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A facile method to construct cyclic α,α-difluoromethylenephosphonate—A novel cyclic phosphate mimic

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ABSTRACT

A facile and efficient synthesis of cyclic α,α-difluoromethylenephosphonates by halogen-induced intramolecular cyclization of β-allenic α,α-difluoromethylenephosphonates is described. The protocol gives multi-substituted six-membered phosphonates with high regioselectivity, providing a new entry to the cyclic phosphate mimics which is still an unexplored but promising area.

1. Introduction

Recently, there has been considerable interest in the development of phosphate mimics owing to the vital role of phosphate-containing molecules in the intracellular signal process. The driving force for the development of phosphate mimics is often the unwanted lability of the ester P–O bond. Many years ago, Blackburn et al. [1] demonstrated that the electronic properties of pyrophosphate were more effectively mimicked by its difluoromethylene bis-phosphonic acid analogue than by methylene bis-phosphonic acid. His results raised the possibility that the isoelectronic and isosteric CF_2/O transposition in phosphate analogues could be especially hydrolytically stable and effective mimics of their corresponding phosphates, possibly with applicability in designing biologically active molecules.

Up to now, numerous structurally novel and biologically interesting acyclic phosphate mimics—α,α-difluoromethylenephosphonate-containing phospholipids, nucleosides, isoprenoids, phosphotyrosine, and phosphoserinen alogues [2] have been prepared and studied as potential enzyme inhibitors and useful probes in the elucidation of biochemical process [3]. In contrast, the biological activity of cyclic phosphate mimics—cyclic α,α-difluoromethylenephosphonates still remains unexplored. The main reason behind this situation is the synthetic problem underlying their preparation, since methods commonly used for the preparation of phosphonates usually cannot be applied to fluorinated analogues. To the best of our knowledge, to date there are only few papers [4] regarding the formation of five or six-membered α,α-difluoromethylenephosphonates as byproducts or intermediates.

On the other hand, a series of compounds bearing a cyclic phosphate moiety play vital roles in diverse biological processes. Cyclic phosphates of foremost biological importance are the universal second messengers cyclic AMP and cyclic GMP. Other cyclic phosphates which were detected in biological systems include glucose cyclic phosphodiester, cyclic phosphodiester nucleotides, riboflavin cyclic phosphodiester, myo-inositol 1,2 phosphodiester, cyclic lysophosphatidic acid [5] and cyclic glycerophosphates [6]. Recently, much attention has been focused on the role of cyclic phosphates in the cellular signal transition [7]. For these reasons, we became interested in the development of synthetic approaches to cyclic α,α-difluoromethylenephosphonates for the screening of new bioactive compounds.

Electrophile-induced heteroannulation process involving unsaturated compounds bearing a tethered nucleophilic substituent has been proven to be an efficient synthetic method towards a large variety of heterocyclic systems. It was well documented that halogen promoted intramolecular cyclization of allenes bearing nucleophiles including N and O in suitable positions not only yielded five to ten-membered heterocycles [8], but also afforded vinyl halogen moiety which may permit further elaboration to form more complex compounds.

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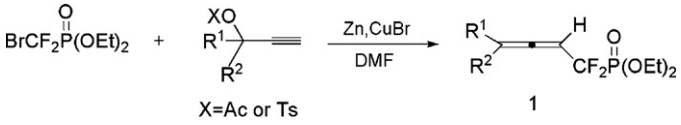
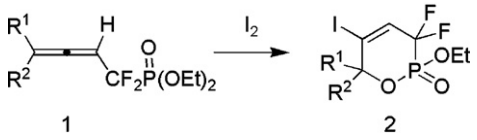
In preliminary communications [9], we first established a high-yielding procedure for the synthesis of cyclic α,α-difluoromethylenephosphonates through the electrophile-induced cyclization of 2,3-allenic phosphonate. In this paper we present a full account of our recent investigation on this high regioselective synthesis of cyclic α,α-difluoromethylenephosphonates as a new approach to cyclic phosphate mimics.

2. Results and discussion



Scheme 1.

The key starting materials **1** were readily prepared according to the reported procedure [10] with slight modification (Scheme 1). First, iodine-mediated lactonization reaction of **1** to afford cyclic α,α-difluoromethylenephosphonate was tried (Scheme 2). To our delight, starting from **1a** ($R^1 = R^2 = CH_3$) with 2 equivalents of iodine in CH_3CN, we observed in our first try the formation of the six-membered cyclic α,α-difluoromethylenephosphonate **2a** in 64% yield. The structure of **2a** was determined by its spectral data as well as X-ray crystallography (Fig. 1).



Scheme 2.

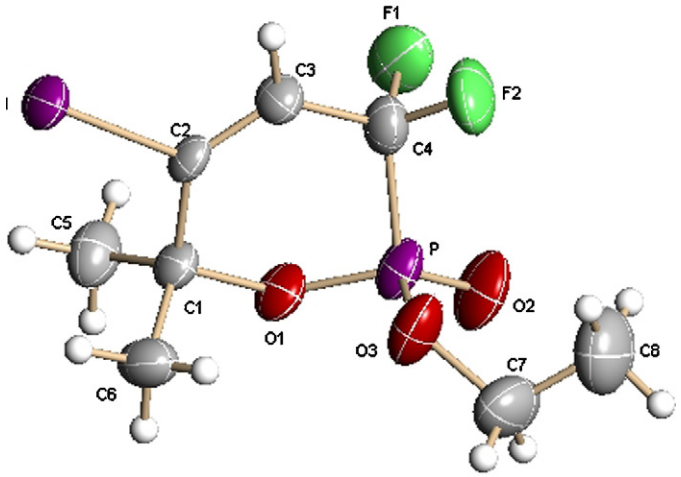
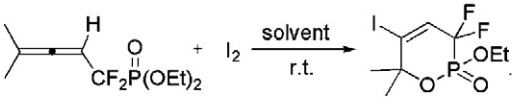


Fig. 1. The X-ray Crystallographic Structure of **2a**.

In order to improve the yield of this iodolactonization reaction, we screened several conditions. As shown in Table 1, CH_3CN was suitable solvent for the reaction and a small amount of water in the reaction mixture favored the cyclization. Furthermore, the reaction was influenced by the amount of iodine and the best result was obtained when 3 equivalents of iodine was used (entry 7, 82% yield).

Table 1
The reaction of **1a** with iodine under different conditions[a].



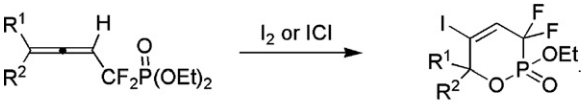
1a **2a**

Entry	I_2 (equiv.)	Solvent	Time (h)	Isolated yield (%)
1	2	CH_3CN	3	64
2	2	CH_2Cl_2	6	61
3	2	C_6H_6	6	40
4	2	DMF	6	35
5	2	CH_3CN/H_2O (30:1)	3	70
6	2.5	CH_3CN/H_2O (30:1)	3	75
7	3	CH_3CN/H_2O (30:1)	3	82

[a] The reaction was carried out using 0.5 mmol of **1a** as starting material.

Using the optimized conditions, the reactions of other β-allenic phosphonates with iodine, ICl, NIS were investigated. The results are summarized in Table 2. In most cases iodine was efficient electrophile and the corresponding α,α-difluoromethylenephosphonates were obtained in moderate to high yields. The reaction was strongly influenced by the substitution pattern on the allene skeleton: δ,δ-disubstituted allenic phosphonates gave good to excellent yields (Table 2, entries 1, 4–7), probably caused by the stabilization effect of two alkyl substitutes on the iodonium intermediate formed in the reaction. Bulky groups such as *t*-Bu and Ph at δ-carbon may block the attack of iodine or phosphonyl and make the yield lower. The reaction of δ-monosubstituted allenic phosphonates with iodine gave very low yield (Table 2, entry 10). However, the desired products **2h–2j** could be obtained in moderate yields when stronger electrophile ICl was used (Table 2, entries 11–13). In the case of terminal allenic phosphonate (Table 2, entry 14), the reaction was complicated and the product was not stable enough for isolation. In the cases of allenes with different terminal substitutes, the reaction gave cyclization products as a mixture of two diastereoisomers. The ratios of two isomers were approximate 1:1 with 4,4-disubstituted allenic phosphonates (Table 2, entries 7–9) and approximate 2:3 with 4-monosubstituted allenic phosphonates (Table 2, entries 11–13) as indicated by ^1H NMR. The reaction was regiospecific. In all reactions only six-membered phosphonates were obtained.

Table 2
Synthesis of α-difluoromethylenephostones via iodocyclization of **1**[a].

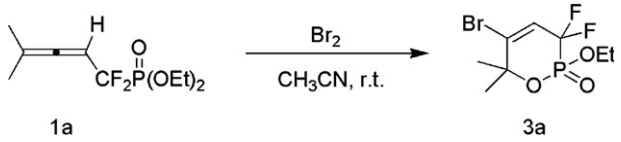


1 **2**

Entry	R_1	R_2	Electrophile	Product	Isolated yield (%)
1	CH_3	CH_3	I_2	**2a**	82
2[b]	CH_3	CH_3	ICl	**2a**	83
3[c]	CH_3	CH_3	NIS	**2a**	43
4	Et	Et	I_2	**2b**	92
5	$-(CH_2)_5-$		I_2	**2c**	90
6	$-(CH_2)_4-$		I_2	**2d**	81
7	CH_3	Et	I_2	**2e**	91
8	CH_3	*t*-Bu	I_2	**2f**	53
9	CH_3	Ph	I_2	**2g**	64
10	Et	H	I_2	**2h**	25
11[c]	Et	H	ICl	**2h**	80
12[c]	*n*-Pr	H	ICl	**2i**	78
13[c]	*i*-Pr	H	ICl	**2j**	75
14	H	H	I_2	**2l**	Unstable product

[a] The reaction was carried out in CH_3CN/H_2O (30:1) at room temperature using 0.5 mmol **1** and 1.5 mmol I_2.
[b] The reaction was carried out using 0.5 mmol **1** and 0.75 mmol ICl.
[c] The reaction was carried out using 0.5 mmol **1** and 0.75 mmol NIS.

Under similar conditions, bromocyclization of **1a** was then investigated (Scheme 3). By using Br_2 instead of I_2, the expected product **3a** was obtained only in 25% yield, and changing reaction conditions did not improve the yield either.

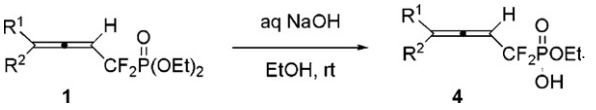


1a 3a

Scheme 3.

According to the results obtained with the reaction of O,O-dialkyl-ω-alkenylphosphonate and Br_2 by Zhao and Yan [11] and Shibuya and co-workers [12], we considered that due to the relative low nucleophilicity of the oxygen atom of phosphonyl group as well as to some difficulty in the collapse of the O-Et bond with the assistance of bromine anion in the presumed bromonium

Table 3
Synthesis of β-allenic phosphonic acid monoesters[a].

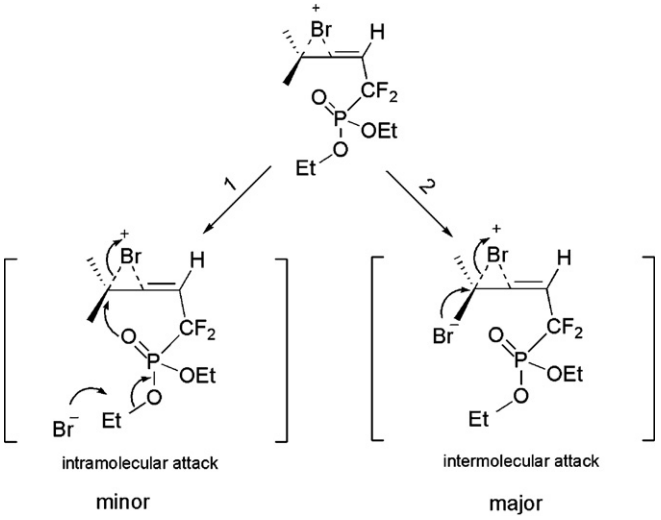


1 4

Entry	R^1	R^2	Product	Isolated yield (%)
1	CH_3	CH_3	**4a**	93
2	Et	Et	**4b**	90
3		$-(CH_2)_5-$	**4c**	91
4		$-(CH_2)_4-$	**4d**	87
5	CH_3	Et	**4e**	88
6	CH_3	*t*-Bu	**4f**	94
7	Et	H	**4g**	92
8	*n*-Pr	H	**4h**	90
9	*i*-Pr	H	**4i**	91
10	Ph	CH_3	**4j**	defluorinated products
11	H	H	**4k**	defluorinated products

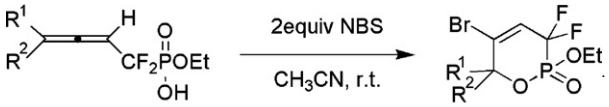
[a] All reactions were conducted at room temperature with 2.0 equiv. NaOH.

intermediate A (Scheme 4), intramolecular attack (path 1) may be highly suppressed by its competitive intermolecular reaction (path 2). Therefore, our attention was next turned to the synthesis of β-allenic phosphonic acid monoesters **4** which might facilitate intramolecular cyclization by readily losing proton in the cyclization key step, and hydrolysis of **1** was investigated. To



Scheme 4.

Table 4
The bromocyclization reaction of **4**[a].



4 3

Entry	R^1	R^2	Product	Isolated yield (%)
1[b]	CH_3	CH_3	**3a**	55
2	CH_3	CH_3	**3a**	87
3	Et	Et	**3b**	90
4		$-(CH_2)_5-$	**3c**	88
5		$-(CH_2)_4-$	**3d**	79
6	CH_3	Et	**3e**	90
7	CH_3	*t*-Bu	**3f**	58
8	Et	H	**3g**	89
9	*n*-Pr	H	**3h**	88
10	*i*-Pr	H	**3i**	87

[a] All reactions were conducted at room temperature with 2.0 equiv. NBS in CH_3CN unless otherwise noted.
[b] The reaction was conducted using 2.0 equiv. Br_2 in CH_3CN.

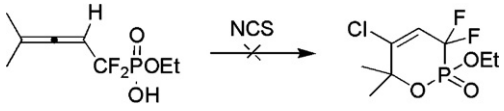
our delight, in contrast to non-fluorinated phosphonates, these fluorine-containing diethyl β-allenic phosphonates hydrolyzed readily in aqueous sodium hydroxide solution at room temperature and gave the corresponding phosphonic acid monoesters in high yields without destroying the allenic moiety (Table 3) except 4-phenyl and methyl disubstituted and 4-nonsubstituted allenic phosphonates which defluorinated under the reaction conditions.

With these β-allenic phosphonic acid monoesters in hand, their bromocyclization reactions with Br_2 and NBS were then investigated and better results were obtained when NBS was used as electrophile (Table 4, entries 1–2). As expected, all the reactions took place readily at room temperature, affording the corresponding six-membered bromine-containing α,α-difluoromethylene-phosphonates **3** in moderate to good yields (Table 4, entries 2–10).

The reaction was very fast and usually completed in less than 1 h. As shown in Table 4, the results were similar to those of iodocyclization. Both δ-monosubstituted and δ,δ-disubstituted β-allenic phosphonic acid monoesters gave the cyclization products in high yields except for **3f** in which bulky group *t*-Bu at δ-carbon may block the attack of Br^+ or oxygen and make the yield lower. In the cases of allenic phosphonic acid monoesters with different terminal substitutes, the reaction gave cyclization products as a mixture of two diastereoisomers which could be distinguished by ^1H NMR spectroscopy, but could not be separated by common chromatographic methods. The ratios of two isomers were approximate 1:1 with different terminal substituents (Table 4, entries 6–10), as indicated by ^1H NMR spectra.

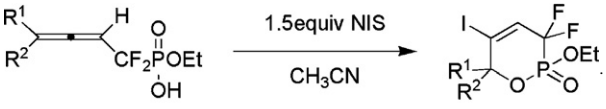
Encouraged by the above results that the yield of bromocyclization dramatically increased when allenic phosphonate diesters were hydrolyzed to monoesters, we envisioned that similar results might be obtained from iodocyclization reaction. As expected, the yield of iodosubstituted cyclic phosphonates **2**, especially those prepared from δ-monosubstituted phosphonic acid monoesters were improved (Table 5, entries 8–10), while with diesters, the desired products could be obtained in moderate yields only when stronger and more expensive electrophile—ICl was used (Table 2, entries 11–13).

We also studied the chlorocyclization of **4a** (Scheme 5), unfortunately, no desired product was obtained.



Scheme 5.

Table 5
The iodocyclization of **4**[a].



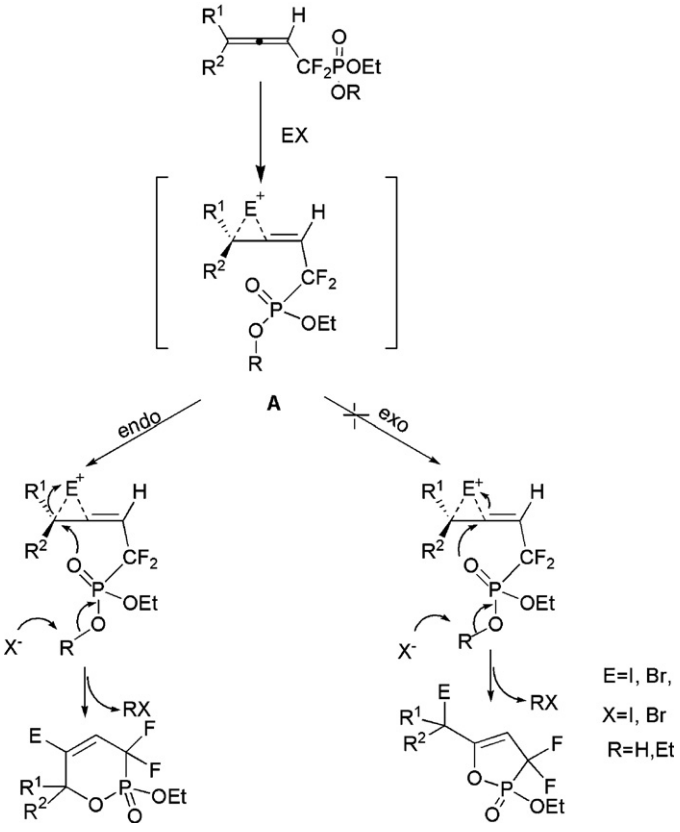
4 **2**

Entry	R^1	R^2	Product	Isolated yield (%)
1	Me	Me	**2a**	88
2[b]	Me	Me	**2a**	53
3	Et	Et	**2b**	90
4		$-(CH_2)_5-$	**2c**	86
5		$-(CH_2)_4-$	**2d**	76
6	Me	Et	**2e**	87
7	Me	*t*-Bu	**2f**	58
8	Et	H	**2h**	89
9	*n*-Pr	H	**2i**	91
10	*i*-Pr	H	**2j**	93

[a] All reactions were conducted at room temperature with 1.5 equiv. NIS in CH_3CN for 45 min under N_2 in the dark.
[b] The reaction was conducted using 2.0 equiv. I_2 in CH_3CN.

All the reactions were regioselective. In all cases, only six-membered phosphonates were obtained, and five-membered products were not detected. The reason is not very clear right now. A possible explanation is that the longer C–P and P–O bond may make the *endo* ring closure much easier which leads to the formation of six-membered ring.

Based on the above results, a plausible mechanism was proposed for the formation of cyclic α,α-difluoromethylenephosphonate **2** and **3**, as outlined in Scheme 6. Electrophilic attack of EX to allenic phosphonate terminal double bond gave three-membered ring intermediate A and released an X anion at the same time. With the assistance of X anion, intramolecular nucleophilic attack of oxygen on phosphonyl group in the terminal carbon of allene in the favored *endo* mode afforded the corresponding cyclization product accompanied by the elimination of RX.



Scheme 6.

In conclusion, we have established a regioselective halogen-induced intramolecular addition of β-allenic α,α-difluoromethylenephosphonates for the first time, providing a convenient strategy for the preparation of novel cyclic α,α-difluoromethylenephosphonates—a vital yet unexplored cyclic phosphate mimics. The presence of vinyl iodine/bromine in the product makes it possible to incorporate this novel subunit into other molecules with potential bioactivities. Further investigation in this area is in progress in our laboratory.

3. Experimental

Melting points were uncorrected. IR spectra were taken on a Perkin-Elmer Jeol 983 spectrophotometer using liquid films and KBr pellets for solids. ^{1}H NMR spectra were measured on a Bruker AM300 (300 MHz) spectrometer using TMS as internal standard. ^{13}C NMR spectra were taken on a Bruker AM500 (125 MHz), 400 (100 MHz) and 300 (75 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM300 (282 MHz) spectrometer using $CFCl_3$ as external standard. ^{31}P NMR spectra were taken on a Bruker AM300 (121 MHz) spectrometer using 85% H_3PO_4 as external reference. Mass spectra were taken on Agilent HP5973 spectrometer (EI, 70 ev), Agilent LC/MSDSL(ESI), Waters GCTCA176(HPESI) and Ionspec4.7T (HPMALDI) spectrometers. Elemental analysis was preformed with an Elemental VARIO EL apparatus. Column chromatography was performed on silica gel H, particle size 300–400 m.

3.1. Typical experimental procedure for the synthesis of **1**

Under N_2 atmosphere, to a stirred suspension of Zn dust (1.3 g, 20 mmol) in dry DMF (10 mL) was added slowly a solution of $BrCF_2PO(OEt)_2$ (5.34 g, 20 mmol) in DMF (10 mL). The addition was controlled so that the internal temperature was maintained at 50–60 °C. After addition was completed, the solution was stirred at room temperature for an additional 3 h, then CuBr (2.87 g, 20 mmol) was added in one portion. The mixture was stirred at the same temperature for 30 min to give organocopper reagent in DMF. Propargylic acetate or tosylate (12 mmol) in dry DMF (8 mL) was added dropwise at room temperature. After the mixture was stirred at room temperature for 12 h, water was added to quench the reaction. The biphasic mixture was passed through Celite and extracted with Et_2O. The extracts were washed with brine, dried over Na_2SO_4 and evaporated in vacuum. The residue was chromatographed on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding product **1**.

(4-Ethyl-1,1-difluoro-hexa-2,3-dienyl)-phosphonic acid diethyl ester (1b). Prepared from propargylic acetate (X = Ac, $R^1 = R^2$ = Et). 80% yield. IR (film): 1973, 1274, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50–5.39 (m, 1 H), 4.28–4.18 (m, 4 H), 2.10–1.96 (m, 4 H), 1.37–1.31 (m, 6 H), 1.04–1.00 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.6–202.4 (m), 116.0 (td, J_{C-F} = 257.5 Hz, J_{C-P} = 225.0 Hz), 115.1, 88.8 (td, J_{C-F} = 20.0 Hz, J_{C-P} = 15.8 Hz), 64.1 (d, J_{C-P} = 6.7 Hz), 25.0, 16.1 (d, J_{C-P} = 5.4 Hz), 11.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −105.12 (dd, J_{P-F} = 106.6 Hz, J_{H-F} = 10.1 Hz); EIMS *m*/*z* (%): 282 (M^+, 19.48), 125 (76.63), 121 (60.87), 109 (86.22), 93 (92.44), 91 (70.17), 81 (83.22), 77 (72.85), 65 (100.00); Anal. Calcd. for $C_{12}H_{21}F_2O_3P$: C, 51.06; H, 7.50. Found: C, 51.00; H, 7.65.

(3-Cyclopentylidene-1,1-difluoro-allyl)-phosphonic acid diethyl ester (1d). Prepared from propargylic acetate (X = Ac, R^1, $R^2 = (CH_2)_4$). 71% yield. IR (film): 1979, 1274, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.41–5.35 (m, 1 H), 4.33–4.22 (m, 4 H), 2.51–2.43 (m, 4 H), 1.74–1.68 (m, 4 H), 1.41–1.34 (m, 6 H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 199.2-199.0 (m), 116.2 (td, J_{C-F} = 258.1 Hz, J_{C-P} = 220.1 Hz), 110.1, 88.8 (td, J_{C-F} = 26.7 Hz, J_{C-P} = 15.5 Hz), 64.1 (td, J_{C-F} = 30.5 Hz, J_{C-P} = 6.4 Hz), 30.8, 26.7, 16.1 (d, J_{C-P} = 5.0 Hz), 16.0 (d, J_{C-P} = 5.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.92 (dd, J_{P-F} = 107.0 Hz, J_{H-F} = 9.6 Hz); EIMS *m/z* (%): 280 (M^+, 12.11), 123 (83.95), 121 (66.40), 109 (57.02), 93 (91.37), 91 (73.02), 81 (69.82), 77 (74.53), 65 (100.00); Anal. Calcd. for $C_{12}H_{19}F_2O_3P$: C, 51.43; H, 6.83. Found: C, 51.43; H, 7.04.

(1,1-Difluoro-4-methyl-hexa-2,3-dienyl)-phosphonic acid diethyl ester (1e). Prepared from propargylic acetate (X = Ac, R^1 = Me, R^2 = Et), 75% yield. IR (film): 1975, 1274, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.43–5.37 (m, 1 H), 4.32–4.22 (m, 4 H), 2.10–2.01 (m, 2 H), 1.81–1.78 (m, 3 H), 1.40–1.36 (m, 6 H), 1.08–1.04 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.2–202.9 (m), 116.1 (td, J_{C-F} = 257.7 Hz, J_{C-P} = 221.0 Hz), 108.4, 86.9 (td, J_{C-F} = 26.4 Hz, J_{C-P} = 15.7 Hz), 64.3 (d, J_{C-P} = 6.5 Hz), 64.2 (d, J_{C-P} = 6.5 Hz), 26.4, 17.9, 16.2 (d, J_{C-P} = 5.5 Hz), 11.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.97 to −105.46 (m); EIMS *m/z* (%): 268 (M^+, 4.10), 121 (33.03), 111 (51.14), 109 (61.29), 93 (76.22), 91 (47.63), 81 (56.63), 77 (3), 65 (100.00); HRMS (MALDI): Calcd. for $C_{11}H_{19}F_2O_3PNa^+$: 291.0931; Found: 291.0932.

(1,1-Difluoro-4,5,5-trimethyl-hexa-2,3-dienyl)-phosphonic acid diethyl ester (1f). Prepared from propargylic acetate (X = Ac, R^1 = Me, R^2 = *t*-Bu), 78% yield. IR (film): 1971, 1275, 1041 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36–5.34 (m, 1 H), 4.32–4.22 (m, 4 H), 1.77 (d, *J* = 2.7 Hz, 3 H), 1.37 (t, *J* = 7.3 Hz, 6 H), 1.10 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.4–202.2 (m), 116.2 (td, J_{C-F} = 257.3 Hz, J_{C-P} = 221.0 Hz), 115.3, 86.9 (td, J_{C-F} = 26.3 Hz, J_{C-P} = 15.9 Hz), 64.1 (d, J_{C-P} = 6.9 Hz), 64.1 (d, J_{C-P} = 6.9 Hz), 33.4, 28.3, 16.1 (d, J_{C-P} = 5.0 Hz), 14.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.78 to −105.28 (m); EIMS *m/z* (%): 296 (M^+, 11.92), 143 (40.53), 138 (40.16), 111 (71.11), 109 (41.07), 93 (38.43), 65 (39.96), 57 (100.00), 41 (70.07); Anal. Calcd. for $C_{13}H_{23}F_2O_3P$: C, 52.70; H, 7.82. Found: C, 52.79; H, 7.69.

(1,1-Difluoro-4-phenyl-penta-2,3-dienyl)-phosphonic acid diethyl ester (1g). Prepared from propargylic acetate (X = Ac, R^1 = Me, R^2 = Ph), 66% yield. IR (film): 1961, 1274, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.23 (m, 5 H), 5.81–5.73 (m, 1 H), 4.32–4.19 (m, 4 H), 2.20 (t, *J* = 6.0 Hz, 3 H), 1.36–1.25 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.4–206.2 (m), 134.3, 128.3, 127.6, 125.9, 115.9 (td, J_{C-F} = 258.5 Hz, J_{C-P} = 220.0 Hz), 107.1, 89.0 (td, J_{C-F} = 26.7 Hz, J_{C-P} = 14.8 Hz), 64.3 (d, J_{C-P} = 6.6 Hz), 16.1 (d, J_{C-P} = 5.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −105.12 to −105.98 (m); EIMS *m/z* (%): 316 (M^+, 76.53), 240 (100.00), 176 (70.18), 159 9 (71.14), 128 (90.23), 121 (73.41), 93 (96.59), 65 (87.32); Anal. Calcd. for $C_{15}H_{19}F_2O_3P$: C, 56.96; H, 6.06. Found: C, 56.73; H, 5.96.

(1,1-Difluoro-hexa-2,3-dienyl)-phosphonic acid diethyl ester (1h). Prepared from propargylic tosylate (X = Ts, R^1 = Me, R^2 = H), 74% yield. IR (film): 1975, 1274, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72–5.64 (m, 1 H), 5.52–5.41 (m, 1 H), 4.32–4.22 (m, 4 H), 2.18–2.07 (m, 2 H), 1.37 (t, *J* = 6.9 Hz, 6 H), 1.06 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.2–205.0 (m), 115.8 (td, J_{C-F} = 258.8 Hz, J_{C-P} = 221.7 Hz), 98.9, 87.9 (td, J_{C-F} = 26.5 Hz, J_{C-P} = 15.9 Hz), 64.4 (d, J_{C-P} = 5.2 Hz), 64.3 (d, J_{C-P} = 6.5 Hz), 20.9, 16.2 (d, J_{C-P} = 5.3 Hz), 12.6; ^{19}F NMR (282 MHz, $CDCl_3$): δ −105.16 to −105.63 (m); EIMS *m/z* (%): 255 (M^++H, 53.95), 109 (48.98), 97 (83.46), 93 (57.21), 82 (44.38), 81 (81.78),77 (90.44), 65 (100.00); HRMS (EI) Calcd. for $C_{10}H_{17}F_2O_3P$: 254.0883; Found: 254.0883.

3.2. Typical procedure for the synthesis of **2**

Method A: This procedure was used for the preparation of **2a–2g** from **1**. To a solution of **1** (0.5 mmol) in CH_3CN–H_2O (30:1, 6 mL) was added I_2 (1.5 mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated in vacuum. The residue was chromatographed on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding product **2a–2g**.

Method B: This procedure was used for the preparation of **2h–2j** from **1**. To a solution of **1** (0.5 mmol) in CH_3CN (5 mL) was added ICl (0.75 mmol) in CH_3CN (2 mL), the resulting mixture was stirred in dark under nitrogen at room temperature for 30 min. The reaction mixture was then diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuum. The residue was chromatographed on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding product **2h–2j**.

Method C: This procedure was used for the preparation of **2a–2f** and **2h–2j** from **4**. To a solution of **4** (0.5 mmol) in CH_3CN (6 mL) was added NIS (0.75 mmol) in CH_3CN (2 mL), the resulting mixture was stirred in dark under nitrogen at room temperature for 45 min. The reaction mixture was then diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated in vacuum. The residue was chromatographed on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding product **2**.

2-Ethoxy-3, 3-difluoro-5-iodo-6,6-dimethyl-3,6-dihydro-[1,2]-oxaphosphinine2-oxide (2a). Crystal data. $C_8H_{12}F_2IO_3P$, *M* = 352.05, crystal size 0.503 mm × 0.408 mm × 0.375 mm, orthorhombic, space group *pbca*, *a* = 9.3668(8), *b* = 11.8779(10), *c* = 21.8049(18) Å, α = 90, β = 90, γ = 90, *V* = 2426.0(4) $Å^3$, *T* = 293(2) K, *Z* = 8, *Dc* =1.928 g cm^{-3}, μ (moKα) = 2.783 mm^{-1}, 13559 reflections measured, 2762 unique which were used in all calculations. *R*int = 0.0947. R_1 = 0.0410. The final *wR* (F^2) was 0.0487 (all data). (CCDC 602472).

82% yield. m.p.: 90–91 °C; IR (KBr): 1623, 1268, 1046, 1005 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56–6.45 (m, 1 H), 4.36-4.26 (m, 2 H), 1.75 (s, 3 H), 1.69 (s, 3 H), 1.36 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.6–131.9 (m), 116.3–116.1(m), 108.6 (td, J_{C-F} = 254.0 Hz, J_{C-P} = 200.0 Hz), 89.4 (d, J_{C-P} = 8.0 Hz), 65.6 (d, J_{C-P} = 6.0 Hz), 29.7, 29.4, 16.3 (d, J_{C-P} = 5.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.51 (ABdd, J_{F-F} = 316.6 Hz, J_{P-F} = 92.8 Hz, J_{H-F} = 10.7, 9.0, 8.2, 7.6, 7.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.07 to −0.12 (m); EIMS *m/z* (%): 353 (M^++1, 4.78), 244 (34.00), 197 (9.18), 117 (100.00), 97 (52.12), 77 (29.19), 65 (8.49), 51 (11.43), 43 (9.14); Anal. Calcd. for $C_8H_{12}F_2IO_3P$: C, 27.29; H, 3.44. Found: C, 27.31; H, 3.43.

2-Ethoxy-6, 6-diethyl-3,3-difluoro-5-iodo–3,6-dihydro-[1,2]-oxaphosphinine2-oxide (2b). 92% yield. m.p.: 39–40 °C; IR (KBr): 1619, 1285, 1053, 1001 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76–6.64 (m, 1 H), 4.39–4.31(m, 2 H), 2.11–1.94 (m, 4 H), 1.41 (t, *J* = 6.9 Hz, 3 H), 1.02 (t, *J* = 7.2 Hz, 3 H), 0.96 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.6–134.1 (m), 115.2–115.0 (m), 110.0 (td, J_{C-F} = 253.7 Hz, J_{C-P} = 199.1 Hz), 94.5 (d, J_{C-P} = 9.8 Hz), 65.6 (d, J_{C-P} = 6.0 Hz), 32.0, 31.7, 16.3 (d, J_{C-P} = 5.1 Hz), 7.2, 7.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ −102.21 (ABdd, J_{F-F} = 318 Hz, J_{P-F} = 93 Hz, J_{H-F} = 10.1, 9.3, 8.7, 7.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.51 to −3.02 (m); EIMS *m/z* (%): 380 (M^+, 63.06), 331 (48.38), 303 (100.00), 233 (50.65), 145 (41.77), 125 (37.70), 77 (42.07), 65 (30.71); Anal. Calcd. for $C_{10}H_{16}F_2IO_3P$: C, 31.60; H, 4.24. Found: C, 31.77; H, 4.28.

2-Ethoxy-3, 3-difluoro-5-iodo-1-oxa-2-phospha-spiro [5.5] undec-4-ene 2-oxide (2c). 90% yield. m.p.: 73–74 °C; IR (KBr): 1616, 1289, 1046, 1003 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.66–6.55 (m, 1 H), 4.44–4.33 (m, 2 H), 2.15–2.09 (m, 3 H), 1.91–1.64 (m, 6 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.27–1.19 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$,): δ 134.0–132.5 (m), 117.8–117.6 (m), 110.3 (td, J_{C-F} = 254.8 Hz, J_{C-P} = 200.8 Hz), 90.6 (d, J_{C-P} = 8.9 Hz), 65.6 (d, J_{C-P} = 6.3 Hz), 36.1, 35.7, 24.2, 20.7, 20.6, 16.4 (d, J_{C-P} = 5.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −103.12 (ABdd, J_{F-F} = 317.0 Hz, J_{P-F} = 92.2 Hz, J_{H-F} = 9.0, 8.7, 7.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.48 to −3.34 (m); EIMS *m/z* (%): 393 (M^++1, 60.78), 245 (64.64),

157 (100), 137 (78.58), 115 (59.63), 109 (70.17), 91 (69.09), 77 (57.74); Anal. Calcd. for $C_{11}H_{16}F_2IO_3P$: C, 33.69; H, 4.11. Found: C, 33.95; H, 4.05.

7-Ethoxy-8, 8-difluoro-10-iodo-6-oxa-7-phospha-spiro [4.5] dec-9-ene 7-oxide (2d). 81% yield. m.p.: 101–102 °C; IR (KBr): 1619, 1287, 1044, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.69–6.57 (m, 1 H), 4.41–4.31 (m, 2 H), 2.40–2.33 (m, 3 H), 2.19–2.11 (m, 1 H), 2.00–1.72 (m, 4 H), 1.42 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.9–133.4 (m), 116.4–116.2 (m), 109.5 (td, $J_{C\text{-}F}$ = 255.2 Hz, $J_{C\text{-}P}$ = 200.5 Hz), 98.9 (d, $J_{C\text{-}P}$ = 8.8 Hz), 65.7 (d, $J_{C\text{-}P}$ = 6.1 Hz), 41.1, 40.6, 24.3, 24.2, 16.4 (d, $J_{C\text{-}P}$ = 5.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −103.34 (ABdd, $J_{F\text{-}F}$ = 318.1 Hz, $J_{P\text{-}F}$ = 94.0 Hz, $J_{H\text{-}F}$ = 9.6, 8.7, 8.2, 7.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.47 to −3.29 (m); EIMS m/z (%): 378 (M^+, 1.96), 270 (51.69), 203 (27.17), 143 (100), 101 (36.62), 91 (31.29), 79 (58.06), 77 (48.18); Anal. Calcd. for $C_{10}H_{14}F_2IO_3P$: C, 31.77; H, 3.73. Found: C, 31.61; H, 3.86.

2-Ethoxy-6-ethyl-3, 3-difluoro-5-iodo-6-methyl-3, 6-dihydro-[1,2]oxaphosphinine 2-oxide (2e). 91% yield. IR (film): 1619, 1288, 1054, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.70–6.59 (m, 1 H), 4.39–4.29 (m, 2 H), 2.10–2.00 (m, 1 H), 1.92–1.80 (m, 1 H), 1.83–1.80 (m, 1.5 H), 1.72–1.71 (m, 1.5 H), 1.43–1.35 (m, 3 H), 0.96–0.86 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.0–133.2 (m), 115.4–115.0 (m), 112.8–107.0 (m), 92.1 (d, $J_{C\text{-}P}$ = 10.6 Hz), 91.4 (d, $J_{C\text{-}P}$ = 7.5 Hz), 65.6 (d, $J_{C\text{-}P}$ = 6.1 Hz), 65.4 (d, $J_{C\text{-}P}$ = 6.3 Hz), 34.7, 34.6, 27.2, 27.0, 16.3, 7.0, 6.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.09 to −98.57 (m), −109.27 to −110.94 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 0.66 to −3.54 (m); EIMS m/z (%): 367 (M^++1, 28.84), 258 (34.82), 245 (32.83), 131 (100), 111 (52.45), 109 (36.60), 91 (37.83), 65 (33.84), 43 (41.22); Anal. Calcd. for $C_9H_{14}F_2IO_3P$: C, 29.53; H, 3.85. Found: C, 29.74; H, 3.98.

6-tert-Butyl-2-ethoxy-3,3-difluoro-5-iodo-6-methyl-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (2f). 53% yield. IR (KBr): 1608, 1282, 1052, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.91–6.80 (m, 1 H), 4.41–4.34 (m, 2 H), 1.87 (s, 1.5 H), 1.78 (s, 1.5 H), 1.45–1.37 (m, 3H), 1.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7–135.8 (m), 115.0–105.3 (m), 96.2 (d, $J_{C\text{-}P}$ = 12.9 Hz), 95.1(d, $J_{C\text{-}P}$ = 9.8 Hz), 65.7–65.4 (m), 40.5–40.2 (m), 27.0, 23.8, 23.6, 16.5–16.4 (m); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.64 to −98.49 (m), −109.75 to −111.73 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.86 to −5.05 (m); EIMS m/z (%): 395 (M^++1, 7.54), 338 (30.88), 318 (89.98), 290 (33.93), 246 (48.03), 226 (35.74), 57 (100), 43 (28.63), 41 (72.02); Anal Calcd. for $C_{11}H_{18}F_2IO_3P$: C, 33.52; H, 4.60. Found: C, 33.75; H, 4.70.

2-Ethoxy-3,3-difluoro-5-iodo-6-methyl-6-phenyl-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (2g). 64% yield. IR (KBr): 1620, 1451, 1377, 1281, 1042, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48–7.38 (m, 5 H), 6.75–6.64 (m, 1 H), 4.43–4.30 (m, 2 H), 2.30 (d, J = 2.1 Hz, 1.5 H), 2.20 (d, J = 1.8 Hz, 1.5 H), 1.45–1.39 (m, 1.5 H), 1.36–1.31 (m, 1.5 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.3–138.9 (m), 132.8–132.1 (m), 129.3, 128.5, 128.4, 126.6, 126.5, 116.9–116.5 (m), 112.8-106.9 (m), 91.7(d, $J_{C\text{-}P}$ = 10.4 Hz), 90.9 (d, $J_{C\text{-}P}$ = 6.7 Hz), 65.7 (d, $J_{C\text{-}P}$ = 6.3 Hz), 25.6, 25.5, 16.4, 16.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −94.55 to −98.02 (m), −109.18 to −110.97 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.25 to −4.47 (m); ESIMS m/z: 415 (M^++H), 432 (M^++NH_4), 437 (M^++Na); Anal. Calcd. for $C_{13}H_{14}F_2IO_3P$: C, 37.70; H, 3.41. Found: C, 37.75; H, 3.54.

2-Ethoxy-6-ethyl-3,3-difluoro-5-iodo-3,6-dihydro-1,2-oxaphosphorin 2-oxide (2h). 80% yield. IR (film): 1623, 1459, 1137, 1047, 1006 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.66–6.52 (m, 1 H), 5.01–4.93 (m, 0.4 H), 4.91–4.88 (m, 0.6 H), 4.40–4.26 (m, 2 H), 2.18–1.98 (m, 2 H), 1.42–1.34 (m, 3 H), 0.99–0.92 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.5–133.9 (m), 109.5–109.3 (m), 86.4 (d, $J_{C\text{-}P}$ = 9.6 Hz), 85.1(d, $J_{C\text{-}P}$ = 6.5 Hz), 65.9 (d, $J_{C\text{-}P}$ = 6.3 Hz), 65.5 (d, $J_{C\text{-}P}$ = 4.9 Hz), 28.2, 28.1, 16.3, 7.7, 7.6; ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.66 to −98.89 (m), −108.88 to −110.56 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.12 to −2.71 (m); EIMS m/z (%): 352 (M^+, 55.14), 244 (17.55), 117 (70.25) 97 (100.00), 77 (46.03), 75 (14.46), 65 (17.25), 51 (15.24); Anal. Calcd. for $C_8H_{12}F_2IO_3P$: C, 27.29; H, 3.44. Found: C, 27.27; H, 3.54.

2-Ethoxy-3,3-difluoro-5-iodo-6-propyl-3,6-dihydro-1,2-oxaphosphorin 2-oxide (2i). 78% yield. IR (film): 1623, 1466, 1285, 1139, 1052, 1020, 1004 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.66–6.55 (m, 1 H), 5.06–5.03 (m, 0.4 H), 4.94–4.93 (m, 0.6 H), 4.43–4.31 (m, 2 H), 2.14–1.93 (m, 2 H), 1.55–1.40 (m, 5 H), 0.99–0.93 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.8–133.2 (m), 109.9–109.6 (m), 85.4 (d, $J_{C\text{-}P}$ = 8.9 Hz), 84.2 (d, $J_{C\text{-}P}$ = 6.8 Hz), 65.8 (d, $J_{C\text{-}P}$ = 5.6 Hz), 65.5 (d, $J_{C\text{-}P}$ = 6.0 Hz), 36.8, 36.7, 16.9, 16.3, 13.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.29 to −99.41 (m), −108.22 to −109.78 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 0.99 to −2.81(m); EIMS m/z (%): 366 (M^+, 31.59), 131 (67.97), 111 (100.00) 109 (40.69), 91 (38.06), 77 (52.18), 67 (40.29), 65 (43.27), 41 (44.40); Anal. Calcd. for $C_9H_{14}F_2IO_3P$: C, 29.53; H, 3.85. Found: C, 29.62; H, 4.12.

2-Ethoxy-3,3-difluoro-5-iodo-6-isopropyl-3,6-dihydro-1,2-oxaphosphorin 2-oxide (2j). 75% yield. IR (KBr): 1619, 1465, 1284, 1284, 1137, 1052, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.70–6.55 (m, 1 H), 4.91–4.87 (m, 0.4 H), 4.87–4.75 (m, 0.6 H), 4.39–4.28 (m, 2 H), 2.64–2.55 (m, 1 H), 1.43–1.33 (m, 3 H), 1.33–1.06 (m, 3 H), 0.83–0.79 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.8–134.0 (m), 113.6–107.8 (m), 89.2 (d, $J_{C\text{-}P}$ = 10.5 Hz), 87.5 (d, $J_{C\text{-}P}$ = 6.3 Hz), 65.9 (d, $J_{C\text{-}P}$ = 6.3 Hz), 65.5 (d, $J_{C\text{-}P}$ = 6.1 Hz), 32.1–31.9 (m), 18.9, 16.3, 13.2, 13.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ −93.41 to −96.72 (m), −110.773 to −113.15 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.98 to −2.19 (m); EIMS m/z (%): 366 (M^+, 27.05), 303 (57.06), 258 (39.74), 131 (62.83), 111 (41.84), 65 (50.14), 43 (100), 41 (65.84); Anal Calcd. for $C_9H_{14}F_2IO_3P$: C, 29.53; H, 3.85. Found: C, 29.71; H, 3.84.

3.3. Typical procedure for the synthesis of **4**

To a mixture of **1** (5 mmol), EtOH (5 mL) and water (10 mL) was added 1 N NaOH solution (10 mL) slowly. The mixture was stirred at room temperature for about 0.5–5 h (monitored by TLC). Then the reaction mixture was diluted with water (15 mL), acidified with 10% HC1 to pH 2–3 and extracted with EtOAc (20 mL 3×). The organic layer was washed with brine and dried over Na_2SO_4. After removal of solvent in vacuum, compound **4** was obtained without further purification.

(1,1-Difluoro-4-methyl-penta-2,3-dienyl)-phosphonic acid monoethyl ester (4a). 93% yield. IR (film): 3400, 2250, 1979, 1640, 1233, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.40 (br s, 1H), 5.30–5.23 (m, 1 H), 4.27–4.18 (m, 2 H), 1.75 (s, 6 H), 1.35 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.3–204.0 (m), 116.7 (td, $J_{C\text{-}F}$ = 247.1 Hz, $J_{C\text{-}P}$ = 189.1 Hz), 102.3, 84.9 (td, $J_{C\text{-}F}$ = 26.7 Hz, $J_{C\text{-}P}$ = 15.9 Hz), 64.8 (d, $J_{C\text{-}P}$ = 6.6 Hz), 19.4, 16.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.91 (dd, $J_{P\text{-}F}$ = 117.0 Hz, $J_{H\text{-}F}$ = 10.1 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.97 (t, $J_{P\text{-}F}$ = 117.0 Hz); EIMS m/z (%): 227 (M^++1, 21.16), 206 (43.86), 134 (59.72), 119 (73.56), 117 (43.58), 97 (100.00), 96 (44.83), 77 (88.85), 65 (58.65); HRMS (MALDI): Calcd. for $C_8H_{13}F_2O_3PNa$ (M^+ + Na): 249.0471, Found: 249.0462.

(4-Ethyl-1, 1-difluoro-hexa-2,3-dienyl)-phosphonic acid monoethyl ester (4b). 90% yield. IR (film): 3400, 2230, 1973, 1650, 1234, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.62 (br s, 1H), 5.67–5.50 (m, 1 H), 4.34–4.24 (m, 2 H), 2.15–2.06 (m, 4 H), 1.40 (t, J = 6.9 Hz, 3 H); 1.07 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.7–202.4 (m), 115.5 (td, $J_{C\text{-}F}$ = 256.3 Hz, $J_{C\text{-}P}$ = 224.7 Hz), 115.0, 88.8 (td, $J_{C\text{-}F}$ = 26.1 Hz, $J_{C\text{-}P}$ = 15.9 Hz), 64.5 (d, $J_{C\text{-}P}$ = 6.5 Hz), 25.1, 16.2, 17.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.19 (dd, $J_{P\text{-}F}$ = 118.4 Hz, $J_{H\text{-}F}$ = 10.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.94–6.91 (m); EIMS m/z (%): 255 (M^++1, 3.46), 133 (65.43), 125 (85.41), 109 (65.00), 97 (68.40), 91 (65.40), 81 (81.30), 77 (100), 65 (97.15); HRMS (EI): Calcd. for $C_{10}H_{17}F_2O_3P$: 254.0883, Found: 254.0882.

(3-Cyclohexylidene-1,1-difluoro-allyl)-phosphonic acid monoethyl ester (4c). 91% yield. IR (film): 2240, 1974, 1660, 1237, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.96 (br s, 1H), 5.32–5.24 (m, 1 H), 4.27–4.18 (m, 2 H), 2.21–2.16 (m, 4 H), 1.66–1.50 (m, 6 H), 1.35 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.7–202.6 (m), 116.2 (td, $J_{C\text{-}F}$ = 257.0 Hz, $J_{C\text{-}P}$ = 221.3 Hz), 108.0, 84.7 (td, $J_{C\text{-}F}$ = 26.4 Hz, $J_{C\text{-}P}$ = 15.6 Hz), 64.6 (d, $J_{C\text{-}P}$ = 6.0 Hz), 30.4, 26.9, 25.8, 16.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.22 (dd, $J_{P\text{-}F}$ = 118.2 Hz, $J_{H\text{-}F}$ = 11.0 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.65 (t, $J_{P\text{-}F}$ = 117.2 Hz); EIMS m/z (%): 267 (M^++1, 7.70), 137 (66.89), 115 (68.08), 109 (83.53), 91 (92.41), 81 (100.00), 79 (87.68), 77 (74.39), 41 (73.84); HRMS (EI): Calcd. for $C_{11}H_{17}F_2O_3P$: 266.0895, Found: 266.0894.

(3-Cyclopentylidene-1,1-difluoro-allyl)-phosphonic acid monoethyl ester (4d). 87% yield. IR (film): 2250, 1980, 1650, 1237, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (br s, 1H), 5.39–5.31 (m, 1 H), 4.28–4.18 (m, 2 H), 2.54–2.42 (m, 4 H), 1.75–1.66 (m, 4 H), 1.36 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.6–199.4 (m), 116.2 (td, $J_{C\text{-}F}$ = 257.0 Hz, $J_{C\text{-}P}$ = 220.3 Hz), 110.4, 87.0 (td, $J_{C\text{-}F}$ = 26.7 Hz, $J_{C\text{-}P}$ = 15.6 Hz), 64.8 (d, $J_{C\text{-}P}$ = 5.6 Hz), 31.0, 27.1, 16.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −105.74 (dd, $J_{P\text{-}F}$ = 118.0 Hz, $J_{H\text{-}F}$ = 11.0 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.65 (t, $J_{P\text{-}F}$ = 118.8 Hz); EIMS m/z (%): 253 (M^++1, 3.95), 85 (12.75), 71 (29.56), 60 (17.95), 57 (31.41), 45 (39.10), 43 (100.00), 42 (14.21), 41 (21.40); HRMS (EI): Calcd. for $C_{10}H_{15}F_2O_3P$: 252.0738, Found: 252.0738.

(1,1-Difluoro-4-methyl-hexa-2,3-dienyl)-phosphonic acid monoethyl ester (4e). 88% yield. IR (film): 2230, 1976, 1640, 1234, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.34 (br s, 1H), 5.41–5.32 (m, 1 H), 4.28–4.19 (m, 2 H), 2.08–1.99 (m, 2 H), 1.77 (d, J = 2.7 Hz, 3 H), 1.35 (t, J = 6.9 Hz, 3 H); 1.03 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.4–203.0 (m), 116.0 (td, $J_{C\text{-}F}$ = 256.4 Hz, $J_{C\text{-}P}$ = 224.9 Hz), 108.4, 86.8 (td, $J_{C\text{-}F}$ = 26.3 Hz, $J_{C\text{-}P}$ = 15.8 Hz), 64.6 (d, $J_{C\text{-}P}$ = 6.4 Hz), 26.4, 17.9, 16.2, 11.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.04 to −106.14 (m), −106.46 to −106.56 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.73 (t, $J_{P\text{-}F}$ = 115.4 Hz); EIMS m/z (%): 241 (M^++1, 4.27), 177 (64.91), 133 (78.56), 115 (64.53), 111 (76.74), 109 (99.00), 91 (89.47), 81 (81.73), 65 (100.00); HRMS (EI): Calcd. for $C_9H_{15}F_2O_3P$: 240.0727, Found: 240.0737.

(1,1-Difluoro-4,5,5-trimethyl-hexa-2,3-dienyl)-phosphonic acid monoethyl ester (4f). 94% yield. IR (film): 2270, 1971, 1630, 1236, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ10.87 (br s, 1H), 5.37–5.30 (m, 1 H), 4.27–4.18 (m, 2 H), 1.76 (d, J = 3 Hz, 3 H), 1.35 (t, J = 6.9 Hz, 3 H); 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.6–202.3 (m), 116.1 (td, $J_{C\text{-}F}$ = 256.3 Hz, $J_{C\text{-}P}$ = 224.8 Hz), 115.3, 86.5 (td, $J_{C\text{-}F}$ = 26.6 Hz, $J_{C\text{-}P}$ = 15.9 Hz), 64.5 (d, $J_{C\text{-}P}$ = 6.5 Hz), 33.5, 28.6, 16.2, 14.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ −105.97 to −106.11 (m), −106.40 to −106.53 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.04 (t, $J_{P\text{-}F}$ = 118.6 Hz); EIMS m/z (%): 269 (M^++1, 0.62), 143 (57.81), 123 (29.38), 110 (29.33), 101 (28.11), 83 (29.56), 82 (44.88), 57 (100.00), 41 (57.81); HRMS (EI): Calcd. for $C_{11}H_{19}F_2O_3P$: 268.1040, Found: 268.1049.

(1,1-Difluoro-hexa-2,3-dienyl)-phosphonic acid monoethyl ester (4g). 92% yield. IR (film): 2230, 1976, 1625, 1234, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.32 (br s, 1H), 5.72–5.64 (m, 1 H), 5.52–5.41 (m, 1 H), 4.29–4.20 (m, 2 H), 2.17–2.07 (m, 2 H), 1.37 (t, J = 6.0 Hz, 3 H), 1.07 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5–205.2 (m), 115.7 (td, $J_{C\text{-}F}$ = 257.7 Hz, $J_{C\text{-}P}$ = 226.1 Hz), 99.0, 87.8 (td, $J_{C\text{-}F}$ = 26.1 Hz, $J_{C\text{-}P}$ = 15.7 Hz), 64.9 (d, $J_{C\text{-}P}$ = 6.5 Hz), 20.9, 16.2, 12.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.46 to −106.51 (m), −106.87 to −106.93 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.68–5.39 (m); EIMS m/z (%): 227 (M^++1, 11.72), 119 (60.74), 115 (37.98), 97 (100.00), 96 (43.27), 82 (54.89), 81 (43.52), 77 (87.95), 65 (68.78); HRMS (EI): Calcd for $C_8H_{13}F_2O_3P$: 226.0570, Found: 226.0572.

(1,1-Difluoro-hepta-2,3-dienyl)-phosphonic acid monoethyl ester (4h). 90% yield. IR (film): 2230, 1975, 1625, 1238, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.77 (br s, 1H), 5.64–5.56 (m, 1 H), 5.48–5.38 (m, 1 H), 4.28–4.19 (m, 2 H), 2.12–2.03 (m, 2 H), 1.53–1.40 (m, 2 H), 1.36 (t, J = 7.5 Hz, 3 H), 0.93 (t, J = 7.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6–205.2 (m), 115.9 (td, $J_{C\text{-}F}$ = 256.1 Hz, $J_{C\text{-}P}$ = 229.6 Hz), 97.1, 87.1 (td, $J_{C\text{-}F}$ = 24.0 Hz, $J_{C\text{-}P}$ = 13.5 Hz), 64.8, 29.9, 22.0, 16.3, 13.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.72 to 106.78 (m), −107.13 to −107.20 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.10–6.08 (m); EIMS m/z (%): 240 (M^+, 1.36), 119 (100.00), 109 (47.15), 91 (50.41), 82 (60.70), 81 (51.10), 79 (46.59), 65 (90.86), 41 (42.86); HRMS (EI): Calcd. for $C_9H_{15}F_2O_3P$: 240.0727, Found: 240.0734.

(1,1-Difluoro-5-methyl-hexa-2,3-dienyl)-phosphonic acid monoethyl ester (4i). 91% yield. IR (film): 2235, 1973, 1630, 1237, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.77 (br s, 1H), 5.66–5.60 (m, 1 H), 5.51–5.46 (m, 1 H), 4.29–4.20 (m, 2 H), 2.45–2.38 (m, 1 H), 1.36 (t, J = 6.9 Hz, 3 H), 1.06 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.4–204.3 (m), 115.6 (td, $J_{C\text{-}F}$ = 261.2 Hz, $J_{C\text{-}P}$ = 227.2 Hz), 104.4, 88.3 (td, $J_{C\text{-}F}$ = 25.7 Hz, $J_{C\text{-}P}$ = 15.0 Hz), 64.7 ($J_{C\text{-}P}$ = 4.7 Hz), 29.6, 22.0, 21.9, 16.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.49 to −106.61 (m), −106.91 to −107.03 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.45–6.00 (m); EIMS m/z (%): 241 (M^++1, 4.83), 133 (73.55), 111 (62.22), 109 (68.97), 91 (71.57), 81 (60.57), 65 (81.47), 41 (66.52); HRMS (EI): Calcd. for $C_9H_{15}F_2O_3P$: 240.0727, Found: 240.0728.

3.4. Typical procedure for the synthesis of **3**

To a solution of **4** (0.5 mmol) in CH_3CN (6 mL) was added NBS (178 mg, 1 mmol). After stirring at room temperature for 45 min, the mixture was diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated in vacuum. The residue was chromatographed on silica gel using petroleum ether/ethyl acetate as eluent to give **3**.

5-Bromo-2-ethoxy-3,3-difluoro-6,6-dimethyl-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (3a). 87% yield. m.p: 43–44 °C; IR (KBr): 1636, 1287, 1055, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.36–6.25 (m, 1 H), 4.41–4.32 (m, 2 H), 1.78 (s, 3 H), 1.70 (s, 3 H), 1.40 (t, J = 6.9 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −103.3 (ABdd, $J_{F\text{-}F}$ = 317.7 Hz, $J_{P\text{-}F}$ = 94.9 Hz, $J_{H\text{-}F}$ = 11.1, 9.6, 8.0, 6.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.07 to −3.67 (m); EIMS m/z (%): 305 (M^++1, 8.40), 198 (46.51), 196 (37.81), 117 (100.00), 97 (46.51), 77 (29.62), 51 (15.05), 43 (18.05), 41 (14.01); Anal. Calcd. for $C_8H_{12}BrF_2O_3P$: C, 31.50; H, 3.96. Found: C, 31.78; H, 4.20.

5-Bromo-2-ethoxy-6,6-diethyl-3,3-difluoro-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (3b). 90% yield. IR (film): 1636, 1288, 1050, 999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.48–6.36 (m, 1 H), 4.39–4.33 (m, 2 H), 2.06–1.96 (m, 4 H), 1.43–1.39 (m, 3 H), 1.04–0.99 (m, 6 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −101.74 (ABdd, $J_{F\text{-}F}$ = 315.9 Hz, $J_{P\text{-}F}$ = 91.9 Hz, $J_{H\text{-}F}$ = 10.5, 9.6, 7.9, 6.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.80 to −3.65 (m); EIMS m/z (%): 335 (M^++3, 95.34), 333 (M^++1, 100.00), 233 (40.73), 257 (38.06), 253 (37.41), 143 (31.85), 103 (38.42), 101 (30.19); Anal. Calcd. for $C_{10}H_{16}BrF_2O_3P$: C, 36.06; H, 4.84. Found: C, 36.35; H, 5.06.

5-Bromo-2-ethoxy-3,3-difluoro-1-oxa-2-phospha-spiro[5.5]undec-4-ene 2-oxide (3c). 88% yield. IR (film): 1630, 1276, 1055, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.38–6.26 (m, 1 H), 4.40–4.34 (m, 2 H), 2.08–1.63 (m, 10 H), 1.42 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −102.73 (ABdd, $J_{F\text{-}F}$ = 316.4 Hz, $J_{P\text{-}F}$ = 93.1 Hz, $J_{H\text{-}F}$ = 9.6, 8.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.71 to −3.65 (m); EIMS m/z (%): 347 (M^++3, 47.21), 345 (M^++1, 50.52), 115 (51.43), 91 (51.49), 77 (47.45), 68 (100.00), 67 (78.98), 41 (49.77); Anal. Calcd. for $C_{11}H_{16}BrF_2O_3P$: C, 38.28; H, 4.67. Found: C, 38.57; H, 4.78.

10-Bromo-7-ethoxy-8,8-difluoro-6-oxa-7-phospha-spiro[4.5]dec-9-ene 7-oxide (3d). 79% yield. IR (film): 1633, 1298, 1054, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.42–6.30 (m, 1 H), 4.41–4.31 (m, 2 H), 2.36–1.81 (m, 8 H), 1.41 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −102.97 (ABdd, J_{F-F} = 317.2 Hz, J_{P-F} = 93.6 Hz, J_{H-F} = 9.3, 8.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.75 to −3.57 (m); EIMS m/z (%): 333 (M^++3, 58.95), 331 (M^++1, 59.73), 123 (100.00), 101 (95.32), 91 (80.68), 79 (60.54), 77 (61.33), 41 (58.68); Anal. Calcd. for $C_{10}H_{14}BrF_2O_3P$: C, 36.28; H, 4.26. Found: C, 36.39; H, 4.14.

5-Bromo-2-ethoxy-6-ethyl-3,3-difluoro-6-methyl-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (3e). 90% yield. IR (film): 1635, 1298, 1056, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.42–6.36 (m, 1 H), 4.41–4.33 (m, 2 H), 2.06–2.00 (m, 1 H), 1.88–1.81 (m, 1H), 1.80 (s, 1.5 H), 1.71 (s, 1.5 H), 1.45–1.38 (m, 3 H), 0.96–0.90 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −94.68 to −97.99 (m), −108.77 to −110.30 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ −0.87 to −3.74 (m); EIMS m/z (%): 318 (M^+, 41.71), 211 (60.81), 209 (66.91), 131 (100.00), 111 (63.88), 109 (56.30), 91 (56.94), 65 (46.90), 43 (69.05); Anal. Calcd. for $C_9H_{14}BrF_2O_3P$: C, 33.88; H, 4.42. Found: C, 34.00; H, 4.64.

5-Bromo-6-tert-butyl-2-ethoxy-3,3-difluoro-6-methyl-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (3f). 58% yield. IR (film): 1622, 1292, 1058, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.54–6.39 (m, 1 H), 4.41–4.30 (m, 2 H), 1.85 (s, 1.5 H), 1.74 (s, 1.5 H), 1.46–1.36 (m, 3H), 1.14 (s, 9 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.18 to −97.98 (m), −109.47 to −111.49 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ −1.82 to −5.09 (m); EIMS m/z (%): 349 (M^++3, 51.90), 347 (M^++1, 54.99), 272 (25.01), 270 (25.41), 180 (23.84), 57 (100.00), 43 (33.40), 41 (66.95); Anal. Calcd. for $C_{11}H_{18}BrF_2O_3P$: C, 38.06; H, 5.23. Found: C, 37.81; H, 5.20.

5-Bromo-2-ethoxy-6-ethyl-3,3-difluoro-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (3g). 89% yield. IR (film): 1638, 1282, 1142, 1047, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.48–6.34 (m, 1 H), 5.01–5.06 (m, 0.5 H), 4.99–4.94 (m, 0.5 H), 4.46–4.34 (m, 2 H), 2.15–1.98 (m, 2 H), 1.47–1.39 (m, 3 H), 1.06–0.99 (m, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.40 to −98.47 (m), −108.44 to −110.28 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.11 to −2.88 (m); EIMS m/z (%): 304 (M^+, 7.90), 198 (30.55), 196 (37.26), 117 (100.00), 115 (19.30), 97 (83.62), 77 (47.24), 75 (18.10), 65 (26.81); Anal. Calcd. for $C_8H_{12}BrF_2O_3P$: C, 31.50; H, 3.96. Found: C, 31.56; H, 3.80.

5-Bromo-2-ethoxy-3,3-difluoro-6-propyl-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (3h). 88% yield. IR (film): 1638, 1305, 1294, 1143, 1053, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.45–6.31 (m, 1 H), 5.09–5.06 (m, 0.5 H), 4.97–4.94 (m, 0.5 H), 4.45–4.34(m, 2 H), 2.09–1.92 (m, 2 H), 1.54–1.40 (m, 5 H), 1.00–0.95 (m, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.09 to −99.02 (m), −107.83 to −109.54 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 0.87 to −2.96 (m); EIMS m/z (%): 318 (M^+, 8.72), 170 (95.93), 168 (97.50), 131 (52.62), 102 (40.34), 89 (100.00), 77 (41.39), 65 (43.73), 41 (79.28); Anal. Calcd. for $C_9H_{14}BrF_2O_3P$: C, 33.88; H, 4.42. Found: C, 34.04; H, 4.43.

5-Bromo-2-ethoxy-3,3-difluoro-6-isopropyl-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (3i). 87% yield. IR (film): 1637, 1297, 1284, 1144, 1058, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.51–6.35 (m, 1 H), 4.98–4.94 (m, 0.5 H), 4.85–4.81 (m, 0.5 H), 4.43–4.33 (m, 2 H), 2.61–2.54 (m, 1 H), 1.47–1.38 (m, 3 H), 1.13–1.09 (m, 3 H), 0.90–0.86 (m, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −93.04 to −96.30 (m), −110.45 to −112.85 (m); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.98 to −2.52 (m); EIMS m/z (%): 320 (M^++2, 76.02), 318 (M^+, 73.63), 239 (31.02), 166 (30.58), 164 (30.73), 65 (29.51), 43 (100.00), 41 (99.39)); Anal. Calcd. for $C_9H_{14}BrF_2O_3P$: C, 33.88; H, 4.42. Found: C, 34.10; H, 4.39.

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