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Iodocyclization of trifluoromethylallenic phosphonates: an efficient approach to trifluoromethylated oxaphospholenes

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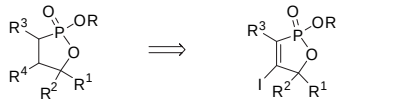
ABSTRACT

α-Trifluoromethylallenic phosphonates were prepared by the reaction of diethyl chlorophosphite (DECP) and 4,4,4-trifluorobut-2-yn-1-ols in the presence of Et_3N. The iodocyclization of these fluorine-containing allenic phosphonates was achieved with iodine under mild conditions to give the corresponding trifluoromethylated oxaphospholenes in moderate to good yields.

1. Introduction

Organophosphorus compounds continue to receive widespread attention due to the recognition of their potential use as novel pharmaceutical, agricultural, and chemical agents.[1,2] Among them, a number of phosphorus heterocycles displaying potent biological activities have emerged. 1,2-Oxaphospholane 2-oxides (I), as a notable example, have attracted much attention as sugar surrogates since analogues with phosphorus atoms replacing the anomeric carbons could potentially serve as carbohydrate mimics.[3]



1,2-oxaphospholane 2-oxide I

1,2-oxaphosphol-3-ene 2-oxide II

Meanwhile, the presence of fluorine atoms in a potentially bioactive molecule can dramatically change not only its physical but also its chemical properties,[4] accordingly might give rise to enhancement or alteration of the native biological activity of the substrate. This has been particularly true for fluoroheterocycles. Taking the biological importance of phosphorus heterocycles into consideration, introduction of fluorine atoms or fluoroalkyl groups into this framework would offer effective modification toward the original properties of the resulted compounds. However, despite such interests, few reports have been found for the construction of these types of molecules.[5] In continuation of our earlier work on fluorine-containing allenes, and in connection with our ongoing interest in construction of biologically active fluorine-containing compounds,[6] we represent herein a facile synthesis of trifluoromethylated 1,2-oxaphosphol-3-ene 2-oxide (II, R^3=CF_3), a divergent intermediate for various trifluoromethylated oxaphospholanes.

2. Results and discussion

Synthetic investigation of the target oxaphospholenes was initiated by the preparation of allenic phosphonates **2** (Table 1). It is well known that allenic phosphonates are readily available from alk-2-yn-l-ols.[7] Using this method, the rearrangement reaction of 3-trifluoromethylalk-2-yn-1-ols (**1**), prepared according to the literature,[8] was studied first. As shown in Table 1, the reaction went smoothly and afforded the corresponding allenic phosphonates **2** in good yields with 1,1-disubstituted or phenyl substituted substrates under mild conditions (entries 1–3 and 6–9). In the case of secondary aliphatic alk-2-yn-l-ols, however, the reaction became complicated and gave relatively lower yields (entries 4–5). No elimination of HF was observed in these reactions as Commeyras reported about the rearrangement of perfluorobutyl substituted prop-2-ynyl diethylphosphites.[9] The trifluoromethyl acetylenic carbon atom probably has a lower electrophilic character than those of nonfluorinated acetylenes, which would make attack by the phosphorus atom less likely. Bulky 1,1-disubstituents or phenyl

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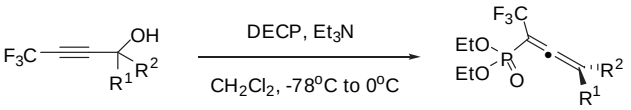
substituents, however, could decrease the C–C–O angle and favor hybridization at the initially saturated carbon atom, thus facilitate the rearrangement reaction.

Table 1
Preparation of allenic phosphonates **2** from 3-trifluoromethylalk-2-yn-1-ols **1**



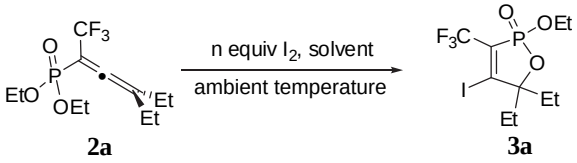
1 **2**

Entry	**1**	R^1	R^2	Product	Yield[a] (%)
1	**1a**	Et	Et	**2a**	85
2	**1b**	Me	Me	**2b**	68
3	**1c**	Me	Et	**2c**	74
4	**1d**	^{n}Pr	H	**2d**	37
5	**1e**	^{t}Bu	H	**2e**	35
6	**1f**	Ph	H	**2f**	78
7	**1g**	Ph	Me	**2g**	80
8	**1h**	$-(CH_2)_5-$		**2h**	77
9	**1i**	$-(CH_2)_4-$		**2i**	86

[a] Isolated yield.

With intermediates **2** in hand, the construction of oxaphospholenes **3** via iodocyclization reaction[6c,10] was next studied. Using the reaction of diethyl 1-trifluoromethyl-3-ethyl-1,2-pentadien-1-ylphosphonate (**2a**) and iodine as the model reaction, various conditions were examined (Table 2). The amount of iodine had an important effect on the reaction. With 3 equiv of iodine, **2a** was converted to **3a** completely within 3 h in CH_3CN or CH_2Cl_2 (entries 1 and 4). A longer time (27 h) was needed for the reaction to go to completion in CH_3CN when 2 equiv of iodine was used (entry 2). Further decreasing the amount of iodine made the reaction become much slower (entry 3). In other solvents, such as toluene, DMF, and THF the reaction was also very slow (entries 5–7).

Table 2
Condition optimization for the iodocyclization of **2a**



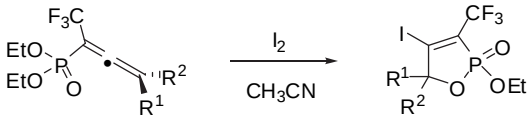
2a **3a**

Entry	*n*	Solvent	Time (h)	Conversion[a] (%)
1	3	CH_3CN	3	100
2	2	CH_3CN	27	100
3	1.5	CH_3CN	52	87
4	3	CH_2Cl_2	3	100
5	3	DMF	18	95
6	3	$PhCH_3$	18	90
7	3	THF	18	84

[a] Determined by ^{19}F NMR.

Using the optimized conditions in Table 2, entry 2, the iodocyclization reactions of other allenic phosphonates were investigated. As shown in Table 3, the reaction was strongly influenced by the substitution pattern on the allenic skeleton: C-terminal aryl or dialkyl substituted allenic phosphonates (**2a**–**c** and **2f**–**i**) investigated could afford the desired γ-phosphonate lactones in moderate to good yields (entries1–3 and 6–9). In the case of allenic phosphonates with one C-terminal alkyl substituent (**2d**–**e**), however, no desired cyclization products were obtained, even if stronger electrophile ICl[6c] was used (entries 4and 5), probably due to the difficulty to form the iodonium intermediates. The ratio of two isomers was about 1:1 to 8:5 with allenic phosphonates with different C-terminal substituents (entries 3, 6, and 7).

Table 3
Iodocyclization of allenic phosphonates **2a**–**i**

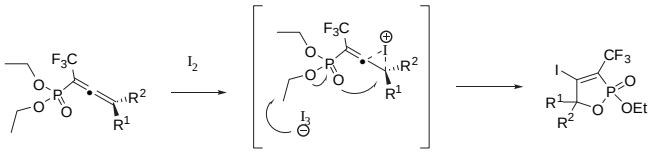


2 **3**

Entry	**2**	Product	Yield[a] (%)
1	**2a**	**3a**	92
2	**2b**	**3b**	83
3	**2c**	**3c**	48; 30[b]
4	**2d**	**3d**	—[c]
5	**2e**	**3e**	—[c]
6	**2f**	**3f**	61[d]
7	**2g**	**3g**	70[d]
8	**2h**	**3h**	82
9	**2i**	**3i**	87

[a] Isolated yield.
[b] Two diastereomers were isolated.
[c] I_2 or ICl was used as the electrophile, the substrate was recovered.
[d] Total isolated yield of two diastereomers.

A similar mechanism as Angelov[10b] reported was proposed for the formation of **3** as illustrated in Scheme 1. Allenic phosphonates **2** reacted with polarized I_2 to form iodonium **A** and release an iodine anion at the same time. With the assistance of iodine anion, intramolecular nucleophilic attack of oxygen in phosphonyl group on the terminal carbon of allene in the 5-*endo* mode afforded the cyclization product **3** accompanied by the elimination of ethyl iodine. Therefore, substituents which can stabilize the iodonium intermediate **A** facilitate the cyclization as demonstrated by the results above.



2 **A** **3**

Scheme 1. Proposed mechanism for the iodocyclization reaction.

3. Conclusion

In summary, the synthesis and iodocyclization of trifluoromethylallenic phosphonates have been achieved under mild conditions for the first time, providing a convenient method for the synthesis of trifluoromethylated oxaphospholenes. The presence of vinyl iodine in the resulted fluorine-containing oxaphospholenes makes it possible to incorporate this novel subunit into other molecules to prepare various carbohydrate mimics with potential bioactivities.

4. Experimental section

4.1. General

Melting points were measured with a Temp-Melt apparatus and uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on Bruker AM-300 instruments with TMS as the internal standard. ^{19}F NMR and ^{31}P NMR spectra were recorded on the same spectrometer using $CFCl_3$ and 85% H_3PO_4 as external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer.

Mass spectra and high resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 and a Finnigan MAT-8430 spectrometer, respectively. Elemental analyses were performed by this institute. Dichloromethane was freshly distilled from sodium before use. Diethyl chlorophosphite was prepared according to literature.[11] All other chemicals were commercially available and were used as received.

4.2. Typical procedure for the preparation of 2

To a mixture of alkynol **1a** (0.45 g, 2.5 mmol) and Et_3N (0.36 mL, 2.6 mmol) in CH_2Cl_2 (8 mL) was added slowly a solution of diethyl chlorophosphite (0.42 g, 2.7 mmol) in CH_2Cl_2 (2 mL) at −78 °C. After stirred at that temperature for 10 min, the reaction mixture was warmed to ambient temperature and stirred for 2 h, then quenched with H_2O (10 mL) and extracted with Et_2O (3×10 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography to give 0.64 g of **2a** as a colorless oil (isolated yield: 85%).

*4.2.1. Diethyl 1-trifluoromethyl-3-ethylpenta-1,2-dien-1-ylphosphonate (**2a**).* Colorless oil. IR (thin film, cm^{-1}): 2976, 1966, 1461, 1401, 1378, 1271, 1172, 1133, 1054, 1025, 976, 585. ^1H NMR (300 MHz, $CDCl_3$): δ 4.21–4.10 (m, 4H), 2.21–2.12 (m, 4H), 1.35 (t, *J*=6.9 Hz, 6H), 1.08 (t, *J*=7.4 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.56 (d, *J*=2.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.71 (s). ^{13}C NMR (75 MHz, $CDCl_3$): 209.6 (m), 120.2 (qd, J_{C-F}=272.2 Hz, J_{C-P}=16.4 Hz), 110.3 (d, J_{C-P}=13.1 Hz), 91.2 (m), 62.8 (d, J_{C-P}=5.6 Hz), 24.9 (d, J_{C-P}=5.1 Hz), 16.1 (d, J_{C-P}=6.8 Hz), 11.6 (d, J_{C-P}=1.9 Hz). EI-MS *m*/*z* (%): 300 (M^+, 12.29), 231 (16.16), 163 (13.96), 138 (71.06), 111 (100.00), 81 (64.36). HRMS: calcd for $C_{12}H_{20}F_3O_3P$ requires *m*/*z* 300.1102, found 300.1107.

*4.2.2. Diethyl 1-trifluoromethyl-3-methylbuta-1,2-dien-1-ylphosphonate (**2b**).* Colorless oil. IR (thin film, cm^{-1}): 2990, 1974, 1448, 1384, 1263, 1175, 1134, 1025, 979, 585. ^1H NMR (300 MHz, $CDCl_3$): δ 4.22–4.09 (m, 4H), 1.89 (s, 3H), 1.87 (s, 3H), 1.35 (t, *J*=6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.61 (d, *J*=1.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.06 (s). EI-MS *m*/*z* (%): 272 (M^+, 2.68), 203 (16.36), 147 (49.37), 109 (57.67), 81 (100.00), 69 (15.74), 65 (63.38). Anal. Calcd for $C_{10}H_{16}F_3O_3P$: C, 44.12; H, 5.92. Found: C, 44.06; H, 5.97.

*4.2.3. Diethyl 1-trifluoromethyl-3-methylpenta-1,2-dien-1-ylphosphonate (**2c**).* Colorless oil. IR (thin film, cm^{-1}): 2981, 2938, 2913, 1959, 1457, 1442, 1392, 1378, 1268, 1174, 1134, 1024, 974, 799, 747, 710, 586. ^1H NMR (300 MHz, $CDCl_3$): δ 4.21–4.10 (m, 4H), 2.20–2.11 (m, 2H), 1.88 (d, *J*=5.7 Hz, 3H), 1.35 (t, *J*=7.2 Hz, 6H), 1.09 (t, *J*=7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.60 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.65 (s). ^{13}C NMR (100 MHz, $CDCl_3$): 209.4 (m), 122.0 (qd, J_{C-F}=272.2 Hz, J_{C-P}=16.2 Hz), 110.53 (d, J_{C-P}=13.3 Hz), 91.2 (dq, J_{C-P}=200.3 Hz, J_{C-F}=37.0 Hz), 65.4 (d, J_{C-P}=6.0 Hz), 32.3 (d, J_{C-P}=5.4 Hz), 26.2 (d, J_{C-P}=5.1 Hz), 18.6 (d, J_{C-P}=4.8 Hz), 17.3 (d, J_{C-P}=5.5 Hz), 16.0 (d, J_{C-P}=6.5 Hz), 13.4 (d, J_{C-P}=3.4 Hz), 11.4 (d, J_{C-P}=1.8 Hz). EI-MS *m*/*z* (%): 286 (M^+, 7.37), 217 (8.30), 149 (11.99), 109 (100.00), 57 (69.29). HRMS: calcd for $C_{11}H_{18}F_3O_3P$ requires *m*/*z* 286.0946, found 286.0947.

*4.2.4. Diethyl 1-trifluoromethylhexa-1,2-dien-1-ylphosphonate (**2d**).* Colorless oil. IR (thin film, cm^{-1}): 2968, 1972, 1396, 1277, 1195, 1138, 1053, 1023, 975, 584. ^1H NMR (300 MHz, $CDCl_3$): δ 5.95–5.87 (m, 1H), 4.24–4.10 (m, 4H), 2.24–2.14 (m, 2H), 1.58–1.47 (m, 2H), 1.36 (t, *J*=7.2 Hz, 6H), 0.98 (t, *J*=7.5 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.48 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ 8.99 (s). EI-MS *m*/*z* (%): 286 (M^+, 3.58), 257 (6.94), 230 (9.71), 149 (3.47), 109 (100.00), 81 (85.27), 77 (30.17), 69 (9.18). HRMS: calcd for $C_{11}H_{18}F_3O_3P$ requires *m*/*z* 286.0946, found 286.0945. Anal. Calcd for $C_{11}H_{18}F_3O_3P$: C, 46.16; H, 6.34. Found: C, 45.98; H, 6.62.

*4.2.5. Diethyl 1-trifluoromethyl-4,4-dimethylpenta-1,2-dien-1-ylphosphonate (**2e**).* Colorless oil. IR (thin film, cm^{-1}): 2966, 2910, 1960, 1737, 1479, 1464, 1398, 1369, 1280, 1216, 1180, 1138, 978, 587. ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (dq, *J*=11.1, 3.0 Hz, 1H), 4.23–4.14 (m, 4H), 1.37 (t, *J*=7.2 Hz, 6H), 1.17 (s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.19 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.33 (s). EI-MS *m*/*z* (%): 300 (M^+, 12.93), 243 (100.00), 209 (89.85), 188 (64.31), 81 (26.18), 57 (22.74). Anal. Calcd for $C_{12}H_{20}F_3O_3P$: C, 48.00; H, 6.71. Found: C, 47.98; H, 6.88.

*4.2.6. Diethyl 1-trifluoromethyl-3-phenylpropa-1,2-dien-1-ylphosphonate (**2f**).* Colorless oil. IR (thin film, cm^{-1}): 2986, 1961, 1731, 1459, 1392, 1262, 1197, 1020, 974, 584. ^1H NMR (300 MHz, $CDCl_3$): δ 7.29–7.40 (m, 5H), 6.90 (dq, *J*=11.4, 3.0 Hz, 1H), 4.27–4.13 (m, 4H), 1.34 (dt, *J*=8.4, 7.5 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.02 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.36 (s). EI-MS *m*/*z* (%): 320 (M^+, 29.18), 272 (14.56), 244 (55.14), 228 (37.14), 182 (11.89), 164 (100.00), 75 (12.75), 65 (11.97). Anal. Calcd for $C_{14}H_{16}F_3O_3P$: C, 52.51; H, 5.04. Found: C, 52.17; H, 5.18.

*4.2.7. Diethyl 1-trifluoromethyl-3-phenylbuta-1,2-dien-1-ylphosphonate (**2g**).* Colorless oil. IR (thin film, cm^{-1}): 2990, 2935, 2912, 1955, 1716, 1497, 1460, 1446, 1373, 1264, 1170, 1135, 1053, 587. ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.40 (m, 5H), 4.16 (m, 4H), 2.28 (d, *J*=5.7 Hz, 3H), 1.33 (dt, *J*=7.2, 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.11 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ 8.20 (s). EI-MS *m*/*z* (%): 334 (M^+, 4.38), 265 (2.57), 197 (36.48), 104 (17.94), 81 (100.00), 77 (40.28), 69 (14.61). Anal. Calcd for $C_{15}H_{18}F_3O_3P$: C, 53.90; H, 5.43. Found: C, 53.63; H, 5.49.

*4.2.8. Diethyl 1-trifluoromethyl-2-cyclohexylidene-1-vinylphosphonate (**2h**).* Colorless oil. IR (thin film, cm^{-1}): 2988, 2938, 2860, 1967, 1448, 1409, 1271, 1164, 1137, 1053, 1025, 973, 584. ^1H NMR (300 MHz, $CDCl_3$): δ 4.23–4.08 (m, 4H), 2.36–2.23 (m, 4H), 1.54–1.75 (m, 6H), 1.35 (t, *J*=7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.61 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.53 (s). EI-MS *m*/*z*(%): 313 (M^++1, 22.56), 312 (M^+, 9.01), 243 (13.76), 158 (100.00), 137 (13.03), 82 (76.84), 69 (13.26). Anal. Calcd for $C_{13}H_{20}F_3O_3P$: C, 50.00; H, 6.46. Found: C, 49.87; H, 6.54.

*4.2.9. Diethyl 1-trifluoromethyl-2-cyclopentylidene-1-vinylphosphonate (**2i**).* Colorless oil. IR (thin film, cm^{-1}): 2964, 1962, 1726, 1394, 1288, 1256, 1172, 1133, 1053, 1024, 979, 585. ^1H NMR (300 MHz, $CDCl_3$): δ 4.21–4.08 (m, 4H), 2.67–2.58 (m, 4H), 1.83–1.76 (m, 4H), 1.35 (t, *J*=7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.40 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.89 (s). EI-MS *m*/*z* (%): 299 (M^++1, 46.39), 298 (M^+, 14.13), 230 (14.22), 161 (14.66), 137 (12.12), 91 (100.00), 137 (13.03), 69 (16.54). Anal. Calcd for $C_{12}H_{18}F_3O_3P$: C, 48.33; H, 6.08. Found: C, 48.28; H, 6.21.

4.3. Typical procedure for the cyclization reaction of allenic phosphonates 2 with iodine

To a solution of **2a** (136 mg, 0.5 mmol) in 5 mL of CH_3CN was added I_2 (250 mg, 1.0 mmol). The mixture was stirred at room temperature for 27 h. The resulting mixture was diluted with ether, washed with saturated $Na_2S_2O_3$ solution and brine, and the organic layer was dried over Na_2SO_4. After the removal of solvents under vacuum, the residue was purified by flash chromatography on silica gel to give **3a** as a white solid (170 mg, 92% yield).

*4.3.1. 5,5-Diethyl-2-ethoxy-4-iodo-3-trifluoromethyl-1,2-oxaphosphol-3-ene 2-oxide (**3a**).* Mp 102–103 °C. IR (KBr, cm^{-1}): 2972,

2939, 1610, 1299, 1251, 1173, 1146, 1054, 1037, 981, 831, 582. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.38–4.25 (m, 2H), 1.92 (q, J=7.2 Hz, 4H), 1.37 (t, J=6.9 Hz, 3H), 0.90 (t, J=7.5 Hz, 3H), 0.85 (t, J=8.4 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.11 (d, J=6.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.45 (d, J=7.2 Hz). EI-MS m/z (%): 399 (M^++1, 11.09), 398 (M^+, 9.13), 369 (81.06), 341 (100.00), 271 (49.12), 194 (65.33), 92 (3.19), 69 (5.21). Anal. Calcd for $C_{10}H_{15}F_3IO_3P$: C, 30.17; H, 3.80. Found: C, 30.26; H, 3.88.

*4.3.2. 5,5-Dimethyl-2-ethoxy-4-iodo-3-trifluoromethyl-1,2-oxaphosphol-3-ene 2-oxide (**3b**).* White solid, mp 93–94 °C. IR (KBr, cm^{-1}): 2995, 1607, 1458, 1397, 1385, 1369, 1299, 1257, 1167, 1140, 1046, 1031, 982, 806, 788, 585. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32–4.21 (m, 2H), 1.64 (s, 3H), 1.59 (s, 3H), 1.38 (t, J=7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.71 (d, J=6.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.63 (s). ESI-MS m/z: 370.9 $[M+H]^+$, 392.9 $[M+Na]^+$, 402.9 $[M+MeOH+H]^+$. EI-MS m/z (%): 371 (M^++1, 24.20), 355 (21.27), 301 (6.08), 243 (45.16), 196 (51.04), 108 (0.77), 69 (19.57), 43 (100.00). Anal. Calcd for $C_8H_{11}F_3IO_3P$: C, 25.97; H, 3.00. Found: C, 25.98; H, 3.23.

*4.3.3. 2-Ethoxy-5-ethyl-4-iodo-5-methyl-3-trifluoromethyl-1,2-oxaphosphol-3-ene 2-oxide (**3c**).* Less polar isomer: white solid, mp 191–193 °C. IR (KBr, cm^{-1}): 2987, 2939, 1610, 1291, 1254, 1180, 1143, 1054, 1029, 970, 820, 580. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.34–4.23 (m, 2H), 1.96–1.88 (m, 2H), 1.56 (s, 3H), 1.36 (t, J=7.2 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.78 (d, J=7.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.51 (q, J=5.8 Hz). EI-MS m/z (%): 369 (M^+-CH_3, 0.98), 355 (24.43), 327 (28.54), 315 (1.15), 257 (49.12), 127 (24.94), 69 (11.93), 44 (100.00). Anal. Calcd for $C_9H_{13}F_3IO_3P$: C, 28.14; H, 3.41. Found: C, 27.90; H, 3.45. More polar isomer: white solid, mp 186–187 °C. IR (KBr, cm^{-1}): 2987, 2939, 1610, 1291, 1254, 1180, 1143, 1054, 1029, 970, 820, 580. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.34–4.23 (m, 2H), 1.91 (q, J=7.2 Hz, 2H), 1.61 (s, 3H), 1.37 (t, J=6.9 Hz, 3H), 0.87 (t, J=7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.11 (d, J=6.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.27 (q, J=5.8 Hz).

*4.3.4. 2-Ethoxy-4-iodo-5-phenyl-3-trifluoromethyl-1,2-oxa-phosphol-3-ene 2-oxide (**3f**).* A 1:1 mixture of two diastereomers. IR (KBr, cm^{-1}): 2966, 2910, 2873, 1960, 1737, 1479, 1464, 1398, 1369, 1280, 1216, 1180, 1138, 1039, 978, 587. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.31 (m, 5H), 5.73–5.66 (m, 1H), 4.41–4.29 (m, 2H), 1.42 (t, J=7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.52 (s, **3f′**), −58.41 (d, J=7.6 Hz, **3f″**). ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.07 (s, **3f′**), 26.44 (s, **3f″**). ^{13}C NMR (125 MHz, $CDCl_3$): 133.9, 130.3 (m), 129.1, 128.2, 128.1, 122.8 (qd, J_{C-F}=271.6 Hz, J_{C-P}=16.3 Hz), 87.9, 65.4 (d, J_{C-P}=7.5 Hz), 16.4 (d, J_{C-P}=12.6 Hz). EI-MS m/z (%): 389 ($M^+-C_2H_5$, 100.00), 369 (88.77), 254 (51.82), 133 (68.44), 105 (60.48), 77 (43.26), 51 (26.81). HRMS: calcd for $C_{12}H_{11}F_3IO_3P$ requires m/z 417.9443, found 417.9442. Anal. Calcd for $C_{12}H_{11}F_3IO_3P$: C, 34.47; H, 2.65. Found: C, 34.07; H, 2.58.

*4.3.5. 2-Ethoxy-4-iodo-5-methyl-5-phenyl-3-trifluoromethyl-1,2-oxaphosphol-3-ene 2-oxide (**3g**).* A 1:1.2 mixture of two diastereomers. IR (KBr, cm^{-1}): 2993, 2939, 1606, 1301, 1255, 1141, 1039, 983, 952, 759, 695. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.40 (m, 5H), 4.42–4.34 (m, 2H), 2.00 (s, 1.25H), 2.07 (s, 1.75H), 1.42 (t, J=7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.60 (s, **3g′**), −58.64 (d, J=7.8 Hz, **3g″**). ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.30 (s, **3g′**), 25.88 (s, **3g″**). ^{13}C NMR (100 MHz, $CDCl_3$): 133.9, 130.3 (m), 129.4, 128.7, 127.6, 126.6, 120.5 (qd, J_{C-F}=273.5 Hz, J_{C-P}=16.4 Hz), 90.5, 65.1 (d, J_{C-P}=6.6 Hz), 25.2, 16.4 (d, J_{C-P}=5.4 Hz). EI-MS m/z (%): 432 (M^+, 22.66), 305 (10.69), 257 (27.46), 149 (100.00), 77 (48.25). HRMS: calcd for $C_{13}H_{13}F_3IO_3P$ requires m/z 431.9599, found 431.9598.

*4.3.6. 2-Ethoxy-4-iodo-5,5-pentamethylene-3-trifluoromethyl-1,2-oxaphosphol-3-ene 2-oxide (**3h**).* White solid, mp 102–104 °C. IR (KBr, cm^{-1}): 2943, 1604, 1452, 1445, 1299, 1262, 1245, 1180, 1147, 1049, 1033, 963, 910, 818, 686, 580. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32–4.19 (m, 2H), 2.04–1.97 (m, 2H), 1.81–1.68 (m, 6H), 1.60–1.21 (m, 2H), 1.37 (t, J=7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.12 (d, J_{F-P}=6.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.66 (q, J_{F-P}=6.2 Hz). EI-MS m/z (%): 410 (M^+, 2.08), 341 (3.05), 327 (29.98), 283 (100.00), 69 (6.74). Anal. Calcd for $C_{11}H_{15}F_3IO_3P$: C, 32.22; H, 3.69. Found: C, 32.25; H, 3.79.

*4.3.7. 5,5-Butamethylene-2-ethoxy-4-iodo-3-trifluoromethyl-1,2-oxaphosphol-3-ene 2-oxide (**3i**).* White solid, mp 90–91 °C. IR (KBr, cm^{-1}): 2988, 1603, 1331, 1299, 1259, 1169, 1144, 1048, 1032, 977, 945, 815, 790, 578. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29–4.19 (m, 2H), 2.23–2.18 (m, 2H), 2.06–1.89 (m, 6H) 1.36 (t, J=7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.15 (d, J_{F-P}=6.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.73 (q, J_{F-P}=6.2 Hz). EI-MS m/z (%): 397 (M^++1, 0.90), 339 (4.56), 327 (11.77), 269 (69.91), 221 (100.00), 69 (23.01). Anal. Calcd for $C_{10}H_{13}F_3IO_3P$: C, 30.32; H, 3.31. Found: C, 30.27; H, 3.43.

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References and notes

1. *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley-Interscience, a division of John Wiley: New York, NY, 1976.
2. (a) Caruthers, M. H. *Acc. Chem. Res.* **1991**, *24*, 278; (b) Sproat, B. S. *J. Biotechnol.* **1995**, *41*, 221; (c) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239; (d) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177.
3. Hah, J. H.; Lee, B. S.; Lee, S. Y.; Lee, H. Y. *Tetrahedron Lett.* **2003**, *44*, 5811.
4. (a) Organo-Fluorine Compounds In *Houben-Weyl Methods of Organic Chemistry; Georg Thieme: Sttutgart, 2000; (b) Fluorine-Containing Amino Acids: Synthesis and Properties; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, UK, 1995; (c) Beeson, T. D.; MacMillan, D. W. C. J. Am. Chem. Soc.* **2005**, *127*, 8826; (d) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjoersgaard, A.; Jùrgensen, R. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3707; (e) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706; (f) Enders, D.; Hüttl, M. R. *Synlett* **2005**, 991.
5. (a) Francke, R.; Roeschenthaler, G. V. *Chem. Ztg.* **1989**, *113*, 115; (b) Sevenard, D. V.; Lork, E.; Pashkevich, K. I.; Roschenthaler, G. V. *Heteroat. Chem.* **2002**, *13*, 97.
6. (a) Wang, X.-J.; Lin, Y.; Liu, J.-T. *Chin. J. Chem.* **2006**, *24*, 775; (b) Lin, Y.; Liu, J.-T. *Chin. Chem. Lett.* **2007**, *18*, 33; (c) Lin, Y.; Liu, J.-T. *Tetrahedron Lett.* **2006**, *47*, 6075.
7. Altenbach, H.; Korff, R. *Tetrahedron Lett.* **1981**, *22*, 5175.
8. (a) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1995**, *60*, 6046; (b) Katritzky, A. R.; Qi, M.; Wells, A. P. *J. Fluorine Chem.* **1996**, *80*, 145; (c) Qing, F.-L.; Gao, W.-Z.; Ying, J.-W. *J. Org. Chem.* **2000**, *65*, 2003.
9. Collet, H.; Calas, P.; Commeyras, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1152.
10. (a) Macomber, R. S.; Krudy, G. A.; Seff, K.; Rendon- Diazmiron, L. E. *J. Org. Chem.* **1983**, *48*, 1425; (b) Angelov, K. M.; Enchev, D. D.; Kirilov, M. *J. Gen. Chem. USSR (Engl. Transl.)* **1983**, *53*, 1766; (c) Alabugin, I. V.; Sereda, G. A.; Abramkin, E. V.; Brel, V. K.; Zyk, N. V.; Zefirov, N. S. *Dokl. Chem.* **1995**, *345*, 301; (d) Alabugin, I. V.; Sereda, G. A.; Abramkin, E. V.; Brel', V. K.; Zyk, N. V.; Zefirov, N. S. *Russ. J. Org. Chem.* **1996**, *32*, 1353.
11. Ebetino, F. H.; Berk, J. D. *J. Organomet. Chem.* **1997**, *529*, 135.