

# Conjugate Addition of Diethyl 1-Fluoro-1-phenylsulfonylmethanephosphonate to $\alpha,\beta$ -Unsaturated Compounds

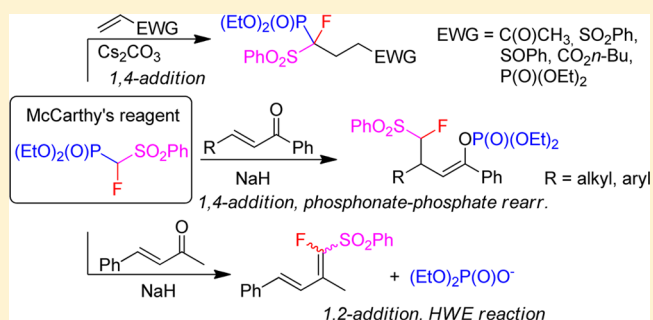
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**S** Supporting Information

**ABSTRACT:** Diethyl 1-fluoro-1-phenylsulfonylmethanephosphonate (1) in the presence of cesium carbonate undergoes efficient 1,4-addition to Michael acceptors having terminal double bonds such as  $\alpha,\beta$ -unsaturated ketones, esters, sulfones, sulfoxides, and phosphonates to yield the corresponding adducts in good to excellent yields. In the presence of sodium hydride, 1 reacts with  $\alpha,\beta$ -enones to provide  $\gamma$ -fluoro- $\gamma$ -phenylsulfonylenol phosphates arising from 1,4-addition followed by phosphonate to phosphate rearrangement.

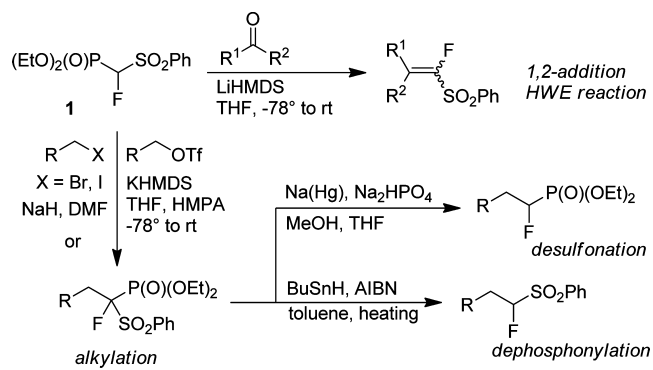


Organic phosphates are ubiquitous molecules that play important roles in living organisms, ranging from information storage and transfer (DNA, RNA), energy transfer (ATP), to separation of a cell membrane from the environment (phospholipids).<sup>1</sup> Phosphonates, containing nonhydrolyzable C–P bonds, can serve as mimics for natural phosphates in terms of their function and bioactivity. Indeed, many synthetic phosphonates display interesting biological activities.<sup>2</sup> Moreover, it has been realized that adjunction of electronegative elements such as fluorine atoms to the  $\alpha$ -position of a phosphonate enables closer phosphate mimicry.<sup>3</sup>  $\alpha$ -Fluorinated phosphonates<sup>4</sup> are often utilized as enzyme inhibitors and metabolic probes.<sup>5</sup> In recent years, there has been significant progress in studying the chemistry and bioactivity of  $\alpha,\alpha$ -difluoro phosphonates.<sup>6</sup> However, the less studied  $\alpha$ -mono-fluoro phosphonates have second  $pK_a$ 's more closely correlating with the  $pK_a$  of natural phosphates.<sup>3b,7</sup>

Diethyl 1-fluoro-1-phenylsulfonylmethanephosphonate (1), also known as McCarthy's reagent, was introduced into organic synthesis in 1987 by Koizumi<sup>8</sup> and further developed as a fluoromethylene synthon by McCarthy.<sup>9</sup> Compound 1 reacts under basic conditions with aldehydes, ketones, and  $\alpha,\beta$ -unsaturated aldehydes in the course of the Horner–Wadsworth–Emmons reaction to provide 1-fluoro-1-phenylsulfonylalkenes.<sup>8–10</sup> Furthermore, 1 has been employed as a precursor of  $\alpha$ -fluoro phosphonates or  $\alpha$ -fluorosulfones. The synthetic strategy is based on alkylation of 1 and further desulfonation or dephosphorylation (Scheme 1).<sup>11</sup>

Introduction of (poly)fluoroalkyl groups by nucleophilic addition to electrophiles has been extensively studied in recent years. Many strategies and reagents were developed for efficient

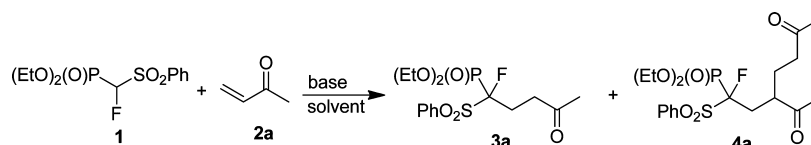
**Scheme 1. Published HWE and Alkylation Reactions of 1**



nucleophilic mono-, di-, and trifluoromethylations as well as perfluoroalkylations and polyfluoroalkylations.<sup>12</sup> The reactive species in these processes are  $\alpha$ -fluorinated carbanions which are, in comparison to nonfluorinated carbanions, less polarizable and less nucleophilic. As a consequence, unless several electron delocalization groups which increase polarizability (soft character) are present on an  $\alpha$ -fluorinated carbanionic center, the reagent behaves as a hard nucleophile. For example, the Ruppert–Prakash reagent (TMSCF<sub>3</sub>) is known to undergo 1,2-addition to  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>12a,13</sup> The same behavior was observed for diethyl difluoromethylphosphonate in the presence of LDA; however, in the presence of lithium-coordinating HMPA or transmetalation with Ce<sup>III</sup> salts,

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Table 1. Optimization of the 1,4-Addition of **1** to Methyl Vinyl Ketone (**2a**)<sup>a</sup>

entry	base (equiv)	solvent	temp (°C)	time (h)	yield <sup>b</sup> (%)	
					3a	4a
1	Cs <sub>2</sub> CO <sub>3</sub> (2.0)	DMF	rt	1.5	72	16
2	Cs <sub>2</sub> CO <sub>3</sub> (1.0)	DMF	0	0.3	89	8
3	Cs <sub>2</sub> CO <sub>3</sub> (0.1)	DMF	rt	0.1	95 <sup>c</sup>	0
4	Cs <sub>2</sub> CO <sub>3</sub> (0.1)	THF	rt	4.0	>95	1
5	Cs <sub>2</sub> CO <sub>3</sub> (0.1)	MeCN	rt	1.0	95 <sup>c</sup>	0
6	K <sub>2</sub> CO <sub>3</sub> (0.1)	DMF	rt	42	>95	0
7	K <sub>2</sub> CO <sub>3</sub> (0.1)	DMF	50	3.0	>95	0
8	K <sub>2</sub> CO <sub>3</sub> (1.0)	DMF	rt	2.5	>95	2
9	LDA (1.1)	THF	-78 to 0	2.0	32	5
10	NaH (1.1)	THF	-20 to 10	1.5	<1	<1

<sup>a</sup>Reactions were carried out using **1** (0.20 mmol, 1.0 equiv), **2a** (1.2 equiv), and base in solvent (2.5 mL). <sup>b</sup><sup>19</sup>F NMR yield with PhCF<sub>3</sub> as an internal standard unless noted otherwise. <sup>c</sup>Isolated yield.

Table 2. 1,4-Addition of **1** to  $\alpha,\beta$ -Unsaturated Compounds **2**<sup>a</sup>

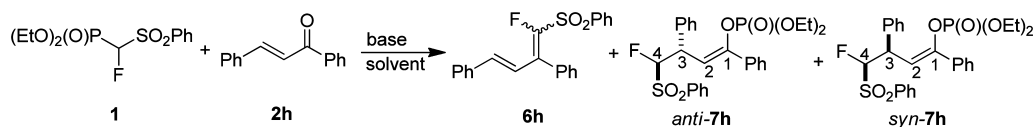
Entry	<b>2</b>	Michael acceptor (equiv.)	Cs <sub>2</sub> CO <sub>3</sub> (equiv.)	Time (h)	<b>3</b>	Product	Yield (%) <sup>b</sup>
1	<b>2a</b>		1.2	0.1	1	<b>3a</b>	95
2	<b>2b</b>		1.0	0.1	1	<b>3b</b>	95
3	<b>2c</b>		1.2	0.1	5	<b>3c</b>	94
4	<b>2d</b>		1.2	1.0	4	<b>3d</b>	63 <sup>c,d</sup> ( <i>E/Z</i> 1:1)
5	<b>2e</b>		1.0	1.0	3	<b>3e</b>	56 (dr 49:51)
6	<b>2f</b>		1.2	2.0	21	<b>3f</b>	48 (dr 22:77)
7	<b>2g</b>		1.0	1.0	25	<b>3g</b>	69
8	<b>2h</b>		1.0	3.0	24	<b>3h</b>	0 <sup>e</sup>
9	<b>2i</b>		1.0	2.0	20	<b>3i</b>	0
10	<b>2j</b>		1.0	2.0	45	<b>3j</b>	0
11	<b>2k</b>		1.0	3.0	22	<b>3k'</b>	28 <sup>c</sup>

<sup>a</sup>Reactions were carried out using **1** (0.30 mmol, 1.0 equiv), **2**, and Cs<sub>2</sub>CO<sub>3</sub> in MeCN (3 mL). <sup>b</sup>Isolated yield unless noted otherwise. <sup>c</sup><sup>19</sup>F NMR yield using PhCF<sub>3</sub> as a standard. <sup>d</sup>Pure (*E*)-**3d** was isolated by silica gel chromatography in 29% yield. <sup>e</sup>Different products were formed (see discussion below).

significant 1,4-addition to  $\alpha,\beta$ -unsaturated ketones was observed.<sup>14</sup> Similarly, lithium salts of mono- and difluoromethyl phenyl sulfone gave exclusive 1,2-addition to 2-cyclohexenone but showed high 1,4-/1,2-addition ratio in the presence of

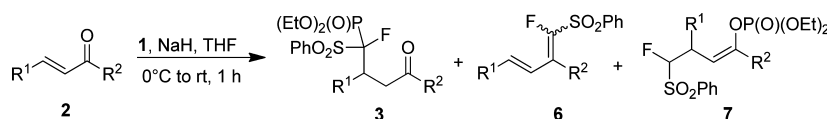
HMPA.<sup>15</sup> On the other hand, more delocalized fluoromethyl carbanions of 1-fluorobis(phenylsulfonyl)methane<sup>15</sup> and tetraethyl fluoromethylenbisphosphonate<sup>16</sup> undergo exclusive conjugate addition to  $\alpha,\beta$ -enones and other Michael acceptors



Table 3. Reaction of **1** with Chalcone (**2h**)<sup>a</sup>

entry	<b>1</b> (equiv)	base (equiv)	solvent	temp (°C)	time (h)	yield <sup>b</sup> (%) of <b>6h</b>	yield <sup>c</sup> (%) of <b>7h</b>	dr <sup>d</sup> of <b>7h</b>
1	1.0	Cs <sub>2</sub> CO <sub>3</sub> (0.1)	MeCN	rt	6	0	0	N/A
2 <sup>e</sup>	1.0	Cs <sub>2</sub> CO <sub>3</sub> (3.0)	MeCN	rt	24	3	31	66:33
3	1.0	LDA (1.1)	THF	-78 to 0	2	21	32	64:36
4	1.0	NaH (1.1)	THF	-60 to rt	1	6	40	62:37
5	2.0	NaH (2.0)	THF	0 to rt	1	7	72	64:36

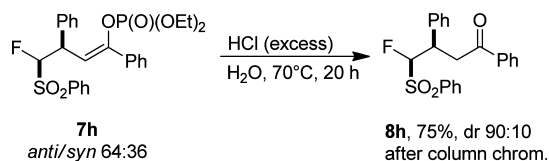
<sup>a</sup>Reactions were carried out using **1**, **2h** (0.20 mmol, 1 equiv), and the base in solvent (2 mL). <sup>b</sup><sup>19</sup>F NMR yield using PhCF<sub>3</sub> as a standard. <sup>c</sup>Isolated yield. <sup>d</sup>Determined by <sup>19</sup>F NMR of the crude product mixture. <sup>e</sup>The same conditions as in Table 2, entry 8.

Table 4. Formation of Enol Phosphates **7** by the Addition of **1** to Unsaturated Ketones (**2**)<sup>a</sup>

entry	<b>2</b>	R <sup>1</sup>	R <sup>2</sup>	yield <sup>b</sup> (%) of <b>3</b>	yield <sup>b</sup> (%) of <b>6</b>	yield <sup>c</sup> (%) of <b>7</b>	dr <sup>d</sup> of <b>7</b>
1	<b>2a</b>	H	Me	30	22	18 <sup>b</sup>	
2	<b>2h</b>	Ph	Ph	0	7	72	64:36
3	<b>2l</b>	<i>p</i> -Tol	Ph	0	12	68	58:42
4	<b>2m</b>	Me	Ph	0	0	68	71:29
5	<b>2n</b>	Ph	Me	0	34, 70 <sup>e</sup>	0	

<sup>a</sup>Reactions were carried out using **1** (2 equiv), **2** (0.20 mmol, 1 equiv), and NaH (2 equiv) in THF (3 mL). <sup>b</sup><sup>19</sup>F NMR yield using PhCF<sub>3</sub> as a standard. <sup>c</sup>Isolated yield unless noted otherwise. <sup>d</sup>Determined by <sup>19</sup>F NMR of the crude product mixture. <sup>e</sup>Using **1** (0.4 mmol, 1 equiv), **2n** (4 equiv), and NaH (1.2 equiv) in THF (3 mL) at -70 to 0 °C for 1 h. *E/Z* ratio of **6n** was 62:38.

### Scheme 3. Formation of $\gamma$ -Fluoro Ketone **8h** by Dephosphonylation of **7h**



In summary, efficient conjugated addition of **1** to Michael acceptors was accomplished using catalytic or equimolar amounts of cesium carbonate. The adducts can be desulfonated using magnesium in methanol to yield  $\alpha$ -fluoro phosphonates. Reaction of **1** with chalcones and related ketones in the presence of sodium hydride resulted in formation of unexpected  $\gamma$ -fluoro- $\gamma$ -phenylsulfonylenol phosphates which can be hydrolyzed to  $\gamma$ -fluoro- $\gamma$ -phenylsulfonyl ketones.

## EXPERIMENTAL SECTION

Compounds **2h**, **2l**, and **2n** were prepared according to literature procedure.<sup>23</sup> HRMS (ESI) analyses were recorded using an ion trap MS analyzer.

**General Procedure for the Synthesis of Compounds 3.** Cs<sub>2</sub>CO<sub>3</sub> (0.03–0.90 mmol, 0.1–3.0 equiv) was placed in a Schlenk flask, and MeCN (3 mL) and **1** (93.1 mg, 0.3 mmol, 1.0 equiv) were added followed by addition of **2** (0.30–0.36 mmol, 1.0–1.2 equiv). The reaction mixture was stirred at rt, followed by addition of saturated NH<sub>4</sub>Cl (15 mL), extraction with Et<sub>2</sub>O (3 × 15 mL), drying, and removal of solvents under reduced pressure. Purification by silica gel column chromatography using hexane/EtOAc as eluent provided compounds **3**.

**3a.** Prepared from Cs<sub>2</sub>CO<sub>3</sub> (10 mg, 0.03 mmol), **1** (93.1 mg, 0.3 mmol) and **2a** (26 mg, 0.36 mmol) in 1 h at rt giving **3a** (112 mg, 95%) as a colorless liquid: *R*<sub>f</sub> 0.30 (hexane–EtOAc, 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.26 (t, 3H, *J* = 7.1 Hz), 1.30 (t, 3H, *J* = 7.1 Hz), 2.14 (s, 3H), 2.37–2.65 (m, 2H), 2.78–3.04 (m, 2H), 4.09–4.26 (m, 4H), 7.53–7.59 (m, 2H), 7.65–7.72 (m, 1H), 7.92–7.97 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.2 (d, <sup>3</sup>*J*<sub>CP</sub> = 4.3 Hz), 16.3 (d, <sup>3</sup>*J*<sub>CP</sub> = 4.3 Hz), 25.4 (dd, <sup>2</sup>*J*<sub>CF</sub> = 19.6 Hz, <sup>2</sup>*J*<sub>CP</sub> = 2.2 Hz), 29.8, 36.7 (dd, <sup>3</sup>*J*<sub>CF</sub> = 5.4 Hz, <sup>3</sup>*J*<sub>CP</sub> = 2.6 Hz), 64.7 (d, <sup>2</sup>*J*<sub>CP</sub> = 7.1 Hz), 64.9 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.8 Hz), 106.9 (dd, <sup>1</sup>*J*<sub>CF</sub> = 228.6 Hz, <sup>1</sup>*J*<sub>CP</sub> = 164.7 Hz), 128.7, 130.7, 134.7, 135.3, 205.7; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -164.5 (ddd, <sup>2</sup>*J*<sub>FP</sub> = 80.5 Hz, <sup>3</sup>*J*<sub>FH</sub> = 23.4, 16.7 Hz); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>)  $\delta$  8.8 (d, <sup>2</sup>*J*<sub>PF</sub> = 80.5 Hz); HRMS (ESI) calcd for C<sub>15</sub>H<sub>23</sub>FO<sub>6</sub>PS [M + H]<sup>+</sup> 381.0932, found 381.0931.

**3b.** Prepared from Cs<sub>2</sub>CO<sub>3</sub> (10 mg, 0.03 mmol), **1** (93 mg, 0.3 mmol), and **2b** (40 mg, 0.30 mmol) in 1 h at rt giving **3b** (139 mg, 95%) as a colorless liquid: *R*<sub>f</sub> 0.22 (hexane–EtOAc, 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.23 (t, 3H, *J* = 7.1 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 2.54–2.68 (m, 2H), 3.39–3.48 (m, 1H), 3.61–3.72 (m, 1H), 4.06–4.23 (m, 4H), 7.52–7.59 (m, 4H), 7.64–7.73 (m, 2H), 7.86–7.90 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.1 (d, <sup>3</sup>*J*<sub>CP</sub> = 5.6 Hz), 16.2 (d, <sup>3</sup>*J*<sub>CP</sub> = 5.6 Hz), 25.4 (dd, <sup>2</sup>*J*<sub>CF</sub> = 20.5 Hz, <sup>2</sup>*J*<sub>CP</sub> = 2.2 Hz), 50.1 (dd, <sup>3</sup>*J*<sub>CF</sub> = 6.0 Hz, <sup>3</sup>*J*<sub>CP</sub> = 2.5 Hz), 65.0 (d, <sup>2</sup>*J*<sub>CP</sub> = 7.1 Hz), 65.2 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.8 Hz), 105.3 (dd, <sup>1</sup>*J*<sub>CF</sub> = 230.7 Hz, <sup>1</sup>*J*<sub>CP</sub> = 164.3 Hz), 128.0, 128.8, 129.4, 130.7 (d, <sup>3</sup>*J*<sub>CF</sub> = 1.2 Hz), 133.9, 134.6, 135.0, 138.3; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -164.4 (ddd, <sup>2</sup>*J*<sub>FP</sub> = 78.8 Hz, <sup>3</sup>*J*<sub>FH</sub> = 18.9, 18.9 Hz); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>)  $\delta$  7.8 (d, <sup>2</sup>*J*<sub>PF</sub> = 78.8 Hz); HRMS (ESI) calcd for C<sub>19</sub>H<sub>24</sub>FNaO<sub>7</sub>PS<sub>2</sub> [M + Na]<sup>+</sup> 501.0577, found 501.0577.

**3c.** Prepared from Cs<sub>2</sub>CO<sub>3</sub> (10 mg, 0.03 mmol), **1** (93 mg, 0.3 mmol), and **2c** (46 mg, 0.36 mmol) in 5 h at rt giving **3c** (124 mg, 94%) as a colorless liquid: *R*<sub>f</sub> 0.52 (hexane–EtOAc, 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.93 (t, 3H, *J* = 7.4 Hz), 1.30 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.1 Hz), 1.33–1.42 (m, 2H), 1.55–1.64 (m, 2H), 2.50–2.66 (m, 2H), 2.67–2.74 (m, 1H), 2.80–2.90 (m, 1H), 4.07 (t,

3H,  $J = 6.7$  Hz), 4.15–4.30 (m, 4H), 7.56–7.61 (m, 2H), 7.69–7.75 (m, 1H), 7.97–8.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.6, 16.2 (d,  $^3J_{\text{CP}} = 4.4$  Hz), 16.3 (d,  $^3J_{\text{CP}} = 4.4$  Hz), 19.0, 26.8 (dd,  $^2J_{\text{CF}} = 19.6$  Hz,  $^2J_{\text{CP}} = 2.0$  Hz), 28.0 (dd,  $^3J_{\text{CF}} = 6.6$  Hz,  $^3J_{\text{CP}} = 2.7$  Hz), 30.5, 64.6, 64.7 (d,  $^2J_{\text{CF}} = 7.0$  Hz), 64.9 (d,  $^2J_{\text{CF}} = 6.8$  Hz), 106.6 (dd,  $^1J_{\text{CF}} = 229.4$  Hz,  $^1J_{\text{CP}} = 164.9$  Hz), 128.7, 130.8 (d,  $^3J_{\text{CF}} = 1.2$  Hz), 134.7, 135.3, 171.9;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -165.5 (ddd,  $^2J_{\text{FP}} = 80.1$  Hz,  $^3J_{\text{FH}} = 22.3$ , 16.8 Hz);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  8.7 (d,  $^2J_{\text{PF}} = 80.5$  Hz); HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{28}\text{FNaO}_7\text{PS}$  [ $\text{M} + \text{Na}$ ] $^+$  461.1170, found 461.1169.

**3d.** Prepared from  $\text{Cs}_2\text{CO}_3$  (100 mg, 0.30 mmol), **1** (93 mg, 0.3 mmol), and **2d** (35 mg, 0.36 mmol) in 4 h at rt giving **3d** (63%  $^{19}\text{F}$  NMR yield). (*E*)-**3d** (36 mg, 29%) a colorless liquid:  $R_f = 0.50$  (hexane-EtOAc, 1:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.28 (t, 3H,  $J = 7.1$  Hz), 1.36 (t, 3H,  $J = 7.1$  Hz), 1.37 (t, 3H,  $J = 7.1$  Hz), 4.15–4.23 (m, 2H), 4.24–4.40 (m, 4H), 5.97 (dd, 1H,  $J = 15.7$  Hz,  $^4J_{\text{FH}} = 4.1$  Hz), 7.15 (ddd, 1H,  $^3J_{\text{FH}} = 24.3$  Hz,  $J = 15.7$  Hz,  $^3J_{\text{PH}} = 3.1$  Hz), 7.53–7.59 (m, 2H), 7.68–7.74 (m, 1H), 7.89–7.93 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 16.2, 16.3, 61.1, 65.6 (d,  $^2J_{\text{CP}} = 7.2$  Hz), 65.7 (d,  $^2J_{\text{CP}} = 6.9$  Hz), 106.0 (dd,  $^1J_{\text{CF}} = 238.8$  Hz,  $^1J_{\text{CP}} = 165.1$  Hz), 125.6 (dd,  $^2J_{\text{CF}} = 10.5$  Hz,  $^2J_{\text{CP}} = 7.8$  Hz), 128.1, 130.1, 133.5, 133.6, 134.5, 163.5;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -168.5 (dd,  $^2J_{\text{FP}} = 74.2$  Hz,  $^3J_{\text{FH}} = 24.3$  Hz);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  5.2 (d,  $^2J_{\text{PF}} = 74.2$  Hz); HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{23}\text{FO}_7\text{PS}$  [ $\text{M} + \text{H}$ ] $^+$  409.0881, found 409.0880.

**3e.** Prepared from  $\text{Cs}_2\text{CO}_3$  (100 mg, 0.30 mmol), **1** (93 mg, 0.3 mmol), and **2e** (46 mg, 0.30 mmol) in 3 h at rt giving a 1:1 mixture of diastereomers of **3e** (78 mg, 56%) as a colorless liquid:  $R_f = 0.48$  (EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.26 (t, 6H,  $J = 7.2$  Hz), 1.28 (t, 3H,  $J = 7.3$  Hz), 1.31 (t, 3H,  $J = 7.1$  Hz), 2.17–2.41 (m, 2H), 2.59–2.81 (m, 2H), 2.99 (ddd, 1H,  $^2J_{\text{HH}} = 16.5$  Hz,  $^3J_{\text{HH}} = 13.5$ , 4.8 Hz), 3.17 (ddd, 1H,  $^2J_{\text{HH}} = 16.5$  Hz,  $^3J_{\text{HH}} = 13.5$ , 4.7 Hz), 3.34 (ddd, 1H,  $^2J_{\text{HH}} = 16.6$  Hz,  $^3J_{\text{HH}} = 13.6$ , 4.6 Hz), 3.52 (ddd, 1H,  $^2J_{\text{HH}} = 16.1$  Hz,  $^3J_{\text{HH}} = 13.5$ , 4.4 Hz), 4.07–4.28 (m, 8H), 7.48–7.61 (m, 14H), 7.68–7.73 (m, 2H), 7.85–7.93 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  16.1 (d,  $^3J_{\text{CP}} = 3.3$  Hz), 16.2 (d,  $^3J_{\text{CP}} = 3.1$  Hz), 16.2 (d,  $^3J_{\text{CP}} = 2.4$  Hz), 16.3 (d,  $^3J_{\text{CP}} = 3.6$  Hz), 23.9 (dd,  $^2J_{\text{CF}} = 20.4$  Hz,  $^2J_{\text{CP}} = 2.4$  Hz), 23.9 (dd,  $^2J_{\text{CF}} = 20.0$  Hz,  $^2J_{\text{CP}} = 2.3$  Hz), 49.0 (dd,  $^3J_{\text{CF}} = 7.0$  Hz,  $^3J_{\text{CP}} = 3.7$  Hz), 49.1 (dd,  $^3J_{\text{CF}} = 6.6$  Hz,  $^3J_{\text{CP}} = 2.5$  Hz), 64.9 (d,  $^2J_{\text{CP}} = 7.1$  Hz), 65.0 (d,  $^2J_{\text{CP}} = 7.1$  Hz), 65.0 (d,  $^2J_{\text{CP}} = 7.2$  Hz), 65.1 (d,  $^2J_{\text{CP}} = 6.5$  Hz), 106.2 (dd,  $^1J_{\text{CF}} = 230.1$  Hz,  $^1J_{\text{CP}} = 164.5$  Hz), 106.3 (dd,  $^1J_{\text{CF}} = 229.7$  Hz,  $^1J_{\text{CP}} = 163.8$  Hz), 124.0, 124.0, 128.8, 128.8, 129.2, 129.2, 130.7, 130.7, 131.0, 131.0, 134.8, 134.8, 134.8, 134.9, 142.4, 142.6;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -164.1 (ddd,  $^2J_{\text{FP}} = 79.3$  Hz,  $^3J_{\text{FH}} = 23.6$ , 16.5 Hz), -163.6 (ddd,  $^2J_{\text{FP}} = 79.2$  Hz,  $^3J_{\text{FH}} = 23.9$ , 15.2 Hz);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  8.0 (d,  $^2J_{\text{PF}} = 79.3$  Hz), 8.1 (d,  $^2J_{\text{PF}} = 79.2$  Hz); HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{25}\text{FO}_6\text{P}_2$  [ $\text{M} + \text{H}$ ] $^+$  463.0809, found 463.0809.

**3f.** Prepared from  $\text{Cs}_2\text{CO}_3$  (200 mg, 0.60 mmol), **1** (93 mg, 0.3 mmol), and **2f** (36 mg, 0.36 mmol) in 21 h at rt giving a 3:1 mixture of diastereomers of **3f** (59 mg, 48%) as a colorless liquid:  $R_f = 0.34$  (hexane-EtOAc, 1:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.20–1.40 (m, 9H, major), 1.20–1.40 (m, 9H, minor), 2.20–2.37 (m, 1H, major), 2.20–2.37 (m, 1H, minor), 2.80–2.96 (m, 1H, major), 2.96–3.08 (m, 1H, minor), 3.11–3.21 (m, 1H, major), 3.11–3.21 (m, 1H, minor), 3.59 (s, 3H, major), 3.69 (s, 3H, minor), 4.12–4.35 (m, 4H, major), 4.12–4.35 (m, 4H, minor), 7.55–7.64 (m, 2H, major), 7.55–7.64 (m, 2H, minor), 7.69–7.75 (m, 1H, major), 7.69–7.75 (m, 1H, minor), 7.97–8.05 (m, 2H, major), 7.97–8.05 (m, 2H, minor);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  16.2 (d,  $^3J_{\text{CP}} = 2.1$  Hz, major), 16.2 (d,  $^3J_{\text{CP}} = 2.1$  Hz, minor), 16.3 (d,  $^3J_{\text{CP}} = 2.1$  Hz, major), 16.3 (d,  $^3J_{\text{CP}} = 2.1$  Hz, minor), 18.9 (minor), 19.5 (major), 33.7 (dd,  $^2J_{\text{CF}} = 18.2$  Hz,  $^2J_{\text{CP}} = 2.1$  Hz, minor), 34.3 (dd,  $^2J_{\text{CF}} = 18.5$  Hz,  $^2J_{\text{CP}} = 2.1$  Hz, major), 34.7 (dd,  $^2J_{\text{CF}} = 4.2$  Hz,  $^3J_{\text{CP}} = 2.0$  Hz, major), 34.8 (dd,  $^2J_{\text{CF}} = 4.2$  Hz,  $^3J_{\text{CP}} = 2.2$  Hz, minor), 51.7 (major), 51.9 (minor), 64.6 (d,  $^2J_{\text{CP}} = 6.9$  Hz, minor), 64.8 (d,  $^2J_{\text{CP}} = 7.0$  Hz, major), 64.8 (d,  $^2J_{\text{CP}} = 6.9$  Hz, minor), 64.9 (d,  $^2J_{\text{CP}} = 6.8$  Hz, major), 107.0 (dd,  $^1J_{\text{CF}} = 231.3$  Hz,  $^1J_{\text{CP}} = 165.0$  Hz, major), 107.2 (dd,  $^1J_{\text{CF}} = 231.3$  Hz,  $^1J_{\text{CP}} = 165.9$  Hz, minor), 128.6 (major), 129.1 (minor), 130.8 (d,  $^3J_{\text{CF}} = 1.4$  Hz, major), 130.9 (d,  $^3J_{\text{CF}} = 1.3$  Hz, minor), 134.6 (major), 134.9 (minor), 135.2 (major), 135.4

(minor), 175.6 (major), 175.9 (minor);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -167.5 (ddd,  $^2J_{\text{FP}} = 81.7$  Hz,  $^3J_{\text{FH}} = 20.9$ , 20.9 Hz, minor), -167.9 (ddd,  $^2J_{\text{FP}} = 81.0$  Hz,  $^3J_{\text{FH}} = 30.8$ , 12.8 Hz, major);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  8.5 (d,  $^2J_{\text{PF}} = 81.8$  Hz, minor), 8.9 (d,  $^2J_{\text{PF}} = 81.0$  Hz, major); HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{24}\text{FNaO}_7\text{PS}$  [ $\text{M} + \text{Na}$ ] $^+$  433.0857, found 433.0855.

**3g.** Prepared from  $\text{Cs}_2\text{CO}_3$  (100 mg, 0.30 mmol), **1** (93 mg, 0.3 mmol), and **2g** (49 mg, 0.30 mmol) in 25 h at rt giving **3g** (98 mg, 69%) as a colorless liquid:  $R_f = 0.18$  (EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (t, 3H,  $J = 7.1$  Hz), 1.32 (t, 6H,  $J = 7.1$  Hz), 1.33 (t, 3H,  $J = 7.1$  Hz), 2.05–2.16 (m, 1H), 2.23–2.37 (m, 1H), 2.45–2.63 (m, 2H), 4.05–4.15 (m, 4H), 4.16–4.30 (m, 4H), 7.56–7.62 (m, 2H), 7.70–7.75 (m, 1H), 7.97–8.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  16.2 (d,  $^3J_{\text{CP}} = 3.7$  Hz), 16.3 (d,  $^3J_{\text{CP}} = 3.9$  Hz), 16.4 (d,  $^3J_{\text{CP}} = 6.2$  Hz), 16.4 (d,  $^3J_{\text{CP}} = 6.2$  Hz), 19.5 (ddd,  $^1J_{\text{CF}} = 142.7$  Hz,  $^3J_{\text{CF}} = 6.0$  Hz,  $^3J_{\text{CP}} = 2.4$  Hz), 25.3 (ddd,  $^2J_{\text{CF}} = 20.1$  Hz,  $^2J_{\text{CP}} = 2.0$ , 2.0 Hz), 61.7 (d,  $^2J_{\text{CP}} = 1.8$  Hz), 61.8 (d,  $^2J_{\text{CP}} = 1.8$  Hz), 64.7 (d,  $^2J_{\text{CP}} = 7.0$  Hz), 65.0 (d,  $^2J_{\text{CP}} = 6.7$  Hz), 106.4 (ddd,  $^1J_{\text{CF}} = 229.9$  Hz,  $^1J_{\text{CP}} = 164.9$  Hz,  $^3J_{\text{CP}} = 18.9$  Hz), 128.7, 130.8 (d,  $^3J_{\text{CF}} = 1.2$  Hz), 134.7, 135.1;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -165.0 (ddd,  $^2J_{\text{FP}} = 80.4$  Hz,  $^3J_{\text{FH}} = 19.8$ , 19.5 Hz);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  8.5 (d,  $^2J_{\text{PF}} = 80.4$  Hz), 29.4 (d,  $^4J_{\text{PF}} = 3.6$  Hz); HRMS (ESI) calcd for  $\text{C}_{17}\text{H}_{30}\text{FO}_8\text{P}_2\text{S}$  [ $\text{M} + \text{H}$ ] $^+$  475.1115, found 475.1113.

**General Procedure for the Synthesis of Compounds 5.** Mg turnings (48 mg, 2 mmol, 10 equiv) were placed in a Schlenk flask followed by addition of MeOH (1.5 mL) and a solution of **3** (0.2 mmol, 1.0 equiv) in MeOH (0.3 mL). The reaction mixture was stirred at rt, followed by addition of 1 M HCl (10 mL) and extraction into  $\text{Et}_2\text{O}$  ( $3 \times 15$  mL). The combined organic phase was washed with brine (10 mL) and dried, and solvent was removed under reduced pressure. Purification by silica gel column chromatography using hexane/EtOAc as eluent gave products **5**.

**5a.** Prepared from **3a** (76 mg, 0.2 mmol) in 1 h at rt giving **5a** (32 mg, 66%) as a colorless liquid:  $R_f = 0.30$  (hexane-EtOAc, 1:2);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (t, 6H,  $J = 7.1$  Hz), 2.07–2.28 (m, 2H), 2.14 (s, 3H), 2.59–2.78 (m, 2H), 4.15 (q, 2H,  $J = 7.1$  Hz), 4.19 (q, 2H,  $J = 7.1$  Hz), 4.73 (dddd, 1H,  $^2J_{\text{FH}} = 46.6$  Hz,  $^2J_{\text{PH}} = 9.5$  Hz,  $^3J_{\text{HH}} = 4.2$ , 3.2 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  16.3 (d,  $^3J_{\text{CP}} = 2.9$  Hz), 16.4 (d,  $^3J_{\text{CP}} = 3.0$  Hz), 24.1 (dd,  $^2J_{\text{CF}} = 20.3$  Hz,  $^2J_{\text{CP}} = 1.5$  Hz), 29.9, 38.2 (dd,  $^3J_{\text{CF}} = 11.1$  Hz,  $^3J_{\text{CP}} = 4.2$  Hz), 62.8 (d,  $^2J_{\text{CP}} = 6.7$  Hz), 63.2 (d,  $^2J_{\text{CP}} = 6.9$  Hz), 87.7 (dd,  $^1J_{\text{CF}} = 179.4$  Hz,  $^1J_{\text{CP}} = 170.9$  Hz), 206.8;  $^{19}\text{F}$  { $^1\text{H}$ } NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -210.8 (d,  $^2J_{\text{PF}} = 75.8$  Hz);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  17.5 (d,  $^2J_{\text{PF}} = 75.7$  Hz); HRMS (ESI) calcd for  $\text{C}_9\text{H}_{18}\text{FO}_4\text{P}$  [ $\text{M}$ ] $^+$  240.0927, found 240.0925.

**5c.** Prepared from **3c** (88 mg, 0.2 mmol) in 2 h at rt giving **5c** (45 mg, 87%) as a colorless liquid:  $R_f = 0.44$  (hexane-EtOAc, 1:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.37 (t, 6H,  $J = 7.1$  Hz), 2.16–2.34 (m, 2H), 2.49–2.66 (m, 2H), 3.70 (s, 3H), 4.20 (q, 2H,  $J = 7.1$  Hz), 4.23 (q, 2H,  $J = 7.1$  Hz), 4.80 (dddd, 1H,  $^2J_{\text{FH}} = 46.8$  Hz,  $^2J_{\text{PH}} = 8.2$  Hz,  $^3J_{\text{HH}} = 5.6$ , 3.8 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  16.3 (d,  $^3J_{\text{CP}} = 2.7$  Hz), 16.4 (d,  $^3J_{\text{CP}} = 2.7$  Hz), 25.5 (d,  $^2J_{\text{CF}} = 20.2$  Hz), 29.1 (dd,  $^3J_{\text{CF}} = 12.7$  Hz,  $^3J_{\text{CP}} = 4.6$  Hz), 51.6, 62.8 (d,  $^2J_{\text{CP}} = 6.6$  Hz), 63.2 (d,  $^2J_{\text{CP}} = 6.8$  Hz), 87.5 (dd,  $^1J_{\text{CF}} = 180.0$  Hz,  $^1J_{\text{CP}} = 171.2$  Hz), 172.6;  $^{19}\text{F}$  { $^1\text{H}$ } NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -211.5 (d,  $^2J_{\text{PF}} = 75.2$  Hz);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  17.3 (d,  $^2J_{\text{PF}} = 75.2$  Hz); HRMS (ESI) calcd for  $\text{C}_9\text{H}_{18}\text{FNaO}_3\text{P}$  [ $\text{M} + \text{Na}$ ] $^+$  279.0768, found 279.0768.

#### General Procedure for the Synthesis of Compounds 6 and 7.

NaH (10 mg, 0.40 mmol, 2 equiv) and THF (2 mL) were placed in a Schlenk flask. The resulting suspension was cooled to 0 °C, and a solution of **1** (128 mg, 0.40 mmol, 2 equiv) in THF (0.5 mL) was added. The color of the solution became yellow, and after a few minutes a solution of **2** (0.20 mmol, 1 equiv) in THF (0.5 mL) was added. The reaction mixture was allowed to warm to rt, and after 1–2 h a solution of saturated  $\text{NH}_4\text{Cl}$  (20 mL) was added. The product was extracted into  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL) and dried, and solvent was removed under reduced pressure. Purification by silica gel column chromatography using hexane/EtOAc as eluent gave products **6** and **7**.

**7h.** Prepared from **2h** (42 mg, 0.2 mmol) in 1 h giving **7h** as a colorless oil (74 mg, 72%). Silica gel column chromatography and crystallization gave *anti*-**7h** (37 mg) as colorless crystals: mp 90–91 °C

(Et<sub>2</sub>O–pentane); *R<sub>f</sub>* 0.60 (hexane–EtOAc, 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.17 (td, 3H, *J* = 7.1 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.1 Hz), 1.31 (td, 3H, *J* = 7.1 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.1 Hz), 3.91–4.29 (m, 4H), 4.94 (ddd, 1H, <sup>3</sup>*J*<sub>HF</sub> = 28.4 Hz, <sup>3</sup>*J*<sub>HH</sub> = 10.1, 4.5 Hz), 5.69 (dd, 1H, <sup>2</sup>*J*<sub>HF</sub> = 46.4 Hz, <sup>3</sup>*J*<sub>HH</sub> = 4.5 Hz), 5.89 (dd, 1H, <sup>3</sup>*J*<sub>HH</sub> = 10.1 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.9 Hz), 7.22–7.27 (m, 3H), 7.31–7.39 (m, 5H), 7.42–7.48 (m, 2H), 7.51–7.55 (m, 2H), 7.56–7.61 (m, 1H), 7.78–7.82 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 15.9 (d, <sup>3</sup>*J*<sub>CP</sub> = 6.9 Hz), 16.1 (d, <sup>3</sup>*J*<sub>CP</sub> = 6.9 Hz), 42.0 (dd, <sup>2</sup>*J*<sub>CF</sub> = 18.2 Hz, <sup>4</sup>*J*<sub>CP</sub> = 1.2 Hz), 64.7 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.0 Hz), 64.8 (d, <sup>2</sup>*J*<sub>CP</sub> = 5.9 Hz), 104.0 (dd, <sup>1</sup>*J*<sub>CF</sub> = 225.2 Hz, <sup>5</sup>*J*<sub>CP</sub> = 2.4 Hz), 113.4 (dd, <sup>3</sup>*J*<sub>CP</sub> = 7.1 Hz, <sup>3</sup>*J*<sub>CF</sub> = 4.7 Hz), 126.1, 127.7, 128.3, 128.5, 128.9, 129.1, 129.2, 129.3, 134.0, 134.7 (d, <sup>3</sup>*J*<sub>CF</sub> = 1.2 Hz), 136.0 (d, <sup>3</sup>*J*<sub>CF</sub> = 0.9 Hz), 136.6, 147.4 (d, <sup>2</sup>*J*<sub>CP</sub> = 8.7 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –185.0 (dd, <sup>2</sup>*J*<sub>HF</sub> = 46.4 Hz, <sup>3</sup>*J*<sub>HF</sub> = 28.4 Hz); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ –5.7 (s); HRMS (ESI) calcd for C<sub>26</sub>H<sub>28</sub>FN<sub>2</sub>O<sub>6</sub>PS [M + Na]<sup>+</sup> 541.1221, found 541.1219. **syn-7h** (26 mg) as colorless oil: *R<sub>f</sub>* 0.56 (hexane–EtOAc 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.17–1.22 (m, 6H), 3.92–4.13 (m, 4H), 5.10 (ddd, 1H, <sup>3</sup>*J*<sub>HF</sub> = 30.0 Hz, <sup>3</sup>*J*<sub>HH</sub> = 9.5, 2.3 Hz), 5.34 (dd, 1H, <sup>2</sup>*J*<sub>HF</sub> = 46.6 Hz, <sup>3</sup>*J*<sub>HH</sub> = 2.5 Hz), 5.87 (dd, 1H, <sup>3</sup>*J*<sub>HH</sub> = 9.5 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.5 Hz), 7.25–7.36 (m, 6H), 7.38–7.46 (m, 4H), 7.47–7.53 (m, 2H), 7.57–7.62 (m, 1H), 7.93–7.97 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 16.0 (d, <sup>3</sup>*J*<sub>CP</sub> = 6.8 Hz), 16.0 (d, <sup>3</sup>*J*<sub>CP</sub> = 6.8 Hz), 41.3 (d, <sup>2</sup>*J*<sub>CF</sub> = 17.4 Hz), 64.5 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.0 Hz), 64.6 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.0 Hz), 104.5 (d, <sup>1</sup>*J*<sub>CF</sub> = 227.3 Hz), 110.4 (dd, <sup>3</sup>*J*<sub>CP</sub> = 7.2 Hz, <sup>3</sup>*J*<sub>CF</sub> = 7.1 Hz), 126.1, 127.6, 128.1, 128.3, 128.9, 129.0, 129.2, 129.6, 134.3, 134.8 (d, <sup>3</sup>*J*<sub>CF</sub> = 1.3 Hz), 136.4, 138.7 (d, <sup>3</sup>*J*<sub>CF</sub> = 1.9 Hz), 148.4 (d, <sup>2</sup>*J*<sub>CP</sub> = 9.2 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –186.3 (dd, <sup>2</sup>*J*<sub>HF</sub> = 46.5 Hz, <sup>3</sup>*J*<sub>HF</sub> = 30.0 Hz); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ –6.4 (s); HRMS (ESI) calcd for C<sub>26</sub>H<sub>28</sub>FN<sub>2</sub>O<sub>6</sub>PS [M + Na]<sup>+</sup> 541.1221, found 541.1219.

**7l**. Prepared from **2l** (44 mg, 0.2 mmol) in 1.5 h giving **7l** as a pale yellow oil (72 mg, 68%). **major-7l**, a colorless oil: *R<sub>f</sub>* 0.55 (hexane–EtOAc 1:1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.17 (td, 3H, <sup>3</sup>*J*<sub>HH</sub> = 7.0 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.1 Hz), 1.32 (td, 3H, <sup>3</sup>*J*<sub>HH</sub> = 7.0 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.1 Hz), 2.29 (s, 3H), 3.91–4.28 (m, 4H), 4.91 (ddd, 1H, <sup>3</sup>*J*<sub>HF</sub> = 28.8 Hz, <sup>3</sup>*J*<sub>HH</sub> = 10.1, 4.4 Hz), 5.68 (dd, 1H, <sup>2</sup>*J*<sub>HF</sub> = 46.4 Hz, <sup>3</sup>*J*<sub>HH</sub> = 4.4 Hz), 5.87 (dd, 1H, <sup>3</sup>*J*<sub>HH</sub> = 10.1 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.9 Hz), 7.04–7.09 (m, 2H), 7.23–7.27 (m, 2H), 7.34 (m, 3H), 7.42–7.47 (m, 2H), 7.50–7.54 (m, 2H), 7.58–7.61 (m, 1H), 7.78–7.82 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 15.9 (d, <sup>3</sup>*J*<sub>CP</sub> = 6.9 Hz), 16.0 (d, <sup>3</sup>*J*<sub>CP</sub> = 6.9 Hz), 21.1, 41.6 (dd, <sup>2</sup>*J*<sub>CF</sub> = 18.2 Hz, <sup>4</sup>*J*<sub>CP</sub> = 1.3 Hz), 64.6 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.0 Hz), 64.8 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.0 Hz), 104.2 (dd, <sup>1</sup>*J*<sub>CF</sub> = 224.9 Hz, <sup>5</sup>*J*<sub>CP</sub> = 2.4 Hz), 113.6 (dd, <sup>3</sup>*J*<sub>CP</sub> = 6.9 Hz, <sup>3</sup>*J*<sub>CF</sub> = 4.6 Hz), 126.1, 128.2, 128.9, 129.1, 129.1, 129.2, 129.3, 132.9 (d, <sup>3</sup>*J*<sub>CF</sub> = 1.1 Hz), 133.9, 134.7 (d, <sup>3</sup>*J*<sub>CF</sub> = 1.3 Hz), 136.7, 137.3, 147.2 (d, <sup>2</sup>*J*<sub>CP</sub> = 8.7 Hz); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δ –185.4 (dd, <sup>2</sup>*J*<sub>HF</sub> = 46.4 Hz, <sup>3</sup>*J*<sub>HF</sub> = 28.9 Hz); <sup>31</sup>P NMR (203 MHz, CDCl<sub>3</sub>) δ –5.7 (s); HRMS (ESI) calcd for C<sub>27</sub>H<sub>31</sub>FO<sub>6</sub>PS [M + H]<sup>+</sup> 533.1558, found 533.1559. **minor-7l**, a pale yellow oil: *R<sub>f</sub>* 0.50 (hexane–EtOAc, 1:1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.19 (td, 3H, <sup>3</sup>*J*<sub>HH</sub> = 7.1 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.1 Hz), 1.21 (td, 3H, <sup>3</sup>*J*<sub>HH</sub> = 7.0 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.1 Hz), 2.31 (s, 3H), 3.93–4.16 (m, 4H), 5.05 (ddd, 1H, <sup>3</sup>*J*<sub>HF</sub> = 29.5 Hz, <sup>3</sup>*J*<sub>HH</sub> = 9.6, 2.6 Hz), 5.33 (dd, 1H, <sup>2</sup>*J*<sub>HF</sub> = 46.6 Hz, <sup>3</sup>*J*<sub>HH</sub> = 2.7 Hz), 5.84 (dd, 1H, <sup>3</sup>*J*<sub>HH</sub> = 9.6 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.5 Hz), 7.11–7.15 (m, 2H), 7.27–7.33 (m, 5H), 7.41–7.45 (m, 2H), 7.47–7.52 (m, 2H), 7.56–7.62 (m, 1H), 7.92–7.96 (m, 2H); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δ –185.9 (dd, <sup>2</sup>*J*<sub>HF</sub> = 46.6 Hz, <sup>3</sup>*J*<sub>HF</sub> = 29.5 Hz); <sup>31</sup>P NMR (203 MHz, CDCl<sub>3</sub>) δ –6.3 (s).

**7m**. Prepared from **2m** (29 mg, 0.2 mmol) in 1 h giving **7m** as a pale yellow oil (62 mg, 68%). **major-7m** (46 mg), a pale yellow liquid: *R<sub>f</sub>* 0.71 (hexane–EtOAc, 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.15 (t, 3H, *J* = 7.1 Hz), 1.32 (t, 3H, *J* = 7.1 Hz), 1.41 (d, 3H, *J* = 6.8 Hz), 3.80–4.30 (m, 5H), 5.44 (dd, 1H, <sup>2</sup>*J*<sub>HF</sub> = 47.5 Hz, <sup>3</sup>*J*<sub>HH</sub> = 3.3 Hz), 5.52 (dd, 1H, <sup>3</sup>*J*<sub>HH</sub> = 9.4 Hz, <sup>4</sup>*J*<sub>PH</sub> = 2.0 Hz), 7.31–7.36 (m, 3H), 7.50–7.54 (m, 2H), 7.55–7.61 (m, 2H), 7.65–7.70 (m, 1H), 7.97–8.01 (m, 2H, C<sub>Ar</sub>H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.1 (d, <sup>3</sup>*J*<sub>CP</sub> = 5.3 Hz), 15.8 (d, <sup>3</sup>*J*<sub>CP</sub> = 7.1 Hz), 16.0 (d, <sup>3</sup>*J*<sub>CP</sub> = 7.0 Hz), 30.9 (d, <sup>2</sup>*J*<sub>CF</sub> = 19.4 Hz), 64.5 (d, <sup>2</sup>*J*<sub>CP</sub> = 5.9 Hz), 64.7 (d, <sup>2</sup>*J*<sub>CP</sub> = 5.9 Hz), 103.7 (d, <sup>1</sup>*J*<sub>CF</sub> = 223.7 Hz), 115.8 (dd, <sup>3</sup>*J*<sub>CP</sub> = 6.7 Hz, <sup>3</sup>*J*<sub>CF</sub> = 2.7 Hz), 126.0, 128.2, 129.0, 129.1, 129.2, 134.2, 134.8, 137.2, 146.9 (d, <sup>2</sup>*J*<sub>CP</sub> = 8.5 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –191.3 (dd, <sup>2</sup>*J*<sub>HF</sub> = 47.0 Hz, <sup>3</sup>*J*<sub>HF</sub> = 27.6 Hz); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ –5.6 (s); HRMS (ESI) calcd for

C<sub>21</sub>H<sub>26</sub>FN<sub>2</sub>O<sub>6</sub>PS [M + Na]<sup>+</sup> 479.1064, found 479.1062. **minor-7m** (16 mg), a pale yellow oil: *R<sub>f</sub>* 0.48 (hexane–EtOAc, 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.21 (t, 3H, *J* = 7.1 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 1.42 (d, 3H, *J* = 7.0 Hz), 3.78–3.92 (m, 1H), 3.95–4.22 (m, 4H), 5.16 (dd, 1H, <sup>2</sup>*J*<sub>HF</sub> = 46.5 Hz, <sup>3</sup>*J*<sub>HH</sub> = 3.9 Hz), 5.49 (dd, 1H, <sup>3</sup>*J*<sub>HH</sub> = 9.9 Hz, <sup>4</sup>*J*<sub>PH</sub> = 1.5 Hz), 7.29–7.34 (m, 3H), 7.43–7.47 (m, 2H), 7.47–7.53 (m, 2H), 7.56–7.62 (m, 1H), 7.92–7.96 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 15.9 (d, <sup>3</sup>*J*<sub>CP</sub> = 7.0 Hz), 16.0 (d, <sup>3</sup>*J*<sub>CP</sub> = 7.0 Hz), 16.9 (d, <sup>3</sup>*J*<sub>CF</sub> = 2.2 Hz), 32.0 (dd, <sup>2</sup>*J*<sub>CF</sub> = 18.7 Hz, <sup>4</sup>*J*<sub>CP</sub> = 1.2 Hz), 64.5 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.4 Hz), 64.6 (d, <sup>2</sup>*J*<sub>CP</sub> = 6.5 Hz), 104.5 (dd, <sup>1</sup>*J*<sub>CF</sub> = 223.6 Hz, <sup>5</sup>*J*<sub>CP</sub> = 1.3 Hz), 113.7 (dd, <sup>3</sup>*J*<sub>CP</sub> = 6.6 Hz, <sup>3</sup>*J*<sub>CF</sub> = 6.6 Hz), 125.9, 128.1, 128.8, 129.1, 129.4, 134.2, 134.9, 136.7, 147.4 (d, <sup>2</sup>*J*<sub>CP</sub> = 9.1 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –183.4 (dd, <sup>2</sup>*J*<sub>HF</sub> = 46.4 Hz, <sup>3</sup>*J*<sub>HF</sub> = 22.8 Hz); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ –6.0 (s); HRMS (ESI) calcd for C<sub>21</sub>H<sub>26</sub>FN<sub>2</sub>O<sub>6</sub>PS [M + Na]<sup>+</sup> 479.1064, found 479.1063.

**8h**. A mixture of **7h** (52 mg, 0.1 mmol) and 36% aqueous HCl (2 mL) was heated at 70 °C for 20 h. A saturated solution of NaHCO<sub>3</sub> (10 mL) was added, and the product was extracted into Et<sub>2</sub>O (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried (MgSO<sub>4</sub>), and solvent was removed under reduced pressure. Purification by silica gel column chromatography using hexane/EtOAc gave **8h** as a pale yellow liquid (28 mg, 75%). **major-8h** (12 mg), a pale yellow oil: *R<sub>f</sub>* 0.49 (hexane–EtOAc, 4:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.68 (dd, 1H, <sup>2</sup>*J*<sub>HH</sub> = 18.0 Hz, <sup>3</sup>*J*<sub>HH</sub> = 10.2 Hz), 3.94 (dd, 1H, <sup>2</sup>*J*<sub>HH</sub> = 17.9 Hz, <sup>3</sup>*J*<sub>HH</sub> = 2.9 Hz), 4.53 (dddd, 1H, <sup>3</sup>*J*<sub>HF</sub> = 30.4 Hz, <sup>3</sup>*J*<sub>HH</sub> = 10.1, 2.7, 2.0 Hz), 5.30 (dd, 1H, <sup>2</sup>*J*<sub>HF</sub> = 47.6 Hz, <sup>3</sup>*J*<sub>HH</sub> = 1.9 Hz), 7.20–7.31 (m, 3H), 7.34–7.38 (m, 2H), 7.41–7.46 (m, 2H), 7.51–7.61 (m, 3H), 7.66–7.72 (m, 1H), 7.90–7.97 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 38.5 (d, <sup>3</sup>*J*<sub>CF</sub> = 5.0 Hz), 39.2 (d, <sup>2</sup>*J*<sub>CF</sub> = 17.6 Hz), 104.5 (d, <sup>1</sup>*J*<sub>CF</sub> = 226.1 Hz), 127.7, 128.0, 128.2, 128.6, 128.9, 129.3, 129.4, 133.2, 134.6, 136.3, 136.6, 139.6, 196.2; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –185.1 (dd, <sup>2</sup>*J*<sub>HF</sub> = 47.6 Hz, <sup>3</sup>*J*<sub>HF</sub> = 30.3 Hz); HRMS (ESI) calcd for C<sub>22</sub>H<sub>19</sub>FN<sub>2</sub>O<sub>3</sub>S [M + Na]<sup>+</sup> 405.0931, found 405.0932. **minor-8h** (isolated in a mixture with **major-8h** 65:35, 16 mg): *R<sub>f</sub>* 0.44 (hexane–EtOAc, 4:1).

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Conformational analysis of *syn*- and *anti*-**7h**. Copies of <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F, and <sup>31</sup>P NMR spectra of newly synthesized products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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