^+$; HRMS (ESI^+): *m/z* $[M+H]^+$ calcd for $C_{25}H_{30}F_2O_5P$: 479.17934, found: 479.17926.

4.2.11. Tetraethyl (1,1-difluoropropane-1,3-diyl)bis(phosphonate) (**4g**) [11]

Not isolated; ^{19}F NMR (470.4 MHz, $CDCl_3$): 8% yield, δ = −114.0 (dt, $^2J_{FP}$ = 107.0 Hz, $^3J_{FH}$ = 18.9 Hz); MS (EI): *m/z* (rel. int.) = 325 (6), 307 (9), 223 (31), 215 (52), 165 (100), 137 (20), 109 (29), 81 (16), 55 (13).

4.2.12. Diethyl (1,1-difluoro-3-(phenylsulfonyl)propyl)phosphonate (**4h**) [6]

Isolated as a colorless oil (131 mg, 39% yield); R_f = 0.57 (EtOAc-PE, 70:30); IR (film): ν_{max} (cm^{-1}) = 3066, 2988, 2934, 1585, 1480, 1323, 1149, 1291, 1020; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, 6H, $^3J_{HH}$ = 7.1 Hz), 2.42–2.57 (m, 2H), 3.33–3.37 (m, 2H), 4.18–4.27 (m, 4H), 7.56–7.70 (m, 3H), 7.89–7.92 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{CP}$ = 5.4 Hz), 27.8 (dt, $^2J_{CF}$ = 21.8 Hz, $^2J_{CP}$ = 16.3 Hz), 48.6–48.7 (m), 64.8 (d, $^2J_{CP}$ = 6.8 Hz), 118.8 (dt, $^1J_{CF}$ = 261.8 Hz, $^1J_{CP}$ = 217.2 Hz), 128.0, 129.5, 134.1, 138.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −112.4 (dt, $^2J_{FP}$ = 104.7 Hz, $^3J_{FH}$ = 18.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 5.72 (t, $^2J_{PF}$ = 104.7 Hz); MS (EI): *m/z* (rel. int.) = 311 (12), 283 (10), 215 (18), 187 (25), 159 (100), 140 (15), 125 (25), 109 (34), 104 (41), 91 (17), 81 (23), 77 (74); HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{19}F_2NaO_5PS$: 379.05511, found: 379.05500.

4.2.13. Diethyl (1,1-difluoro-3-(phenylsulfinyl)propyl)phosphonate (**4i**) [5]

Isolated as a colorless oil (197 mg, 62% yield); R_f = 0.26 (EtOAc-PE, 70:30); IR (film): ν_{max} (cm^{-1}) = 3058, 1583, 1479, 1271, 1163, 1040; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.32 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 2.08–2.27 (m, 1H), 2.45–2.63 (m, 1H), 2.85–2.93 (m, 1H), 3.13–3.20 (m, 1H), 4.14–4.25 (m, 4H), 7.48–7.59 (m, 3H), 7.61–7.63 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{CP}$ = 5.3 Hz), 16.3 (d, $^3J_{CP}$ = 5.4 Hz), 26.2 (dt, $^2J_{CF}$ = 21.7 Hz, $^2J_{CP}$ = 16.1 Hz), 47.6–47.7 (m), 64.6 (d, $^2J_{CP}$ = 6.9 Hz), 64.7 (d, $^2J_{CP}$ = 6.9 Hz), 119.6 (dt, $^1J_{CF}$ = 261.4 Hz, $^1J_{CP}$ = 216.3 Hz), 123.9, 129.3, 131.2, 142.5; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −111.4 (dddd, 1F, $^2J_{FF}$ = 296.7 Hz, $^2J_{FP}$ = 105.9 Hz, $^3J_{FH}$ = 21.3 Hz, $^3J_{FH}$ = 16.0 Hz), −112.1 (dddd, 1F, $^2J_{FF}$ = 296.7 Hz, $^2J_{FP}$ = 106.3 Hz, $^3J_{FH}$ = 21.4 Hz, $^3J_{FH}$ = 16.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.12 (dd, $^2J_{PF}$ = 106.3 Hz, $^2J_{PF}$ = 105.9 Hz); MS (EI): *m/z* (rel. int.) = 252 (11), 250 (59), 184 (16), 141 (40), 125 (100), 109 (49), 77 (82), 65 (38), 51 (38); HRMS (ESI^+): *m/z* $[M+H]^+$ calcd for $C_{13}H_{20}F_2O_4PS$: 341.07825, found: 341.07823.

4.2.14. Diethyl (1,1-difluoro-3-nitro-2-phenylpropyl)phosphonate (**4j**) [7]

Isolated as a colorless oil (265 mg, 83% yield); R_f = 0.38 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3067, 3036, 2987, 2932, 1604, 1561, 1498, 1379, 1271, 1166, 1045; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.26 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 3.82–3.92 (m, 1H), 3.97–4.06 (m, 1H), 4.09–4.22 (m, 2H), 4.29–4.42 (m, 1H), 4.87 (dd, 1H, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 10.0 Hz), 5.19 (dd, 1H, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 4.7 Hz), 7.35–7.39 (m, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.0 (d, $^3J_{CP}$ = 6.3 Hz), 16.1 (d, $^3J_{CP}$ = 6.1 Hz), 48.0–48.4 (m), 64.4 (d, $^2J_{CP}$ = 7.0 Hz), 65.0 (d, $^2J_{CP}$ = 6.7 Hz), 74.0–74.2 (m), 119.4 (ddd, $^1J_{CF}$ = 269.7 Hz, $^1J_{CF}$ = 264.5 Hz, $^1J_{CP}$ = 213.3 Hz), 128.8, 129.0, 129.7, 131.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −110.5 (ddd, 1F, $^2J_{FF}$ = 303.2 Hz, $^2J_{FP}$ = 105.3 Hz, $^3J_{FH}$ = 13.8 Hz), −114.9 (ddd, 1F, $^2J_{FF}$ = 303.2 Hz, $^2J_{FP}$ = 98.6 Hz, $^3J_{FH}$ = 19.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 4.72 (dd, $^2J_{PF}$ = 105.3 Hz, $^2J_{PF}$ = 98.6 Hz); MS (EI): *m/z* (rel. int.) = 337 (3) $[M]^+$, 291 (94), 242 (46), 214 (60), 153 (91), 133 (73), 109 (100), 104 (93), 91 (78), 81 (57), 65 (28), 77 (34); HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{18}F_2NNaO_5P$: 360.07829, found: 360.07809.

*4.2.15. Diethyl (1,1-difluoro-2-(4-methoxyphenyl)-3-nitropropyl)phosphonate (**4k**)*

Isolated as a colorless oil (277 mg, 81% yield); R_f = 0.22 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 2986, 2935, 2841, 1613, 1561, 1516, 1379, 1255, 1166, 1046; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.4 Hz), 1.28 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz), 3.78 (s, 3H), 3.85–3.96 (m, 1H), 3.99–4.08 (m, 1H), 4.11–4.23 (m, 2H), 4.24–4.36 (m, 1H), 4.83 (dd, 1H, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 10.2 Hz), 5.15 (dd, 1H, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 4.7 Hz), 6.87–6.90 (m, 2H), 7.28–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (d, $^3J_{CP}$ = 5.8 Hz), 16.0 (d, $^3J_{CP}$ = 5.8 Hz), 47.5 (dt, $^2J_{CF}$ = 20.0 Hz, $^2J_{CP}$ = 16.5 Hz), 55.0, 64.3 (d, $^2J_{CP}$ = 7.2 Hz), 64.8 (d, $^2J_{CP}$ = 7.1 Hz), 74.1–74.2 (m), 114.0, 119.3 (ddd, $^1J_{CF}$ = 269.2 Hz, $^1J_{CF}$ = 264.2 Hz, $^1J_{CP}$ = 213.0 Hz), 122.6–122.7 (m), 130.7, 160.0; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −110.4 (ddd, 1F, $^2J_{FF}$ = 302.3 Hz, $^2J_{FP}$ = 105.5 Hz, $^3J_{FH}$ = 13.6 Hz), −115.1 (ddd, 1F, $^2J_{FF}$ = 302.3 Hz, $^2J_{FP}$ = 99.1 Hz, $^3J_{FH}$ = 20.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 4.88 (dd, $^2J_{PF}$ = 105.5 Hz, $^2J_{PF}$ = 99.1 Hz); MS (EI): *m/z* (rel. int.) = 367 (15) $[M]^+$, 320 (27), 293 (07), 265 (12), 245 (10), 184 (31), 170 (19), 134 (100), 121 (35), 109 (26), 91 (18), 81 (17); HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{14}H_{20}F_2NNaO_6P$: 390.08885, found: 390.08879.

*4.2.16. Diethyl (1,1-difluoro-2-(nitromethyl)octyl)phosphonate (**4l**)*

Isolated as a colorless oil (244 mg, 74% yield); R_f = 0.50 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 2959, 2931, 2860, 2873, 1560, 1381, 1273, 1167, 1024; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, 3H, $^3J_{HH}$ = 6.9 Hz), 1.26–1.33 (m, 7H), 1.39 (dt, 3H, $^3J_{HH}$ = 7.0 Hz, $^4J_{HP}$ = 0.5 Hz), 1.40 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz), 1.44–1.51 (m, 1H), 1.87–1.94 (m, 1H), 3.08–3.21 (m, 1H), 4.26–4.33 (m, 4H), 4.38 (dd, 1H, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 6.4 Hz), 4.88 (dd, 1H, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 5.7 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.9, 16.3 (d, $^3J_{CP}$ = 5.2 Hz), 22.4, 26.3, 26.5, 29.0, 31.4, 42.3 (dt, $^2J_{CF}$ = 19.8 Hz, $^2J_{CP}$ = 16.3 Hz), 65.0 (d, $^2J_{CP}$ = 6.6 Hz), 73.4, 120.4 (dt, $^1J_{CF}$ = 264.8 Hz, $^1J_{CP}$ = 211.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −111.3 (ddd, 1F, $^2J_{FF}$ = 306.3 Hz, $^2J_{FP}$ = 105.0 Hz, $^3J_{FH}$ = 15.6 Hz), −114.7 (ddd, 1F, $^2J_{FF}$ = 306.3 Hz, $^2J_{FP}$ = 105.2 Hz, $^3J_{FH}$ = 16.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 5.50 (dd, $^2J_{PF}$ = 105.2 Hz, $^2J_{PF}$ = 105.0 Hz); MS (EI): *m/z* (rel. int.) = 265 (9), 215 (17), 187 (23), 159 (51), 127 (79), 109 (95), 99 (100), 81 (57), 55 (48), 41 (38); HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{26}F_2NNaO_5P$: 368.14089, found: 368.14085.

*4.2.17. Diethyl (3,3-dicyano-1,1-difluoro-2-phenylpropyl)phosphonate (**4o**)*

Isolated as a pale yellow oil (312 mg, 97% yield); R_f = 0.15 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3068, 3038, 2987, 2915, 2258, 1605, 1587, 1501, 1269, 1167, 1046; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.31 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 3.73–3.83 (m, 1H), 3.91–4.04 (m, 2H), 4.18–4.29 (m, 2H), 4.82 (d, 1H, $^3J_{HH}$ = 5.3 Hz), 7.43–7.50 (m, 3H), 7.54–7.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (d, $^3J_{CP}$ = 5.6 Hz), 16.1 (d, $^3J_{CP}$ = 5.5 Hz), 23.9–24.1 (m), 49.5–50.1 (m), 64.8 (d, $^2J_{CP}$ = 7.2 Hz), 65.6 (d, $^2J_{CP}$ = 6.9 Hz), 110.8, 111.1, 118.7 (ddd, $^1J_{CF}$ = 273.9 Hz, $^1J_{CF}$ = 265.7 Hz, $^1J_{CP}$ = 212.2 Hz), 128.9–129.0 (m), 129.1, 130.0, 130.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −108.4 (ddd, 1F, $^2J_{FF}$ = 303.9 Hz, $^2J_{FP}$ = 102.5 Hz, $^3J_{FH}$ = 11.1 Hz), −115.4 (ddd, 1F, $^2J_{FF}$ = 303.9 Hz, $^2J_{FP}$ = 93.4 Hz, $^3J_{FH}$ = 20.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 3.68 (dd, $^2J_{PF}$ = 102.5 Hz, $^2J_{PF}$ = 93.4 Hz); MS (EI): *m/z* (rel. int.) = 342 (46) $[M]^+$, 286 (6), 221 (9), 204 (19), 188 (66), 161 (68), 155 (46), 140 (86), 132 (100), 109 (74), 91 (22), 81 (41); HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{15}H_{17}F_2N_2NaO_3P$: 365.08371, found: 365.08363.

*4.2.18. Diethyl (3,3-dicyano-1,1-difluoro-2-(4-methoxyphenyl)propyl)phosphonate (**4p**)*

Isolated as a pale yellow oil (325 mg, 96% yield); R_f = 0.11 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3068, 2986, 2915, 2935, 2843, 2258, 1613, 1584, 1518, 1259, 1167, 1044; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.28 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 3.72–3.82 (m, 1H), 3.78 (s, 3H), 3.88–3.99 (m, 2H), 4.14–4.25 (m, 2H), 4.79 (d, 1H, $^3J_{HH}$ = 5.2 Hz), 6.96–6.98 (m, 2H), 7.46–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (d, $^3J_{CP}$ = 5.7 Hz), 16.1 (d, $^3J_{CP}$ = 5.5 Hz), 24.1–24.2 (m), 48.7–49.3 (m), 55.1, 64.7 (d, $^2J_{CP}$ = 7.1 Hz), 65.5 (d, $^2J_{CP}$ = 6.8 Hz), 110.9, 111.2, 114.4, 118.7 (ddd, $^1J_{CF}$ = 273.8 Hz, $^1J_{CF}$ = 265.3 Hz, $^1J_{CP}$ = 212.0 Hz), 120.6–120.6 (m), 131.3, 160.8; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −107.6 (ddd, 1F, $^2J_{FF}$ = 302.7 Hz, $^2J_{FP}$ = 102.6 Hz, $^3J_{FH}$ = 9.5 Hz), −116.0 (ddd, 1F, $^2J_{FF}$ = 302.7 Hz, $^2J_{FP}$ = 94.0 Hz, $^3J_{FH}$ = 21.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 3.81 (dd, $^2J_{PF}$ = 102.6 Hz, $^2J_{PF}$ = 94.0 Hz); MS (EI): *m/z* (rel. int.) = 372 (42) $[M]^+$, 307 (33), 279 (25), 251 (42), 231 (25), 188 (50), 170 (71), 155 (33), 132 (33), 109 (100), 91 (18), 81 (37); HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{16}H_{19}F_2N_2NaO_4P$: 395.09427, found: 395.09413.

*4.2.19. Diethyl (2-(dicyanomethyl)-1,1-difluoro-3-methylbutyl)phosphonate (**4q**)*

Isolated as a colorless oil (278 mg, 97% yield); R_f = 0.26 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 2985, 2293, 2915, 2258, 1397, 1372, 1269, 1164, 1086, 1027; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.28–1.30 (m, 6H), 1.41 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.7 Hz), 1.42 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.7 Hz), 2.54–2.61 (m, 1H), 2.64–2.71 (m, 1H), 4.31–4.38 (m, 4H), 4.67 (dd, 1H, $^3J_{HH}$ = 2.8 Hz, $^4J_{HF}$ = 1.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{CP}$ = 5.3 Hz), 19.9 (dt, $^2J_{CF}$ = 6.7 Hz, $^2J_{CP}$ = 2.5 Hz), 20.1 (d, $^3J_{CF}$ = 2.7 Hz), 21.2–21.3 (m), 27.5, 49.0–49.4 (m), 65.5 (d, $^2J_{CP}$ = 7.3 Hz), 65.8 (d, $^2J_{CP}$ = 7.0 Hz), 111.6, 112.2, 120.0 (ddd, $^1J_{CF}$ = 270.4 Hz, $^1J_{CF}$ = 266.6 Hz, $^1J_{CP}$ = 211.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −111.3 (ddd, 1F, $^2J_{FF}$ = 311.6, $^2J_{FP}$ = 103.8 Hz, $^3J_{FH}$ = 19.0 Hz), −112.9 (ddd, 1F, $^2J_{FF}$ = 311.6 Hz, $^2J_{FP}$ = 100.2 Hz, $^3J_{FH}$ = 13.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 4.61 (dd, $^2J_{PF}$ = 103.8 Hz, $^2J_{PF}$ = 100.2 Hz); MS (EI): *m/z* (rel. int.) = 265 (9), 209 (26), 137 (100), 109 (90), 81 (28), 65 (17), 43 (16); HRMS (ESI^+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{20}F_2N_2O_3P$: 309.11741, found: 309.11736.

*4.2.20. Ethyl 4-(diethoxy-phosphoryl)-4,4-difluorobutyrate (**4r**) [3a,11,15]*

Isolated as a colorless oil (106 mg, 38% yield); R_f = 0.22 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 2986, 2937, 2875, 1739, 1272, 1165, 1021; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.36 (dt, 6H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz), 2.34–2.46 (m, 2H), 2.56–2.59 (m, 2H), 4.13 (q, 2H, $^3J_{HH}$ = 7.1 Hz), 4.22–4.28 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.1, 16.3 (d, $^3J_{CP}$ = 5.4 Hz), 25.9–26.1 (m), 29.3 (dt, $^2J_{CF}$ = 21.1 Hz, $^2J_{CP}$ = 15.7 Hz), 60.8, 64.5 (d, $^2J_{CP}$ = 6.8 Hz), 119.9 (dt, $^1J_{CF}$ = 259.8 Hz, $^1J_{CP}$ = 216.3 Hz), 171.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −113.3 (dt, $^2J_{FP}$ = 107.2 Hz, $^3J_{FH}$ = 19.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.74 (t, $^2J_{PF}$ = 107.2 Hz); MS (EI): *m/z* (rel. int.) = 243 (65), 182 (100), 215 (37), 155 (58), 138 (26), 109 (57), 81 (39), 65 (19), 55 (15), 42 (16); HRMS (ESI^+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{20}F_2O_5P$: 289.10109, found: 289.10105.

*4.2.21. n-Butyl 4-(diethoxy-phosphoryl)-4,4-difluorobutyrate (**4s**)*

Isolated as a colorless oil (118 mg, 40% yield); R_f = 0.32 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 2963, 2936, 2876, 1739, 1273, 1165, 1021; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, 3H, $^3J_{HH}$ = 7.4 Hz), 1.31–1.38 (m, 2H), 1.35 (dt, 6H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz), 1.55–1.61 (m, 2H), 2.33–2.45 (m, 2H), 2.56–2.59 (m, 2H), 4.07 (t, 2H, $^3J_{HH}$ = 6.7 Hz), 4.25–4.32 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.6, 16.3 (d, $^3J_{CP}$ = 5.4 Hz), 19.0, 25.9–26.0 (m), 29.3 (dt, $^2J_{CF}$ = 21.1 Hz, $^2J_{CP}$ = 15.7 Hz), 30.5, 64.5 (d, $^2J_{CP}$ = 6.8 Hz), 64.7, 119.9 (dt, $^1J_{CF}$ = 259.8 Hz, $^1J_{CP}$ = 216.3 Hz), 171.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −113.3 (dt, $^2J_{FP}$ = 107.2 Hz, $^3J_{FH}$ = 19.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.74 (t,

$^2J_{PF}$ = 107.2 Hz); MS (EI): *m/z* (rel. int.) = 261 (7), 243 (100), 215 (51), 187 (98), 155 (80), 138 (17), 109 (27), 81 (20), 57 (11), 41 (12); HRMS (ESI$^+$): *m/z* [M+H]$^+$ calcd for $C_{12}H_{24}F_2O_5P$: 317.13239, found: 317.13238.

4.2.22. t-Butyl 4-(diethoxy-phosphoryl)-4,4-difluoro-3-phenylbutyrate (4v)

Not isolated; ^{19}F NMR (376 MHz, $CDCl_3$): 17% yield, δ = −111.0 (ddd, 1F, $^2J_{FF}$ = 300.5 Hz, $^2J_{FP}$ = 109.8 Hz, $^3J_{FH}$ = 13.4 Hz), −116.0 (ddd, 1F, $^2J_{FF}$ = 300.5 Hz, $^2J_{FP}$ = 103.0 Hz, $^3J_{FH}$ = 21.4 Hz); MS (EI): *m/z* (rel. int.) = 336 (21), 319 (12), 272 (22), 263 (16), 188 (10), 138 (100), 111 (24), 57 (36), 41 (23).

4.2.23. Diethyl 2-(1-((diethoxy-phosphoryl)-difluoro-methyl)-pentyl)-malonate (4w)

Isolated as a colorless oil (275 mg, 71% yield); R_f = 0.37 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 2984, 2963, 2936, 2875, 1755, 1735, 1273, 1156, 1034; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, 3H, $^3J_{HH}$ = 7.2 Hz), 1.26–1.31 (m, 8H), 1.36–1.41 (m, 8H), 1.68–1.77 (m, 1H), 1.83–1.92 (m, 1H), 3.00–3.15 (m, 1H), 3.94 (d, 1H, $^3J_{HH}$ = 5.7 Hz), 4.21 (q, 4H, $^3J_{HH}$ = 7.1 Hz), 4.25–4.32 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.7, 13.8, 13.9, 16.2 (d, $^3J_{CP}$ = 5.4 Hz), 22.8, 25.4, 30.1, 43.0–43.3 (m), 49.8–49.9 (m), 61.3, 61.7, 64.5 (d, $^2J_{CP}$ = 7.5 Hz), 64.6 (d, $^2J_{CP}$ = 7.8 Hz), 121.4 (ddd, $^1J_{CF}$ = 266.3 Hz, $^1J_{CF}$ = 265.0 Hz, $^1J_{CP}$ = 212.0 Hz), 167.5, 168.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −108.5 (ddd, 1F, $^2J_{FF}$ = 303.6 Hz, $^2J_{FP}$ = 107.7 Hz, $^3J_{FH}$ = 14.0 Hz), −114.4 (ddd, 1F, $^2J_{FF}$ = 303.6 Hz, $^2J_{FP}$ = 107.5 Hz, $^3J_{FH}$ = 21.4 Hz); ^{31}P NMR (162 MHz, CDCl3): δ = 6.37 (dd, $^2J_{PF}$ = 107.7 Hz, $^2J_{PF}$ = 107.5 Hz); MS (EI): *m/z* (rel. int.) = 371 (20), 325 (22), 257 (100), 229 (48), 183 (48), 155 (22), 138 (28), 111 (21), 81 (21), 55 (14); HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{17}H_{31}F_2NaO_7P$: 439.16677, found: 439.16659.

4.2.24. Diethyl 2-(2-diethoxy-phosphoryl)-2,2-difluoro-1-phenyl-ethyl-malonate (4x)

Isolated as a colorless oil (260 mg, 64% yield); R_f = 0.35 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3065, 3036, 2985, 2936, 1761, 1738, 1605, 1590, 1498, 1273, 1158, 1030; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.09 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.4 Hz), 1.18 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz), 1.30 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 3.65–3.75 (m, 1H), 3.76–3.84 (m, 2H), 3.86–3.92 (m, 1H), 3.95–4.04 (m, 1H), 4.07–4.15 (m, 1H), 4.20–4.30 (m, 3H), 4.35–4.47 (m, 1H), 7.27–7.32 (m, 3H), 7.37–7.41 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.4, 13.9, 16.0 (d, $^3J_{CP}$ = 5.8 Hz), 16.1 (d, $^3J_{CP}$ = 5.8 Hz), 49.0–49.6 (m), 52.0–52.2 (m), 61.5, 61.9, 63.9 (d, $^2J_{CP}$ = 6.9 Hz), 64.5 (d, $^2J_{CP}$ = 6.7 Hz), 120.5 (ddd, $^1J_{CF}$ = 271.5 Hz, $^1J_{CF}$ = 264.2 Hz, $^1J_{CP}$ = 213.8 Hz), 128.0, 128.3, 130.8, 132.5 (d, $^3J_{CF}$ = 8.1 Hz), 166.2, 167.3; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −105.7 (ddd, 1F, $^2J_{FF}$ = 302.2 Hz, $^2J_{FP}$ = 107.2 Hz, $^3J_{FH}$ = 4.6 Hz), −119.1 (ddd, 1F, $^2J_{FF}$ = 302.2 Hz, $^2J_{FP}$ = 100.9 Hz, $^3J_{FH}$ = 28.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 5.15 (dd, $^2J_{PF}$ = 107.2 Hz, $^2J_{PF}$ = 100.9 Hz); MS (EI): *m/z* (rel. int.) = 436 (12) [M]$^+$, 396 (13), 370 (8), 345 (22), 317 (16), 299 (100), 253 (14), 203 (50), 138 (47), 111 (34), 91 (10), 81 (13); HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{19}H_{27}F_2NaO_7P$: 459.13547, found: 459.13520.

4.2.25. Diethyl 2-(2-(diethoxy-phosphoryl)-2,2-difluoro-1-(4-methoxy-phenyl)-ethyl)-malonate (4y)

Isolated as a colorless oil (243 mg, 56% yield); R_f = 0.18 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3065, 2985, 2936, 2841, 1762, 1736, 1254, 1160, 1031; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.12 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz), 1.21 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.7 Hz), 1.29 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 3.72–3.77 (m, 1H), 3.77 (s, 3H), 3.80–3.86 (m, 2H), 3.89–3.94(m, 1H), 3.98–4.06 (m, 1H), 4.10–4.17 (m, 2H), 4.19–4.30 (m, 2H), 4.31–4.41 (m, 1H), 6.81–6.84 (m, 2H), 7.29–7.32 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.5, 13.8, 16.0 (d, $^3J_{CP}$ = 5.7 Hz), 16.1 (d, $^3J_{CP}$ = 5.7 Hz), 48.2–48.7 (m), 52.0–52.2 (m), 55.1, 61.5, 61.9, 63.9 (d, $^2J_{CP}$ = 6.7 Hz), 64.5 (d, $^2J_{CP}$ = 6.5 Hz), 113.4, 120.6 (ddd, $^1J_{CF}$ = 271.1 Hz, $^1J_{CF}$ = 265.1 Hz, $^1J_{CP}$ = 213.8 Hz), 124.2(d, $^3J_{CF}$ = 8.5 Hz), 131.9, 159.5, 166.3, 167.3; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = −105.3 (ddd, 1F, $^2J_{FF}$ = 301.2 Hz, $^2J_{FP}$ = 107.0 Hz, $^3J_{FH}$ = 4.4 Hz), −119.4 (ddd, 1F, $^2J_{FF}$ = 301.2 Hz, $^2J_{FP}$ = 101.5 Hz, $^3J_{FH}$ = 28.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 5.30 (dd, $^2J_{PF}$ = 107.0 Hz, $^2J_{PF}$ = 101.5 Hz); MS (EI): *m/z* (rel. int.) = 466 (10) [M]$^+$, 426 (16), 400 (12), 375 (13), 300 (23), 255 (100), 227 (28), 161 (45), 109 (14), 81 (9); HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{20}H_{29}F_2NaO_8P$: 489.14603, found: 489.14571.

4.2.26. Diethyl (1,1-difluoro-3-methyl-2-oxo-but-3-enyl)-phosphonate (5t)

Isolated as a colorless oil (121 mg, 51% yield); R_f = 0.34 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 1744, 1695, 1628, 1278, 1164, 1022; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (dt, 6H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.7 Hz), 1.94–1.95 (m, 3H), 4.26–4.35 (m, 4H), 6.15–6.17 (m, 1H), 6.43–6.44 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{CP}$ = 5.6 Hz), 18.3, 65.2 (d, $^2J_{CP}$ = 6.7 Hz), 114.7 (dt, $^1J_{CF}$ = 275.1 Hz, $^1J_{CP}$ = 200.4 Hz), 132.0 (t, $^3J_{CP}$ = 5.5 Hz), 139.1–139.2 (m), 188.9 (dt, $^2J_{CF}$ = 23.8 Hz, $^2J_{CP}$ = 15.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −109.5 (d, $^2J_{FP}$ = 96.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 3.83 (t, $^2J_{PF}$ = 96.0 Hz); MS (EI): *m/z* (rel. int.) = 228 (7), 211 (6), 201 (7), 184 (7), 132 (14), 121 (13), 109 (5), 81 (10), 69 (100), 41 (41); HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_9H_{15}F_2NaO_4P$: 279.05682, found: 279.05685.

4.2.27. Diethyl (1,1-difluoro-2-oxo-4-phenyl-but-3-enyl)-phosphonate (5u) [3a,3b]

Isolated as a colorless oil (171 mg, 53% yield); R_f = 0.32 (EtOAc-PE, 30:70); IR (film): ν_{max} (cm^{-1}) = 3063, 3030, 1705, 1609, 1599, 1577, 1496, 1277, 1164, 1088, 1021; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, 6H, $^3J_{HH}$ = 7.1 Hz), 4.30–4.38 (m, 4H), 7.21 (d, 1H, $^3J_{HH}$ = 15.9 Hz), 7.40–7.46 (m, 3H), 7.63–7.66 (m, 2H), 7.91 (d, 1H, $^3J_{HH}$ = 15.9 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{CP}$ = 5.6 Hz), 65.3 (d, $^2J_{CP}$ = 6.6 Hz), 113.7 (dt, $^1J_{CF}$ = 272.5 Hz, $^1J_{CP}$ = 197.0 Hz), 118.2, 129.0, 129.1, 131.7, 133.7, 147.9, 186.6 (dt, $^2J_{CF}$ = 23.6 Hz, $^2J_{CP}$ = 15.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −118.8 (d, $^2J_{FP}$ = 98.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 3.72 (t, $^2J_{PF}$ = 98.0 Hz); MS (EI): *m/z* (rel. int.) = 298 (7), 245 (2), 131 (100), 103 (26), 77 (12); HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{14}H_{17}F_2NaO_4P$: 341.07247, found: 341.07242.

4.2.28. Ethyl 2-benzylidene-4-(diethoxy-phosphoryl)-4,4-difluoro-3-oxo-butyrate (5x)

Not isolated; ^{19}F NMR (376 MHz, $CDCl_3$): 13% yield, δ = −110.5 (d, 2F, $^2J_{FP}$ = 95.2 Hz), 10% yield, δ = −113.9 (d, 2F, $^2J_{FP}$ = 97.4 Hz); MS (EI): both isomers *m/z* (rel. int.) = 370 (3), 345 (3), 203 (100), 175 (9), 135 (19), 107 (12).

4.2.29. Ethyl 4-(diethoxy-phosphoryl)-4,4-difluoro-2-(4-methoxy-benzylidene)-3-oxo-butyrate (5y)

Not isolated; ^{19}F NMR (376 MHz, $CDCl_3$): 26% yield, δ = −110.2 (d, 2F, $^2J_{FP}$ = 95.7 Hz), 10% yield, δ = −113.7 (d, 2F, $^2J_{FP}$ = 97.6 Hz); MS (EI): both isomers *m/z* (rel. int.) = 375 (4), 345 (3), 233 (100), 205 (9), 165 (6), 137 (7), 117 (2).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2012.02.003.

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