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# Synthetic application of fluorinated vinamidinium salts: Synthesis of fluorinated 1,3-butadienylphosphonates by the reaction with Horner–Wadsworth–Emmons reagents

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**Abstract**

The reaction of β-fluoro vinamidinium salt **1** with Horner–Wadsworth–Emmons reagents (HWE) such as diethyl(ethoxycarbonyl)methylphosphonate (**2a**), diethyl(methoxycarbonyl)methylphosphonate (**2b**), diethyl-2-oxopropylphosphonate (**2c**), diethyl benzylphosphonate (**2d**), tetraethyl methylenediphosphonate (**2e**) and diethyl cyanomethylphosphonate (**2f**) under basic conditions gave the fluorinated 1,3-butadienylphosphonates **3** in moderate to good yields. The phosphonates **3** could be hydrolyzed with a 10% HCl aqueous solution to afford the corresponding γ-(diethylphosphono)-α-fluoro-α,β-unsaturated aldehydes **7** in good yields. The treatment of the phosphonate **3c** with an $NH_3$ aqueous solution at 70 °C produced the pyridine derivative **8** in 60% yield.


*Keywords:* Fluorinated vinamidinium salt; Horner–Wadsworth–Emmons reagents; Fluorinated 1,3-butadienylphosphonates; γ-(Diethylphosphono)-α-fluoro-α,β-unsaturated aldehydes; Phosphonated pyridine

## 1. Introduction

Vinamidinium (1,5-diazapentadienium) salts are very useful synthons in organic synthesis because of their versatile reactivities. Therefore, much efforts have been made to prepare many kinds of vinamidinium salts having various substituents and to apply them in organic synthesis [1–4]. Recently, the Merck research group has actively investigated the preparation of a variety of vinamidinium salts and successfully applied them to the synthesis of a highly potent, specific COX-2 inhibitor [5–9]. Although the availability of fluorine-containing vinamidinium salts should open new routes to various kinds of fluorinated compounds of biological and materials science interest, there were few reports on fluorinated vinamidinium salts [10–12] prior to our research concerning this area. One of our primary goals is to uncover useful synthetic methodologies for obtaining various organofluorine compounds by use of the fluorinated vinamidinium salts as key building blocks. We have already reported on the preparation of β-fluoro, β-trifluoromethyl and β-polyfluoroalkoxy vinamidinium salts and their applications to the synthesis of regioselectively fluorinated compounds through the reactions with hetero and carbon nucleophiles [13–15]. Herein we wish to report the results of the reaction of a β-fluoro vinamidinium salt with Horner–Wadsworth–Emmons reagents (HWE), which provides a new means for synthesizing useful organophosphorous compounds containing a fluorine substituent [16].

## 2. Results and discussion

We first examined the reaction of 1,1,5,5-tetraethyl-1,5-diaza-2-fluoro-1,3-pentadienium iodide (β-fluoro vinamidinium salt) (**1**) with diethyl(ethoxycarbonyl)methylphosphonate (**2a**) under various conditions (Scheme 1). The results are summarized in Table 1. Thus, to a suspension of sodium hydride (NaH) (1.1 equiv.) in tetrahydrofuran (THF) was added **2a** (1.1 equiv.) at room temperature, and the mixture was stirred

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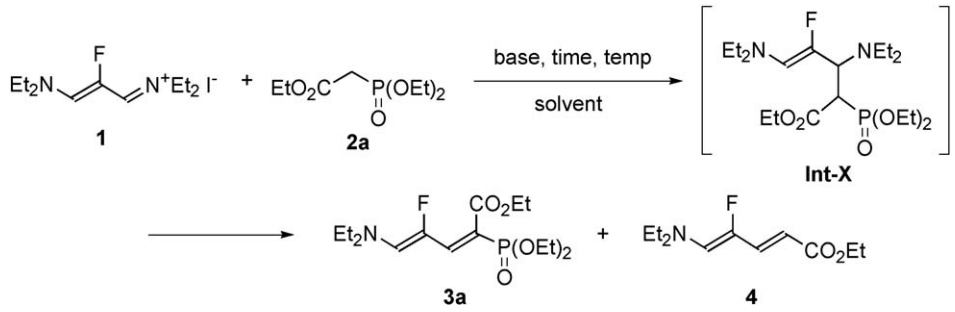



Scheme 1.

for 30 min. To the resultant mixture was added a THF solution of the salt **1** at room temperature, and the whole was stirred for 3 h at room temperature. The $^{19}F$ NMR spectra ($CF_3COOH$ as the external reference) of the reaction mixture showed two peaks at −76 and −81 ppm for the products, along with a peak for unreacted salt **1**. After the usual workup, the products were isolated by column chromatography and identified as diethyl-4-(*N*,*N*-diethylamino)-1-ethoxycarbonyl-3-fluoro-(1*E*,3*Z*)-butadienylphosphonate (**3a**) (36% yield) and ethyl-5-(*N*,*N*-diethylamino)-4-fluoro-(2*E*,4*Z*)-pentadienate (**4**) (5% yield) (entry 1). A slight increase in the product yield was observed for the reaction at reflux temperature for 2 h (entry 2). When 2.2 equiv. each of **2a** and NaH were employed, the yields of **3a** and **4** increased to 51% and 26%, respectively (entry 3). The use of dimethylformamide (DMF) as the solvent gave better result than that of THF; the reaction of **1** with 2.2 equiv. each of **2a** and NaH in DMF at room temperature for 3 h afforded **3a** in 72% yield without formation of **4** (entry 4).

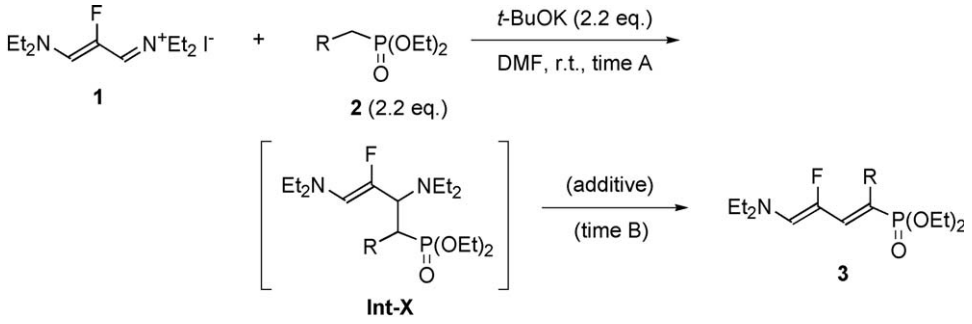
Interestingly, the use of potassium *t*-butoxide (*t*-BuOK) as the base in place of NaH led to the different results. The $^{19}F$ NMR analysis for the reaction of 2.2 equiv. of **2a** with *t*-BuOK in DMF for 1 h showed a large peak at −74 ppm for a new product and a small peak due to **1** (entry 5). As the reaction time was extended, the large peak decreased and the peak for the product **3a** appeared at −76 ppm (entries 6 and 7). Unfortunately the product corresponding to the large peak could not be isolated, but these observations allowed us to assume that the large peak was due to an intermediate (**Int-X**) formed at the initial addition step. When NaH (1.1 equiv.) was added to the reaction mixture employing 2.2 equiv. of *t*-BuOK in DMF for 3 h, followed by stirring for 5 h, the intermediate **Int-X** was smoothly converted to **3a** in 78% yield (entry 8). On adding acetic acid (3.3 equiv.) as the additive, the starting salt **1** was recovered in 77% yield along with **3a** (21% yield) (entry 9). $Et_2O$ and 1,2-dimethoxyethane (DME) as the solvents and lithium diisopropylamide (LDA) as the base were not so effective in producing **3a** (entries 10–12).

The reactions of **1** with other HWE reagents **2** were attempted under the optimized conditions (2.2 equiv. of *t*-BuOK, 1.1 equiv. of NaH, DMF, room temperature) described above (Scheme 2). The results are summarized in Table 2. Diethyl (methoxycarbonyl)methylphosphonate (**2b**) and tetraethyl methylenediphosphonate (**2e**) gave diethyl 4-(*N*,*N*-diethylamino)-3-fluoro-1-methoxycarbonyl-(1*E*,3*Z*)-butadienylphosphonate (**3b**) and tetraethyl-4-(*N*,*N*-diethylamino)-3-fluoro-(1*E*,3*Z*)-butadienylbisphosphonate (**3e**) in 85% and 92% yields, respectively (entries 2 and 9).

Table 1
Investigation of the reaction conditions

| Entry | Eq of **2a** | Solvent | Base (equiv.) | Time (h) | Temp | Additive (equiv.) | Yield of products (%)[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **3a** | **4** | **Int-X** |
| 1 | 1.1 | THF | NaH (l.1) | 3 | r.t. | – | 36 | 5 | ND |
| 2 | 1.1 | THF | NaH (l.1) | 2 | Ref. | – | 48 | 10 | ND |
| 3 | 2.2 | THF | NaH (2.2) | 3 | r.t. | – | 51 | 26 | ND |
| 4 | 2.2 | DMF | NaH (2.2) | 3 | r.t. | – | 72 | 0 | ND |
| 5 | 2.2 | DMF | *t*-BuOK (2.2) | 1 | r.t. | – | 0 | 0 | 94 |
| 6 | 2.2 | DMF | *t*-BuOK (2.2) | 3 | r.t. | – | 10 | 0 | 85 |
| 7 | 2.2 | DMF | *t*-BuOK (2.2) | 12 | r.t. | – | 24 | 0 | 69 |
| 8 | 2.2 | DMF | *t*-BuOK (2.2) | 3 + 5[b] | r.t. | NaH (l.1) | 78 | 0 | ND |
| 9 | 2.2 | DMF | *t*-BuOK (2.2) | 3+0.5[c] | r.t. | AcOH (3.3) | 21 | 0 | ND[d] |
| 10 | 2.2 | $Et_2O$ | *t*-BuOK (2.2) | 3 | r.t. | – | 15 | 0 | 23[e] |
| 11 | 2.2 | DME | *t*-BuOK (2.2) | 3 | r.t. | – | 20 | 0 | 26[e] |
| 12 | 2.2 | THF | LDA (2.2) | 3 | r.t. | – | 0 | 0 | ND[e] |

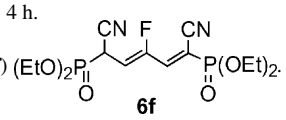
[a] Determined by $^{19}F$ NMR.
[b] After addition of NaH, the mixture was stirred for 5 h.
[c] After addition of acetic acid, the mixture was stirred for 0.5 h.
[d] The salt **1** was recovered in 77% yield.
[e] Recovery of the salt **1** was more than 50%.




Scheme 2.

Table 2
Results of the reaction of **1** with various HWE reagents **2** in DMF

| Entry | R of **2** | Time *A* (h) | Additive (equiv.) | Time *B* (h) | Yield[a]/% of **Int-X** | Yield[a]/% of **3** |
|---|---|---|---|---|---|---|
| 1 | $CO_2Et$ (**2a**) | 3 | NaH (1.1) | 5 | 0 | 78 |
| 2 | $CO_2Me$ (**2b**) | 3 | NaH (1.1) | 5 | 0 | 85 |
| 3 | COMe (**2c**) | 1 | – | – | 0 | 86 |
| 4 | COMe (**2c**) | 3 | – | – | 0 | 52 (17[b]) |
| 5 | COMe (**2c**) | 5[c] | – | – | 0 | 0(81[b]) |
| 6 | Ph (**2d**) | 6 | – | – | 91 | 0 |
| 7 | Ph (**2d**) | 6 | NaH (1.1) | 5 | 90 | 0 |
| 8 | Ph (**2d**) | 6 | AcOH (3.3) | 0.5 | 0 | 88 |
| 9 | $P(O)(OEt)_2$ (**2e**) | 6 | NaH (1.1) | 5 | 0 | 92 |
| 10 | CN (**2f**)[d] | 1 | – | – | 0 | 85 |
| 11 | CN (**2f**) | 3 | – | – | 0 | 6(85[e]) |

[a] Determined by $^{19}F$ NMR.
[b] The yield of diethyl(3-acetyl-5-fluoro-2-methyl)phenylphosphonate (**5**).
[c] The mixture was stirred at room temperature for 1 h and then heated at 50 °C for 4 h.
[d] 1.1 equiv. each of base and **2f** was used.
[e] The yield of 1,5-bis(diethylphosphono)-3-fluoro-1,5-dicyano-(1*E*,3*Z*)-pentadiene (**6f**) 

**6f**

Diethyl(2-oxopropyl)phosphonate (**2c**) participated in the reaction without NaH to produce the expected product, which was unstable for isolation with column chromatography but was presumed to be diethyl-1-acetyl-4-(diethylamino)-3-fluoro-(1*E*,3*Z*)-butadienylphosphonate (**3c**) (86% $^{19}F$ NMR yield) by comparison with fluorine chemical shifts of other **3** (entry 3). Interestingly, the reaction with **2c** at room temperature for 3 h led to the cyclization product, diethyl(3-acetyl-5-fluoro-2-methyl)phenylphosphonate (**5**), in 17% yield as the by-product (entry 4). When this reaction was conducted for 1 h at room temperature, followed by heating at 50 °C for 4 h, the cyclization product **5** was obtained in high yield as the sole product (entry 5).

The reaction with diethyl benzylphosphonate (**2d**) did not give the corresponding product **3d** without or with addition of NaH as the additive (entries 6 and 7). However, when acetic acid was added as the additive and the whole was stirred for 0.5 h, the expected product, diethyl-4-(*N*,*N*-diethylamino)-3-fluoro-1-phenyl-(1*E*,3*Z*)-butadienylphosphonate (**3d**) was obtained in 88% yield (entry 8).

The treatment of **1** with diethyl cyanomethylphosphonate (**2f**) (1.1 equiv.) and *t*-BuOK (1.1 equiv.) in DMF at ambient temperature for 1 h proceeded readily to give diethyl-1-cyano-4-(*N*,*N*-diethylamino)-3-fluoro-(1*E*,3*Z*)-butadienylphosphonate (**3f**) in 85% yield as the sole product (entry 10). The use of 2.2 equiv. each of **2f** and *t*-BuOK led to the formation of tetraethyl-3-fluoro-1,5-dicyano-(1*E*,3*Z*)-pentadiene-1,5-bisphosphonate (**6f**) in 85% yield, together with a small amount of **3f** (6% yield) (entry 11).

The stereochemical assignment of **3** was made on the basis of the relative magnitudes for the H–F and H–P vicinal couplings. The $^1H$ and $^{19}F$ NMR spectra of the 1,3-butadienylphosphonates **3** showed the coupling constants of 30.0–35.5 Hz for Ha–F and 24.0–35.5 Hz for Hb–F, which indicate that the Ha–F and Hb–F relationships are in a transoid and *trans* geometry, respectively (Fig. 1) [17]. The Ha–Px and

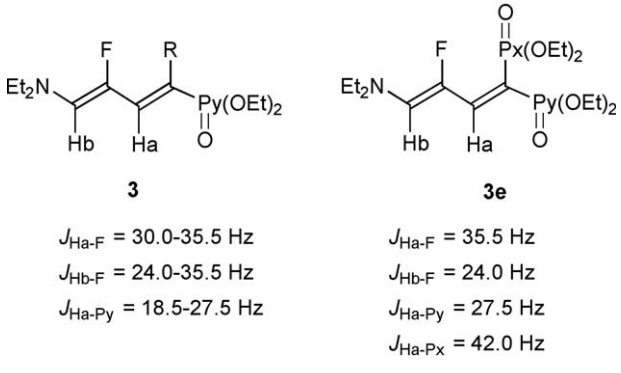
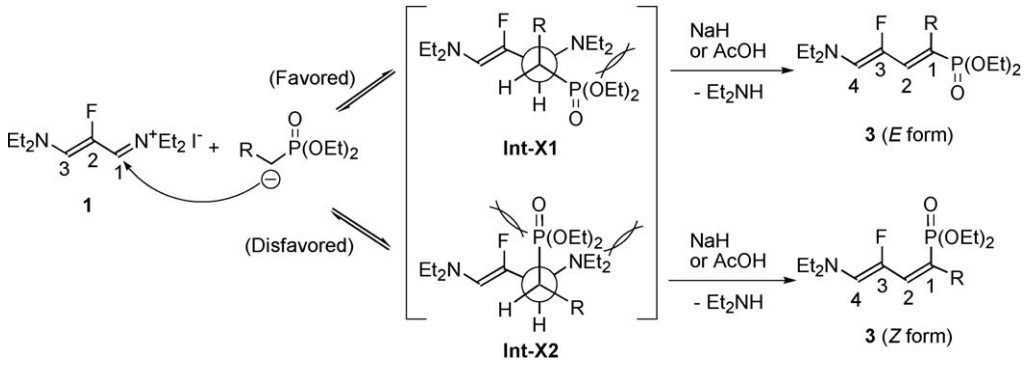



Fig. 1. The coupling constants of **3**.




Scheme 3.

Ha–Py coupling constants of **3e** are 42.0 and 27.5 Hz, respectively, strongly suggesting that the Ha–Px relationship is *trans* and the Ha–Py is *cis* [18]. Based on the fact that the Ha–Py coupling constants of other phosphonates **3** are in a range of 18.5–27.5 Hz, the Ha–Py relationship in **3** was assigned as *cis*.

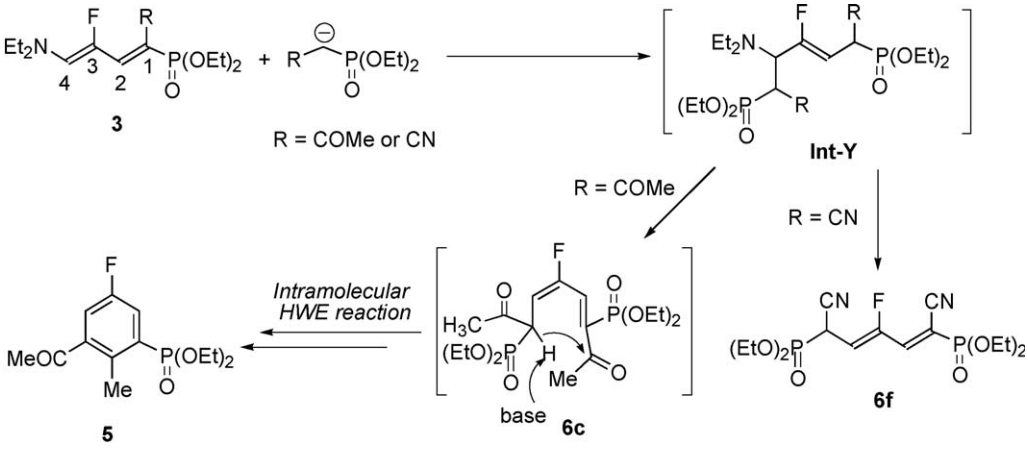
A possible mechanism for the reaction of **1** with **2** is outlined in Scheme 3. Nucleophilic attack of the anion of **2** occurs at the iminium carbon (C1) of the salt **1** to form the intermediate **Int-X**, which subsequently undergoes the β-elimination of diethylamine to give the 1,3-butadienylphosphonate **3**. The exclusive formation of the *E* isomer (at the C1–C2 double bond) of **3** may be explained by an anti-elimination pathway as follows. With the two possible intermediates **Int-X1** and **Int-X2**, in which the hydrogen and diethylamino group occupy the antiperiplanar position, the intermediate **Int-X2** may have much larger gauche repulsion than **Int-X1**. Therefore, the β-elimination of diethylamine can occur more readily through **Int-X1** than **Int-X2**, leading exclusively to the *E* isomer of **3** [19].

The formation of **4** observed in the reaction in THF (Table 1, entries 1–3) would be caused by the elimination of phosphoramidate ($Et_2NP(O)(OEt)_2$) from an azaphosphatane species which results from an effectual interaction between N and P of **Int-X** in THF, a less polar solvent, compared to DMF.

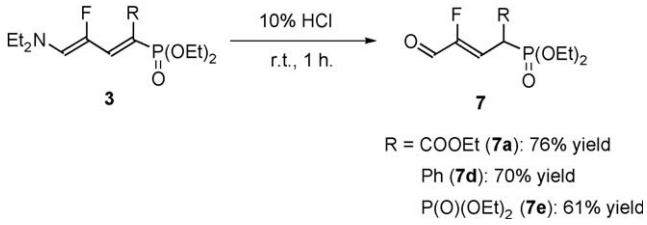
The findings that the intermediate **Int-X** was detected in the reaction using *t*-BuOK as the base but not in the reaction using NaH seem to be explained as follows. In the reaction with NaH, the α-hydrogen adjacent to the phosphonate group of **Int-X** may be activated by coordination of sodium cation with carbonyl and phosphonate groups, and this activation facilitates the elimination of diethylamine from **Int-X** leading to the product **3**. In the case of the reaction using *t*-BuOK, potassium cation may not sufficiently exert the effect of such activation of the α-hydrogen [20], **Int-X** remaining to be detected. The steric bulk of the base will be considered as another factor; the α-hydrogen of **Int-X** is sterically crowded and, therefore, it can be abstracted with a small hydride ion but not with a bulky butoxide ion effectively.

The formation of the cyclization product **5** and bisphosphonate **6f** is explained as follows (Scheme 4). The anion derived from **2c** or **2f** attacks on the C4 carbon of **3** to form an intermediate **Int-Y**, which similarly undergoes the β-elimination of diethylamine to yield **6c** and **6f**, respectively. The diketone **6c** thus formed may undergo the intramolecular Horner–Wadsworth–Emmons reaction to produce the product **5**.

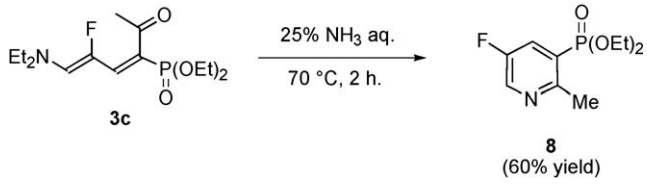
It was found that the 1,3-butadienylphosphonates **3a**, **3d** and **3e** were subjected to hydrolysis with a 10% HCl aqueous solution at room temperature for 1 h, giving rise to the corresponding α,β-unsaturated aldehydes **7** in 61–76% yields (Scheme 5).




Scheme 4.




Scheme 5.




Scheme 6.

Additionally, on treatment of **3c** with a 25% $NH_3$ aqueous solution at 70 °C for 2 h, the pyridine derivative **8** was afforded in 60% yield (Scheme 6).

## 3. Conclusion

In summary, we demonstrated that the fluorinated 1,3-butadienylphosphonates **3** were easily synthesized in moderate to good yields by the reaction of the vinamidinium salt **1** with various Horner–Wadsworth–Emmons reagents **2** in the presence of base at room temperature. When the reaction of **1** with diethyl(2-oxopropyl)phosphonate **2c** was conducted at 50 °C, the benzene derivative **5** was obtained in good yield through the intramolecular Horner–Wadsworth–Emmons reaction. Furthermore, the phosphonates **3** thus obtained could easily be hydrolyzed with 10% HCl aqueous solution to give the corresponding phosphonate-containing fluorinated α,β-unsaturated aldehydes **7** in good yields. The phosphonate **3c** could readily be converted to the phosphonated pyridine derivative **8** by treatment with aqueous ammonia solution at 70 °C.

## 4. Experimental

### 4.1. General

Infrared spectra (IR) were recorded in a liquid film or KBr disk method on a Shimadzu FTIR-8200A (PC) spectrophotometer. $^1$H NMR spectra were measured with a Bruker DRX (500.13 MHz) spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (TMS) as an internal reference. $^{13}$C NMR spectra were recorded on a Bruker DRX (125.77 MHz) spectrometer. A JEOL JNM EX90 (84.21 MHz, FT) spectrometer was used to obtain $^{19}$F NMR spectra in $CDCl_3$ with trichlorofluoromethane ($CCl_3F$) as an internal reference. $C_6F_6$ was used for determining the $^{19}$F NMR yield as an internal standard. High resolution mass spectra (HRMS) were taken on a JEOL JMS-700 mass spectrometer.

All chemicals are of reagent grade and, if necessary, were purified in the usual manner prior to use. The vinamidinium salt **1** was prepared according to the method reported by us [22]. All reactions were carried out under an atmosphere of argon.

### 4.2. General procedure of the reaction of vinamidinium salt *1* with HWE reagent *2*

To a solution of *t*-BuOK (0.13 g, 1.1 mmol) in DMF (1.5 mL) was gradually added a solution of HWE reagent **2** (1.1 mmol) in DMF (1.5 mL) at 0 °C. After stirring at room temperature for 0.5 h, a solution of the salt **1** (0.164 g, 0.5 mmol) in DMF (2.0 mL) was slowly added, and then the whole mixture was stirred at room temperature for the time shown in Table 2. To the reaction mixture was added $C_6F_6$ for determining $^{19}$F NMR yields of the products. In the cases of entries 1, 2 and 7–9 in Table 2, NaH (0.013 g, 0.55 mmol) or acetic acid (0.099 g, 1.65 mmol) was added and then the mixture was stirred at room temperature for 5 or 0.5 h, respectively. When NaH was used as the additive, the reaction was quenched with EtOH (20 mL). The reaction mixture was poured into brine (40 mL), followed by extraction with dichloromethane (5× 20 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. Column chromatography (silica gel, hexane/ethyl acetate = 2/3) of the residue gave the corresponding 1,3-butadienylphosphonate **3**.

#### 4.2.1. Diethyl-4-(N,N-diethylamino)-1-ethoxycarbonyl-3-fluoro-(1E,3Z)-butadienylphosphonate (*3a*)

IR (neat): ν 2989, 1717, 1643, 1574, 1420, 1362, 1265, 1234, 1204, 1180, 1130, 1096, 1053, 1026, 964, 768 cm$^{-1}$; $^1$H NMR: δ 1.21 (t, *J* = 7.0 Hz, 6H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 6H), 3.30 (q, *J* = 7.0 Hz, 4H), 4.05–4.13 (m, 4H), 4.23 (q, *J* = 7.0 Hz, 2H), 5.98 (d, *J* = 27.5 Hz, 1H), 6.80 (dd, *J* = 32.5, 22.5 Hz, 1H); $^{13}$C NMR: δ 14.00, 14.40, 16.09 (d, *J* = 7.0 Hz), 47.70, 60.57, 61.73 (d, *J* = 4.8 Hz), 102.12 (d, *J* = 190.0 Hz), 133.54 (d, J = 4.9 Hz), 136.86 (dd, *J* = 232.6, 22.6 Hz), 141.50 (dd, *J* = 14.1, 10.1 Hz), 166.80 (d, *J* = 12.2 Hz); $^{19}$F NMR: δ −151.68 (dd, *J* = 32.5, 27.5 Hz, 1F); MS (EI) *m/z* (rel intensity) 351 (*M*$^+$, 100), 336 (9), 306 (84), 214 (86); HRMS (EI) calcd for $C_{15}H_{27}FNO_5P$: 351.1595, found: 351.1589.

#### 4.2.2. Diethyl-4-(N,N-diethylamino)-1-methoxycarbonyl-3-fluoro-(1E,3Z)-butadienylphosphonate (*3b*)

IR (neat): ν 2986, 2931, 1713, 1651, 1574, 1435, 1400, 1366, 1311, 1346, 1311, 1269, 1230, 1177, 1130, 872, 799, 748 cm$^{-1}$; $^1$H NMR: δ 1.21 (t, *J* = 7.0 Hz, 6H), 1.32 (t, *J* = 7.0 Hz, 6H), 3.31 (q, *J* = 7.0 Hz, 4H), 3.77 (s, 3H), 4.05–4.13 (m, 4H), 6.00 (d, *J* = 27.5 Hz, 1H), 6.81 (dd, *J* = 32.5, 22.5 Hz, 1H); $^{19}$F NMR: δ −152.12 (dd, *J* = 32.5, 27.5Hz, 1F); MS (EI) *m/z* (rel intensity) 337 (*M*$^+$, 56), 306 (100); HRMS (EI) calcd for $C_{14}H_{25}FNO_5P$: 337.1454, found: 337.1453.

#### 4.2.3. Diethyl-4-(N,N-diethylamino)-3-fluoro-1-phenyl-(1E,3Z)-butadienylphosphonate (*3d*)

IR (neat): ν 3025, 2978, 2900, 1643, 1585, 1416, 1342, 1261, 1234, 1184, 1123, 1096, 1030, 976, 798, 763 cm$^{-1}$; $^1$H NMR: δ

1.11 (t, $J$ = 7.5 Hz, 6H), 1.22 (t, $J$ = 7.0 Hz, 6H), 3.16 (q, $J$ = 7.5 Hz, 4H), 3.97–4.05 (m, 4H), 5.72 (d, $J$ = 28.0 Hz, 1H), 6.80 (dd, $J$ = 31.8, 23.8 Hz, 1H), 7.21–7.29 (m, 5H); $^{13}$C NMR: $\delta$ 14.46, 16.20 (d, $J$ = 6.6 Hz), 47.23, 61.39 (d, $J$ = 5.2 Hz), 102.52 (d, $J$ = 182.3 Hz), 126.33, 127.23, 129.6 (d, $J$ = 2.4 Hz), 129.60 (d, $J$ = 5.9 Hz), 129.90 (d, $J$ = 5.4 Hz), 136.62 (dd, $J$ = 25.3, 12.8 Hz), 138.01 (dd, $J$ = 235.1, 25.7 Hz); $^{19}$F NMR: $\delta$ −150.86 (dd, $J$ = 31.8, 28.0 Hz, 1F); MS (EI) $m/z$ (rel intensity) 356 ($M^+$, 25), 340 (100), 285 (30), 155 (8); HRMS (EI) calcd for $C_{18}H_{28}FNO_3P$: 356.1793, found: 356.1794.

#### *4.2.4. Tetraethyl-4-(N,N-diethylamino)-3-fluoro-(1E,3Z)-butadienylidenediphosphonate (**3e**)*

IR (neat): $\nu$ 2982, 2936, 2905, 1636, 1551, 1427, 1396, 1362, 1300, 1269, 1226, 1184, 1134, 1026, 964, 798 cm$^{-1}$; $^1$H NMR: $\delta$ 1.32 (t, $J$ = 7.0 Hz, 6H), 1.33 (t, $J$ = 6.5 Hz, 6H), 3.36 (q, $J$ = 7.0 Hz, 4H), 4.04–4.25 (m, 8H), 6.18 (d, $J$ = 24.0 Hz, 1H), 7.23 (ddd, $J$ = 42.0, 35.5, 27.5 Hz, 1H); $^{19}$F NMR: $\delta$ −148.44 (dd, $J$ = 35.5, 24.0 Hz, 1F); MS (EI) $m/z$ (rel intensity) 416 ($M^+$, 100), 308 (5), 142 (6); HRMS (EI) calcd for $C_{16}H_{32}FNO_6P_2$: 416.1767, found: 416.1765.

#### *4.2.5. Diethyl-1-cyano-4-(N,N-diethylamino)-3-fluoro-(1E,3Z)butadienylphosphonate (**3f**)*

IR (neat): $\nu$ 2986, 2191, 1639, 1562, 1427, 1396, 1358, 1308, 1234, 1184, 1138, 1022, 964, 802, 768 cm$^{-1}$; $^1$H NMR: $\delta$ 1.27 (t, $J$ = 7.0 Hz, 6H), 1.37 (t, $J$ = 7.0 Hz, 6H), 3.40 (q, $J$ = 7.0 Hz, 4H), 4.09–4.16 (m, 4H), 6.18 (d, $J$ = 26.5 Hz, 1H), 6.98 (dd, $J$ = 30.0, 18.5 Hz, 1H); $^{13}$C NMR: $\delta$ 14.48, 16.18 (d, $J$ = 6.7 Hz), 47.45, 62.60 (d, $J$ = 5.7 Hz), 75.68 (d, $J$ = 208.6 Hz), 117.70 (d, $J$ = 10.9 Hz), 136.71 (d, $J$ = 3.5 Hz), 137.99 (dd, $J$ = 232.7, 20.2 Hz), 147.86 (dd, $J$ = 11.3, 10.8 Hz); $^{19}$F NMR: $\delta$ −152.06 (ddd, $J$ = 30.0, 26.5, 5.5 Hz, 1F); MS (EI) $m/z$ (rel intensity) 304 ($M^+$, 100), 289 (28), 167 (63); HRMS (EI) calcd for $C_{13}H_{22}FN_2O_5P$: 304.1352, found: 304.1351.

#### *4.2.6. Ethyl-5-(diethylamino)-4-fluoro-(2E,4Z)-pentadienoate (**4**)*

Mp 56.5–57.5 °C; IR (Kbr) $\nu$ 2978, 2936, 1736, 1697, 1589, 1419, 1362, 1258, 1157, 1076, 833, 659 cm$^{-1}$; $^1$H NMR: $\delta$ 1.18 (t, $J$ = 7.1 Hz, 6H), 1.27 (t, $J$ = 7.1 Hz, 3H), 3.26 (q, $J$ = 7.1 Hz, 4H), 4.17 (q, $J$ = 7.1 Hz, 2H), 5.54 (d, $J$ = 14.8 Hz, 1H), 5.65 (d, $J$ = 29.5 Hz, 1H), 6.95 (dd, $J$ = 29.9, 14.8 Hz, 1H); $^{13}$C NMR: $\delta$ 14.46, 14.50, 47.42, 47.46, 59.55, 103.16 (d, $J$ = 2.8 Hz), 128.47 (d, $J$ = 4.9 Hz), 137.36 (d, $J$ = 18.1 Hz), 137.41 (d, $J$ = 229.0 Hz), 168.30; $^{19}$F NMR: $\delta$ −156.51 (dd, $J$ = 29.9, 29.5 Hz, 1F); MS (EI) $m/z$ (rel intensity) 215 ($M^+$, 100), 200 (86), 186 (19), 170 (85); HRMS (EI) calcd for $C_{11}H_{18}FNO_2$: 215.1307, found: 215.1295.

#### *4.2.7. Diethyl(3-acetyl-5-fluoro-2-methylphenyl)phosphonate (**5**)*

IR (neat): $\nu$ 3074, 2986, 2989, 1701, 1593, 1435, 1393, 1358, 1293, 1246, 1165, 1088, 1022, 964, 822, 795, 741 cm$^{-1}$; $^1$H NMR: $\delta$ 1.33 (t, $J$ = 7.0 Hz, 6H), 2.54 (s, 3H), 2.57 (s, 3H), 4.08–4.19 (m, 4H), 7.32 (dd, $J$ = 8.3, 2.8 Hz, 1H), 7.76 (ddd, $J$ = 15.5, 8.3, 3.0 Hz, 1H); $^{13}$C NMR: $\delta$ 16.26 (d, $J$ = 7.2 Hz), 17.69 (d, $J$ = 4.0 Hz), 30.45, 62.44 (d, $J$ = 5.8 Hz), 118.13 (d, $J$ = 22.1 Hz), 123.10 (dd, $J$ = 22.4, 10.6 Hz), 131.83 (dd, $J$ = 184.7, 5.3 Hz), 135.60 (dd, $J$ = 10.4, 4.0 Hz), 142.90 (dd, $J$ = 17.0, 4.8 Hz), 159.63 (dd, $J$ = 249.2, 21.5 Hz), 201.67; $^{19}$F NMR: $\delta$ −116.83 (dd, $J$ = 15.5, 8.3 Hz, 1F); MS (FAB) $m/z$ (rel intensity) 289 ($M^+ + H'$, 100), 233 (19), 154 (14); HRMS (FAB) calcd for $C_{13}H_{19}FO_4P$: 289.1005, found: 289.1007.

#### *4.2.8. Tetraethyl-1,5-dicyano-3-fluoro-5-phosphono-(1E,3Z)pentadienylphosphonate (**6f**)*

IR (neat): $\nu$ 2990, 2912, 2218, 1655, 1593, 1547, 1477, 1447, 1393,1369, 1261, 1211, 1165, 1018, 980, 799, 733 cm$^{-1}$; $^1$H NMR: $\delta$ 1.40 (t, $J$ = 7.0 Hz, 12H), 4.16–4.33 (m, 9H), 5.61 (ddd, $J$ = 28.5, 10.0, 6.0 Hz, 1H), 7.34 (dd, $J$ = 25.5, 20.1 Hz, 1H); $^{19}$F NMR: $\delta$ −112.23 (dddd, $J$ = 28.5, 25.5, 11.0, 4.4 Hz, 1F); MS (EI) $m/z$ (rel intensity) 408 ($M^+$, 4), 299 (100), 272 (3), 167 (63); HRMS (EI) calcd for $C_{15}H_{23}FN_2O_6P_2$: 408.1020, found: 408.1022.

### *4.3. General procedure for the synthesis of phosphonated α,β-unsaturated aldehydes **7***

To a solution of **3** (0.5 mmol) in DMF (2 mL) was gradually added 10% aqueous HCl (50 mL), and the mixture was stirred for 1 h at room temperature. To the resulting mixture was added $C_6F_6$ for determining $^{19}$F NMR yields of the products. The reaction mixture was poured into brine (40 mL) and extracted with diethyl ether (3× 30 mL). The combined diethyl ether extracts were dried over sodium sulfate and concentrated under reduced pressure. Column chromatography (silica gel, hexane/ethyl acetate = 1/3) of the residue gave the corresponding aldehydes **7**.

#### *4.3.1. 4-Ethoxycarbonyl-4-(diethylphosphono)-2-fluoro-2(Z)-butenal (**7a**)*

IR (neat): $\nu$ 3395, 2912, 2874, 1736, 1701, 1670, 1447, 1258, 1211, 1161, 1022, 976, 883 cm$^{-1}$; $^1$H NMR: $\delta$ 1.33 (td, $J$ = 7.0, 0.8 Hz, 6H), 1.32 (t, $J$ = 7.0 Hz, 3H), 4.13–4.29 (m, 4H), 4.26 (q, $J$ = 7.0 Hz, 2H), 4.30 (dd, $J$ = 25.0, 10.5 Hz, 1H), 6.26 (ddd, $J$ = 30.5, 10.5, 6.0 Hz, 1H), 9.30 (d, $J$ = 18.5 Hz, 1H); $^{13}$C NMR: $\delta$ 13.96, 16.21 (d, $J$ = 5.2 Hz), 43.41 (d, $J$ = 127.9 Hz), 62.59, 63.75 (d, $J$ = 6.2 Hz), 63.80 (d, $J$ = 6.3 Hz), 119.89 (dd, $J$ = 10.9, 9.3 Hz), 155.98 (dd, $J$ = 268.7, 11.8 Hz), 165.26 (d, $J$ = 7.7 Hz), 182.76 (d, $J$ = 24.7 Hz); $^{19}$F NMR: $\delta$ −128.77 (ddd, $J$ = 30.5, 18.50, 11.5 Hz, 1F); MS (FAB) $m/z$ (rel intensity) 297 ($M^+ + H'$, 100), 251 (9), 224 (3), 136 (40); HRMS (FAB) calcd for $C_{11}H_{19}FO_6P$: 297.0903, found: 297.0802.

#### *4.3.2. 4-Phenyl-4-(diethylphosphono)-2-fluoro-2(Z)-butenal (**7d**)*

IR (neat): $\nu$ 3036, 2986, 2864, 1701, 1666, 1496, 1391, 1238, 1020, 970, 883, 754, 698 cm$^{-1}$; $^1$H NMR: $\delta$ 1.09 (t, $J$ = 7.0 Hz, 3H), 1.30 (t, $J$ = 7.0 Hz, 3H), 3.75–4.126 (m, 4H), 3.96 (m, 1H), 4.45 (dd, $J$ = 23.5, 11.0, 1H), 6.36 (ddd, $J$ = 29.5, 11.0, 7.5 Hz,

1H), 9.30 (d, $J$ = 18.0 Hz, 1H); $^{13}$C NMR: $\delta$ 16.13 (d, $J$ = 6.2 Hz), 16.31 (d, $J$ = 5.8 Hz), 41.75 (d, $J$ = 138.6 Hz), 62.88 (d, $J$ = 7.3 Hz), 63.64 (d, $J$ = 6.8 Hz), 125.06 (dd, $J$ = 10.1, 8.4 Hz), 128.10, 128.74 (d, $J$ = 6.8 Hz), 129.11, 133.19, 156.23 (dd, $J$ = 267.3, 11.2 Hz), 183.16 (d, $J$ = 25.4 Hz); $^{19}$F NMR: $\delta$ 130.36 (ddd, $J$ = 29.5, 18.0, 11.0 Hz, 1F); MS (FAB) $m/z$ (rel intensity) 361 ($M^+ + H'$, 100), 154 (68), 136 (55); HRMS (FAB) calcd for $C_{14}H_{19}FO_4P$: 301.1005, found: 301.1004.

#### 4.3.3. 4,4-Bis(diethylphosphono)-2-fluoro-2(Z)-butenal (7e)

IR (neat): $\nu$ 2990, 2885,1693, 1663, 1443, 1393, 1350, 1250, 1165, 1022, 976, 933, 876, 791 cm$^{-1}$; $^1$H NMR: $\delta$ 1.33 (dt, $J$ = 7.0, 2.5 Hz, 12H), 3.85 (td, $J$ = 22.5, 11.5 Hz, 1H), 4.20 (dq, $J$ = 17.0, 7.0 Hz, 8H), 6.08 (ddt, $J$ = 28.8, 11.5, 6.5 Hz, 1H), 9.29 (d, $J$ = 18.0 Hz, 1H); $^{13}$C NMR: $\delta$ 16.26 (d, $J$ = 5.6 Hz), 36.72 (t, $J$ = 133.7 Hz), 63.55 (d, $J$ = 5.6 Hz), 63.68 (d, $J$ = 6.1 Hz), 119.19 (dt, $J$ = 10.1, 8.7 Hz), 156.89 (dt, $J$ = 268.0, 11.2 Hz), 182.61 (d, $J$ = 24.4 Hz); $^{19}$F NMR: $\delta$ −129.64 (ddt, $J$ = 28.8, 18.0, 8.8 Hz, 1F); MS (FAB) $m/z$ (rel intensity) 361 ($M^+ + H'$, 100), 231 (17), 197 (15), 136 (52); HRMS (FAB) calcd for $C_{12}H_{24}FO_7P_2$: 361.0981, found: 361.0985.

### 4.4. Synthesis of the phosphonated pyridine 8

To the mixture, prepared by the reaction of the salt **1** (0.164 g, 0.50 mmol) with **2a** (0.214 g, 1.1 mmol) and *t*-BuOK (0.123 g, 1.1 mmol) in DMF (3.5 mL) for 1 h at room temperature, was gradually added 25% $NH_3$ aqueous solution (30 mL). The whole mixture was stirred for 2 h at 70 °C. The reaction mixture was extracted with diethyl ether (3× 30 mL) and the combined organic layers were washed with brine (50 mL), followed by drying over sodium sulfate and concentration under reduced pressure. The residual oil was purified by silica gel column chromatography (hexane/ethyl acetate 1/3) to afford pure 2-acetyl-3-(diethoxyphosphono)-5-fluoropyridine **8** (0.075 g, 0.3 mmol, 60% yield).

#### 4.4.1. 2-Acetyl–3-(diethoxyphosphono)-5-fluoropyridine 8

IR (neat): $\nu$ 3491, 2986, 2936, 2874, 1840, 1593, 1570, 1439, 1393, 1254, 1165, 1022, 968, 795, 748, 725, 683 cm$^{-1}$; $^1$H NMR: $\delta$ 1.32 (t, $J$ = 7.0 Hz, 6H), 2.72 (s, 3H), 4.08–4.20 (m, 4H), 7.88 (ddd, $J$ = 15.5, 8.5, 3.0 Hz, 1H), 8.44 (dd, $J$ = 3.0, 2.0 Hz, 1H); $^{13}$C NMR: $\delta$ 16.22 (d, $J$ = 6.4 Hz), 23.62, 62.58 (d, $J$ = 5.4 Hz), 124.49 (d, $J$ = 183.4 Hz), 128.31 (dd, $J$ = 19.6, 9.1 Hz), 140.10 (d, $J$ = 22.1 Hz), 156.98 (dd, $J$ = 10.9, 4.6 Hz), 157.12 (dd, $J$ = 256.4, 16.2 Hz), 201.67; $^{19}$F NMR: $\delta$ −131.65 (dd, $J$ = 8.5, 2.0 Hz, 1F); MS (FAB) $m/z$ (rel intensity) 248 ($M^+ + H'$, 100), 154 (47), 136 (36), 112 (1); HRMS (FAB) calcd for $C_{10}H_{16}FNO_3P$: 248.0852, found: 248.0857.

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