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Nucleophilic Difluoromethylenation of Ketones Using Diethyl (Difluoro(trimethylsilyl)methyl)phosphonate Mediated by 18-Crown-6 Ether/KOAc

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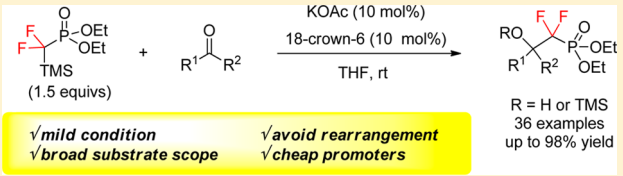
Supporting Information

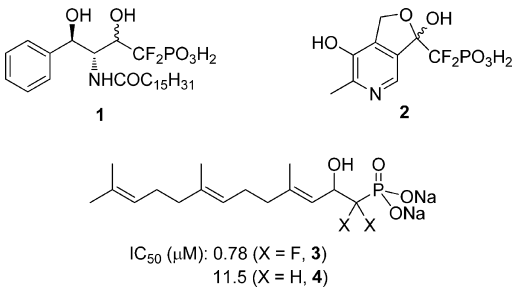
ABSTRACT: We report a general difluoromethylenation of various types of ketones using diethyl (difluoro(trimethylsilyl)-methyl)phosphonate mediated by the combination of 18-crown-6 and KOAc. It provides facile access to structurally diverse β-hydroxy-α,α-difluorophosphonates as interesting targets for medicinal research.



INTRODUCTION

The selective incorporation of a difluoroalkyl group has become a routine and effective approach to modulate the biological activities of organic molecules in drug design.[1,2] In this scenario, the difluorophosphonate unit has drawn special attention due to its potential as an analogue of biologically important phosphate esters and application in new drug development.[3] In particular, β-hydroxy-α,α-difluorophosphonate is a prominent structural motif that occurs in bioactive compounds.[4] As shown in Scheme 1, compound **1**, the analogue of sphingomyelin,

Scheme 1. Representative Bioactive Compounds



inhibits tumor necrosis factor (TNF)-α-induced cell death of PC-12 neurons at a low concentration of 0.1 μM.[4a] Difluoroketophosphonate **2** is able to reduce infarct size in the rat model of ischemia reperfusion injury.[4b] Farnesyl transferase inhibitor **3**, with a difluoromethylene group at the α-position of the phosphonate group, shows a 15-fold increase in inhibition over the nonfluorinated analogue **4**.[4c] Therefore, it is highly desirable to develop new methods to prepare β-hydroxy-α,α-difluoromethylphosphonates.

In this context, a straightforward method is the addition of (diethylphosphinyl)difluoromethyl carbanion to carbonyl compounds. A common method is the use of strong bases such as LDA to deprotonate diethyl (difluoromethyl)phosphonate to react with aldehydes or ketones,[4d,5] which are usually carried out at low reaction temperature. To make the reaction conditions milder, the use of diethyl (difluoro(trimethylsilyl)-methyl)phosphonate **5** as a carbanion equivalent becomes popular.[6] For example, Obayashi and Kondo reported the use of a catalytic amount of CsF to mediate the reaction of carbonyl compounds and **5**.[6a] The use of tetrabutylammonium fluoride (TBAF) to promote the reaction of **5** and aldehydes was also tried, albeit with moderate to good yield.[7a−d] Beier also found the tetrabutylammonium difluorotriphenylsilicate (TBAT) as an efficient initiator for the reaction of **5** with various aldehydes.[7e] In addition to fluorides, oxygen-based Lewis basic promoter was also effective, as evidenced by Shibata and Toru's finding that 1,2-bis(diphenylphosphino)ethane/$Cu(OAc)_2$ mediated the reaction of *p*-nitrobenzaldehyde and **5** well.[7f] However, despite these impressive advances in difluoromethylenation of aldehydes using **5**,[6,7] the corresponding processes using ketone substrates are undeveloped in terms of substrate scope and catalyst systems. To our knowledge, only two reports mentioned preliminary results during the corresponding research using aldehydes. Kondo et al. found that CsF could promote the reaction of **5** with two substituted acetophenones as well.[6a] They also observed that, in the presence of 2 mol % CsF, the reaction of **5** and *p*-$NO_2C_6H_4COMe$ afforded the desired adduct in only 38% yield, along with rearrangement product in 27% yield. Beier et al. found that the reaction of **5** with acetone worked well in the presence of TBAT, but no more ketone substrates were tried.[7e] Owing to the importance of tertiary alcohols in drug

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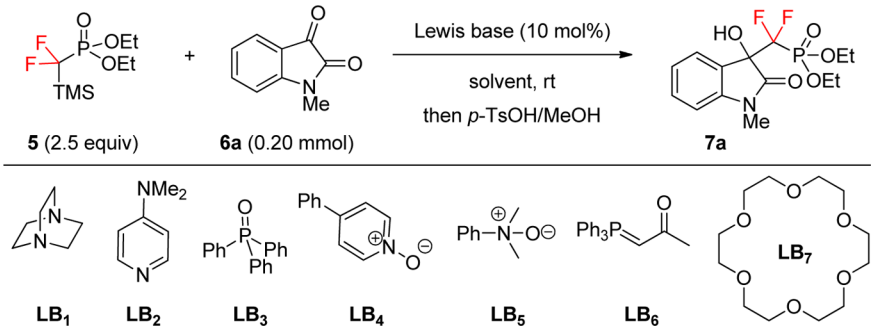
Table 1. Optimization of Conditions



entry	Lewis base	solvent	time (h)	yield[a] (%)
1	KOAc	DMF	12	57
2	LB_7 + KOAc	THF	0.5	86
3	LB_7 + K_2CO_3	THF	20	62
4	LB_7 + K_3PO_4	THF	7	56
5	LB_7 + $KOBu^t$	THF	16	55
6[b]	LB_7 + KOAc	toluene	3.5	90
7[b]	LB_7 + KOAc	MeCN	0.5	90
8[b]	LB_7 + KOAc	CH_2Cl_2	4.0	62
9[c]	LB_7 + KOAc	THF	1.0	87
10[d]	LB_7 + KOAc	THF	2.0	58

[a]Isolated yield. [b]1.0 equiv of KOAc used. [c]1.5 equiv of **5** used. [d]1.2 equiv of **5** used.

development,[8] those featuring a difluoromethylphosphate moiety are interesting targets for medicinal research. Therefore, it is highly desirable to develop efficient methods for the difluoromethylenation of various ketone substrates using reagent **5** for the diverse synthesis of β-hydroxy-α,α-difluorophosphonates.

RESULTS AND DISCUSSION

With our efforts in selective fluoroalkylation,[9] we have found that tertiary or secondary amine based chiral catalysts could activate fluorinated enol silyl ethers to react with activated ketones, ketimines, or Michael acceptors.[10] Based on these results, we wish to use Lewis base promoters other than fluorides to activate difluoro(trimethylsilyl)methylphosphonate **5** for the nucleophilic addition reaction of different ketones, to avoid possible rearrangement reaction caused by fluorides. Herein, we wish to report that the combination of 18-crown-6 and KOAc (10 mol %, each) is found to be powerful for the nucleophilic addition of reagent **5** with a broad scope of ketones.

We began our research with the evaluation of various types of Lewis bases[11] in the reaction of **5** and *N*-methylisatin **6a**, owing to our interests in oxindole chemistry.[12] It is worth mentioning that 3-hydroxyoxindoles widely occur in natural products, drugs, and bioactive compounds,[13] and those with a C3 (diethylphosphinyl)difluoromethylene group are interesting for medicinal research, but the synthesis of which is unknown. Our screenings revealed that the choice of a suitable Lewis base played a key role in reaction development. As shown in Table 1, nitrogen-based Lewis bases LB_1 and LB_2, phosphine oxide LB_3, and nitrogen oxides LB_4 and LB_5, along with phosphorane LB_6, which we found to be a highly active promoter for ketone cyanosilylation using TMSCN,[14] all failed to mediate the desired reaction.

Inspired by literature reports on the use of acetates in DMF to facilitate the addition of trimethylsilyl reagents to carbonyl compounds,[7f,15] we first tried using KOAc to promote the reaction carried out in DMF. The desired product **7a** was obtained in 57% yield after 12 h (entry 1). Considering that the role of DMF as the solvent was possibly to increase the solubility of KOAc, suppress ion-pairing, and make the acetate anion naked and more nucleophilic, we tried using 18-crown-6 LB_7 in combination with KOAc to mediate this reaction, because Liotta et al. had reported that the nucleophilicity of KOAc could be greatly enhanced in the presence of crown ether.[16] As expected, although either 18-crown-6 LB_7 or KOAc alone was unable to mediate this reaction when performed in THF at room temperature, the combination of both allowed the reaction to complete within half an hour, affording the desired product **7a** in 86% isolated yield (entry 2). Based on this result, we further examined the performance of other potassium salts or bases, in combination with 18-crown-6 (entries 3−5), but KOAc still proved to be the best in terms of reactivity and yield of hydroxyoxindole **7a**. Next, the solvent effects were examined by using 18-crown-6 LB_7/KOAc as the promoter (entries 6−8). When using DCM, MeCN, or toluene as the solvent, the reaction proceeded very slowly; 1.0 equiv of KOAc in combination with 10 mol % of 18-crown-6 was required to secure excellent yield of hydroxyoxindole **7a**, and no turnover was observed if only 10 mol % KOAc was used. Possibly, the regeneration of acetate from the resulting alkoxides and AcOTMS in THF was facilitated.[17] Furthermore, it was possible to reduce the amount of reagent **5** from 2.5 equiv to 1.5 equiv, while product **7a** was still obtained in 87% yield (entry 9). But further decreasing the amount of reagent **5** to 1.2 equiv resulted in significantly lower yield of product **7a** (entry 10).

To check whether these conditions could be extended to other ketone substrates, we further examined the reaction of **5** and acetophenone **8a**. To our delight, the reaction in THF mediated by the combination of KOAc and 18-crown-6 could finish within 1 h as well, giving product **9a** in 68% yield. GC−

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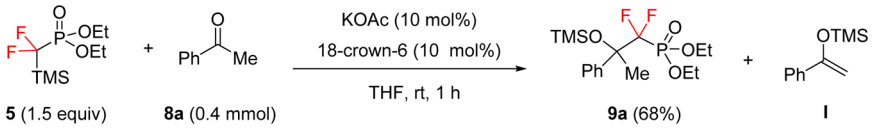
Scheme 2. Control Experiments by Using DMF as Solvent



Control experiments (without the use of 18-crown-6):

1) In THF, 10 mol% *n*-Bu_4NOAc, 27% yield for **9a**, large amount of **I**.

2) In DMF, 10 mol% KOAc, *n*-Bu_4NOAc or LiOAc, 64%, 54% and 45% yield for **9a**, respectively, with **I** detected.

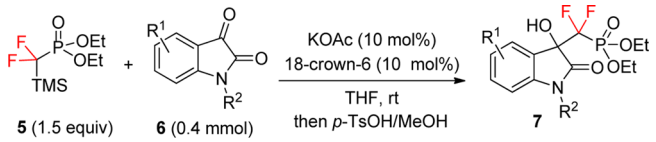
MS and TLC analysis of reaction mixture also revealed the formation of trimethyl((1-phenylvinyl)oxy)silane **I** as the byproduct. On the other hand, the use of *n*-Bu_4NOAc in THF resulted in only 27% yield for **9a**, along with a large amount of **I** by TLC analysis. KOAc, LiOAc, and *n*-Bu_4NOAc in DMF could also mediate this reaction even without 18-crown-6 (Scheme 2), a condition that Mukaiyama et al. developed for trifluoromethylation of carbonyl compounds using $TMSCF_3$.[15a,b] It was found that *n*-Bu_4NOAc and LiOAc promoted the reaction slowly, giving **9a** in 54% and 45% yield, respectively. The use of 10 mol % KOAc enabled the reaction to finish within 1 h, giving product **9a** in 64% yield, comparable to that obtained by our method. In all the cases, **I** was detected by both GC−MS and TLC analysis. It is worth mentioning that although our method involves the use of 18-crown-6, it allows the reactions to be performed in THF, which can be removed by rotary evaporation after the reaction finishes, and then the residue was directly subjected for column chromatography purification. In contrast, the use of DMF as the solvent obviates the use of 18-crown-6, but requires an extraction procedure to remove DMF.

In light of the above screenings, the substrate scope was evaluated by running the reaction in THF, in the presence of 18-crown-6 and KOAc (10 mol %, each), using 1.5 equiv of reagent **5**. To our delight, isatins **6a−i** with different substituents at the C5 or C7 position, no matter whether electron withdrawing or donating, were viable substrates under these conditions, giving the desired product **7a−i** in 83−98% yield (Table 2). However, a methyl or benzyl protecting group on isatin was necessary, as unprotected isatin failed to react with **5** under these conditions, possibly because its N−H bond was deprotonated during the reaction course, which in turn decreased the electrophilicity of the ketone carbonyl group.

The scope of ketones other than isatins also worked well under these conditions (Table 3). Acetophenone **8a** and its analogues **8b−g** bearing a *para* electron-withdrawing group on the phenyl ring readily afforded the desired products **9a−g** in good to high yield (entries 1−7). Nevertheless, the electron-donating substituent retarded the reaction. For example, *p*-methylphenyl methyl ketone **8h** gave product **9h** in only 39% yield, because of the formation of the enol silyl ether from **8h** (entry 8). While *o*-chlorophenyl methyl ketone **8i** yielded product **9i** in only 33% yield (entry 9), *m*-chlorophenyl methyl ketone **8j** provided product **9j** in 77% yield (entry 10), showing the negative effect of the *ortho* substituent of the phenyl ring on the reactivity. Heteroaryl methyl ketones **8k,l** also afforded the desired products **9k,l** in reasonable yield (entries 11 and 12).

Non-methyl ketones were also examined; while ethyl ketone **8m** gave product **9m** in moderate yield (entry 13), α-CF_3 or CF_2H ketones provided the desired products **9n,o** in good yield (entries 14 and 15). 1-Tetralone afforded the desired product **9p** in 56% yield (entry 16).

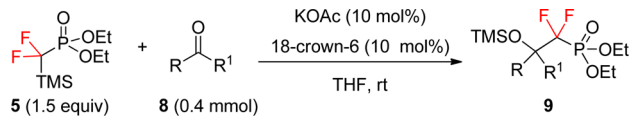
Table 2. Scope of Isatins



entry	isatin **6**	7	time (h)	yield[a] (%)
1	**6a**: R^1 = H, R^2 = Me	**7a**	0.5	92
2	**6b**: R^1 = 5-F, R^2 = Me	**7b**	0.5	91
3	**6c**: R^1 = 5-Cl, R^2 = Me	**7c**	0.5	85
4	**6d**: R^1 = 5-Br, R^2 = Me	**7d**	1.0	92
5	**6e**: R^1 = 5-Me, R^2 = Me	**7e**	0.5	83
6	**6f**: R^1 = 5-MeO, R^2 = Me	**7f**	1.0	94
7	**6g**: R^1 = 7-Cl, R^2 = Me	**7g**	0.6	98
8	**6h**: R^1 = 7-CF_3, R^2 = Me	**7h**	2.0	98
9	**6i**: R^1 = H, R^2 = Bn	**7i**	1.5	92
10	**6j**: R^1 = H, R^2 = H			

[a]Isolated yield.

Table 3. Substrate Scope of Aryl Ketones



Entry	Ketone **8**	**9**	Time (h)	Yield[a] (%)
1	**8a**: R = Ph, R^1 = Me	**9a**	1.0	68
2	**8b**: R = *p*-FC_6H_4, R^1 = Me	**9b**	0.5	74
3	**8c**: R = *p*-ClC_6H_4, R^1 = Me	**9c**	1.0	83
4	**8d**: R = *p*-BrC_6H_4, R^1 = Me	**9d**	0.5	75
5	**8e**: R = *p*-CNC_6H_4, R^1 = Me	**9e**	2.0	57
6	**8f**: R = *p*-$CF_3C_6H_4$, R^1 = Me	**9f**	0.5	75
7	**8g**: R = *p*-$NO_2C_6H_4$, R^1 = Me	**9g**	3.5	62
8	**8h**: R = *p*-MeC_6H_4, R^1 = Me	**9h**	3.0	39
9	**8i**: R = *o*-ClC_6H_4, R^1 = Me	**9i**	1.0	33
10	**8j**: R = *m*-ClC_6H_4, R^1 = Me	**9j**	1.0	77
11	**8k**: R = 2-pyridyl, R^1 = Me	**9k**	1.5	70
12	**8l**: R = 2-thienyl, R^1 = Me	**9l**	5.5	50
13	**8m**: R = *p*-ClC_6H_4, R^1 = Et	**9m**	1.0	46
14	**8n**: R = Ph, R^1 = CF_3	**9n**	1.0	67
15	**8o**: R = Ph, R^1 = CF_2H	**9o**	4.0	73
16	**8p**: 	**9p**	6.0	56

[a]Isolated yield.

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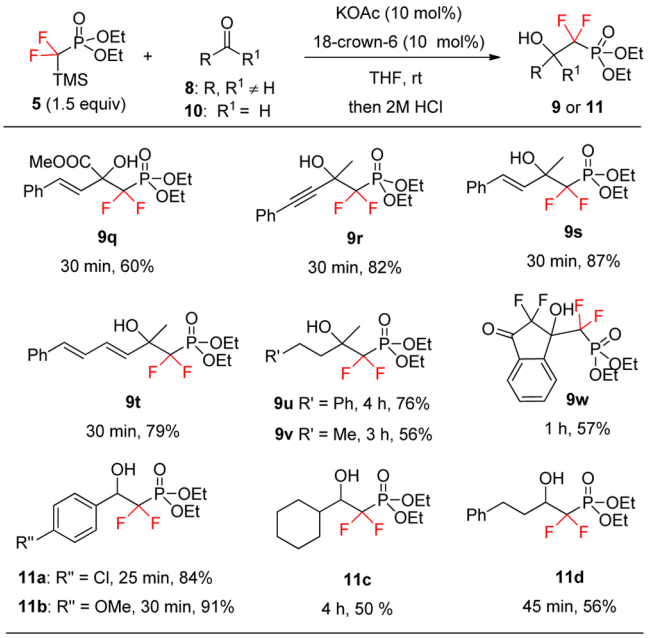
The performance of other ketones and aldehydes was also examined (Scheme 3). β,γ-Unsaturated α-ketoester or α,β-unsaturated ketones underwent aldol reaction selectively, as shown by the synthesis of tertiary alcohols **9q−t** in good to high yield. With an alkene, alkynyl, or diene moiety as a synthetic handle, these adducts could be further elaborated. Aliphatic ketones were also viable substrates, as exemplified by the synthesis of products **9u** and **9v** in 76% and 56% yield, respectively. Furthermore, cyclic fluorinated ketone derived product **9w** was obtained in good yield as well. This method was also workable for the difluoromethylenation of both aryl and aliphatic aldehydes, as shown by the synthesis of adducts **11a−d** in good to high yield.

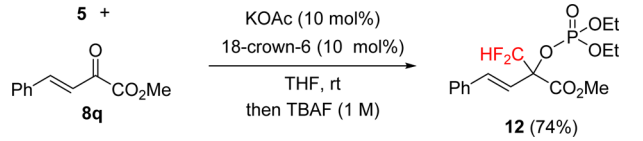
Scheme 3. Scope of Other Ketones and Aldehydes[a]



[a]All reactions were run on a 0.4 mmol scale. Isolated yield is given.

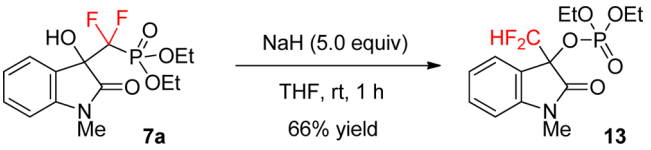
Notably, under the above established conditions, we did not detect side products resulting from the rearrangement of phosphonates into phosphates, or the formation of 1,1-difluoroalkenes via HWE-type elimination. However, when trying to release alcohols **9q−w** and **11** after the reaction completed, to simplify the purification by column chromatography, we found the use of tetrabutylammonium fluoride (TBAF) to remove the TMS group led to side rearrangement reaction, as shown by the synthesis of product **12** from ketoester **8q** in 74% yield (Scheme 4). However, the use of a solution of HCl in MeOH to remove the TMS group did not afford rearrangement products. This was in agreement with a literature report that the use of a fluoride to promote the ketone difluoromethylenation using reagent **5** might lead to side rearrangement reaction.[6a] This result justified the necessity of using oxygen-based Lewis basic promoters.

Scheme 4. Side Rearrangement Reaction Using TBAF To Remove the TMS Group



The thus obtained products were very useful. For example, when treated with NaH, adducts **7** readily convert to a 3-CF_2H 3-hydroxyoxindole derivative via the transfer of the diethoxyphosphoryl group, as shown by the synthesis of compound **7a** in 66% yield (Scheme 5). Notably, despite intensive studies into the synthesis of quaternary 3-hydroxyoxindole derivatives, methods to fluoroalkyl substituted ones are still limited.[18] In addition, other adducts such as **9a** and **11** were known to be able to undergo similar reaction under basic conditions.[19]

Scheme 5. Product Elaboration



CONCLUSION

We have developed a general difluoromethylenation of carbonyl compounds with diethyl difluoro(trimethylsilyl)-methylphosphonate promoted by the combination of 18-crown-6 ether and KOAc. In particular, the use of oxygen-based Lewis basic promoters avoids a possible rearrangement reaction that may take place when using fluoride promoters. The broad substrate scope and the cheap and easily available promoters, along with the mild reaction conditions, makes our method very attractive for the synthesis of β-hydroxy-α,α-difluoromethylphosphates in great structural diversity, which are valuable targets for medicinal research. The development of an enantioselective version of this reaction is now in progress in our laboratory.

EXPERIMENTAL SECTION

General Information. Reactions were monitored by thin layer chromatography using UV light or $KMnO_4$ to visualize the course of reaction. Purification of reaction products was carried out by flash chromatography on silica gel. 300, 400, or 500 MHz NMR spectrometers were used for all structural NMR data. Chemical shifts for ^1H and ^{13}C NMR spectra were reported in ppm from $CDCl_3$ or acetone-d_6 with the solvent resonance as the internal standard. Chemical shifts for ^{19}F NMR spectra were recorded under ^1H decoupling conditions and were reported in ppm with the $PhCF_3$ as the internal standard. Chemical shifts for ^{31}P NMR spectra were recorded under ^1H decoupling conditions and were reported in ppm with 85% H_3PO_4 as the external standard. HRMS measurements were obtained on a TOF analyzer. All reactions were carried out under an atmosphere of nitrogen unless otherwise noted. Anhydrous CH_2Cl_2 and MeCN were prepared by first distillation over P_2O_5 and then from CaH_2. Anhydrous THF and toluene were prepared by distillation over sodium−benzophenone ketyl prior to use. Reagent **5** was prepared using literature procedures.[6]

The abbreviation of AB is used to designate chemical shift multiplicities for classical aromatic AB system in ^1H NMR and classical AB system of CF_2 adjacent to a chiral carbon in ^{19}F NMR (under ^1H decoupling conditions). In most cases, there is a phosphonate group adjacent to a CF_2 group, and each peak in the AB system is further split by the P atom, resulting in an ABd pattern.

General Procedure for the Difluoromethylation of Reagent 5 with Isatins 6a−j. To a 10 mL Schlenk tube were added KOAc (3.9 mg, 10 mol %), 18-crown-6 (10.6 mg, 10 mol %), and anhydrous THF (1.5 mL), followed by the addition of reagent **5** (156.2 mg, 1.5 equiv) and isatins **6a−j** (0.40 mmol). After the mixture was stirred at

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room temperature until almost full conversion of isatins by TLC analysis, a solution of *p*-TsOH in MeOH (1 M, 1 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 1 h, and then was concentrated and directly subjected to column chromatography (DCM:acetone = 10:1) to afford the desired product **7a**−**i**.

Note: The weighing of 18-crown-6 and KOAc is conducted in a glovebox to avoid the absorption of moisture, which has a detrimental effect on the reaction.

Diethyl (difluoro(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-methyl)phosphonate (7a): white solid; 128.4 mg, isolated yield 92%; mp 111−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 4.85 (s, br, 1H), 4.33−4.13 (m, 4H), 3.20 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 172.5−172.4 (m), 145.9, 131.8, 127.3, 125.4 (d, J = 2.6 Hz), 123.2, 118.9 (td, J_1 = 272.9 Hz, J_2 = 204.8 Hz), 109.4, 77.1 (q, J = 21.3 Hz), 65.2 (d, J = 6.6 Hz), 65.0 (d, J = 6.6 Hz), 26.5, 16.5 (d, J = 5.8 Hz), 16.4 (d, J = 5.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −116.66 (ABd, J_1 = 309.1 Hz, J_2 = 91.4 Hz), −118.93 (ABd, J_1 = 309.4 Hz, J_2 = 104.3 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.75 (dd, J_1 = 105.0 Hz, J_2 = 91.9 Hz); IR (neat) 3280, 1729, 1614, 1470, 1367, 1256, 1067, 1013; MS (EI) 349 (M^+, 33), 162 (100), 161 (51), 132 (43), 195 (38), 188 (30), 160 (16), 196 (14); HRMS (EI) exact mass calcd for $C_{14}H_{18}F_2NO_5P$ [M^+] 349.0891, found 349.0889.

Diethyl (difluoro(5-fluoro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)phosphonate (7b): yellow solid; 133.6 mg, isolated yield 91%; mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 1H), 7.14−7.09 (m, 1H), 6.77 (dd, J_1 = 8.4 Hz, J_2 = 4.0 Hz, 1H), 5.00 (s, br, 1H), 4.34−4.21 (m, 4H), 3.19 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 172.1, 159.7 (d, J = 239.7 Hz), 142.0, 127.1 (d, J = 8.4 Hz), 118.8 (td, J_1 = 273.5 Hz, J_2 = 205.6 Hz), 117.9 (d, J = 23.6 Hz), 115.2 (d, J = 25.9 Hz), 110.4 (d, J = 8.0 Hz), 77.2 (q, J = 21.0 Hz), 65.4 (d, J = 6.6 Hz), 65.2 (d, J = 6.7 Hz), 26.7, 16.5 (d, J = 5.6 Hz), 16.4 (d, J = 5.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −117.35 (ABd, J_1 = 310.1 Hz, J_2 = 90.0 Hz, 1F), −119.07(s, 1F), −119.88 (ABd, J_1 = 310.1 Hz, J_2 = 104.1 Hz, 1F); ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.36 (dd, J_1 = 104.2 Hz, J_2 = 89.9 Hz); IR (neat) 3323, 1710, 1624, 1499, 1373, 1268, 1125, 1007; MS (EI) 367 (M^+, 19), 213 (100), 185 (71), 180 (34), 214 (23), 186 (18), 145 (15), 109 (15); HRMS (EI) exact mass calcd for $C_{14}H_{17}F_3NO_5P$ [M^+] 367.0796, found 367.0794.

Diethyl ((5-chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-difluoromethyl)phosphonate (7c): white solid; 130.2 mg, isolated yield 85%; mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.38 (ABd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.77 (AB, J = 8.4 Hz, 1H), 5.00 (s, br, 1H), 4.32−4.19 (m, 4H), 3.19 (s, 3H), 1.36 (t, J = 6.8 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 171.9 (d, J = 3.1 Hz), 144.7, 131.6, 127.9, 127.5, 127.3, 118.7 (td, J_1 = 273.7 Hz, J_2 = 205.7 Hz), 110.9, 76.9 (q, J = 20.6 Hz), 65.4 (d, J = 6.7 Hz), 65.1 (d, J = 6.8 Hz), 26.7, 16.5 (d, J = 6.5 Hz), 16.4 (d, J = 6.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −117.38 (ABd, J_1 = 310.1 Hz, J_2 = 90.0 Hz), −119.84 (ABd, J_1 = 309.9 Hz, J_2 = 103.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.51 (dd, J_1 = 104.2 Hz, J_2 = 89.7 Hz); IR (neat) 3314, 1713, 1612, 1494, 1466, 1270, 1075, 1008; MS (EI) 383 (M^+, 24), 385 ([M + 2]$^+$, 8) 229 (100), 201 (75), 231 (37), 196 (34), 207 (29), 203 (26); HRMS (EI) exact mass calcd for $C_{14}H_{17}{}^{35}ClF_2NO_5P$ [M^+] 383.0501, found 383.0503.

Diethyl ((5-bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-difluoromethyl)phosphonate (7d): pale yellow solid; 157.1 mg, isolated yield 92%; mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.48 (ABd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.70 (AB, J = 8.4 Hz, 1H), 5.22 (s, br, 1H), 4.24−4.10 (m, 4H), 3.13 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 171.8 (d, J = 4.2 Hz), 145.2, 134.6, 130.2, 127.7 (d, J = 2.8 Hz), 118.8 (td, J_1 = 273.3 Hz, J_2 = 205.2 Hz), 115.1, 111.4, 76.9 (q, J = 20.7 Hz), 65.4 (d, J = 6.7 Hz), 65.2 (d, J = 6.7 Hz), 26.6, 16.5 (d, J = 6.0 Hz), 16.4 (d, J = 6.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −117.40 (ABd, J_1 = 309.9 Hz, J_2 = 90.0 Hz), −119.79 (ABd, J_1 = 309.9 Hz, J_2 = 103.8 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.33 (dd, J_1 = 104.2 Hz, J_2 = 90.4 Hz); IR (neat) 3314, 1712, 1610, 1493, 1270, 1162, 1070, 1008; MS (EI) 427 (M^+, 30), 429 ([M + 2]$^+$, 30), 275 (100), 273 (97), 245 (71), 247 (70), 240 (31), 242 (30); HRMS (EI) exact mass calcd for $C_{14}H_{17}{}^{79}BrF_2NO_5P$ [M^+] 426.9996, found 426.9998.

Diethyl (difluoro(3-hydroxy-1,5-dimethyl-2-oxoindolin-3-yl)methyl)phosphonate (7e): pale yellow solid; 120.5 mg, isolated yield 83%; mp 116−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.20 (AB, J = 8.1 Hz, 1H), 6.73 (AB, J = 7.8 Hz, 1H), 4.85 (s, br, 1H), 4.32−4.16 (m, 4H), 3.18 (s, 3H), 2.34 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 172.5−172.4 (m), 143.6, 132.6, 132.0, 128.1, 125.5 (d, J = 2.4 Hz), 119.0 (td, J_1 = 272.8 Hz, J_2 = 204.6 Hz), 109.2, 77.2 (q, J = 20.4 Hz), 65.2 (d, J = 6.7 Hz), 65.0 (d, J = 6.6 Hz), 26.5, 21.0, 16.5 (d, J = 6.7 Hz), 16.4 (d, J = 6.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −117.18 (ABd, J_1 = 309.4 Hz, J_2 = 90.8 Hz), −119.68 (ABd, J_1 = 309.4 Hz, J_2 = 104.9 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.71 (dd, J_1 = 105.3 Hz, J_2 = 91.4 Hz); IR (neat) 3227, 1732, 1618, 1504, 1236, 1166, 1079, 1012; MS (EI) 363 (M^+, 27), 209 (100), 181 (62), 176 (46), 191 (31), 210 (30), 207 (26), 182 (14); HRMS (EI) exact mass calcd for $C_{15}H_{20}F_2NO_5P$ [M^+] 363.1047, found 363.1051.

Diethyl (difluoro(3-hydroxy-5-methoxy-1-methyl-2-oxoindolin-3-yl)methyl)phosphonate (7f): pink solid; 142.5 mg, isolated yield 94%; mp 113−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.93 (ABd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.75 (AB, J = 8.7 Hz, 1H), 4.90 (s, br, 1H), 4.32−4.22 (m, 4H), 3.80 (s, 3H), 3.17 (s, 3H), 1.34 (t, J = 6.9 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 172.2, 156.9, 139.2, 126.6, 119.0 (td, J_1 = 273.2 Hz, J_2 = 204.9 Hz), 116.2, 114.7, 109.9, 77.5 (q, J = 19.9 Hz), 65.2 (d, J = 6.7 Hz), 65.1 (d, J = 6.6 Hz), 56.2, 26.6, 16.5 (d, J = 5.8 Hz), 16.4 (d, J = 6.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −117.20 (ABd, J_1 = 309.6 Hz, J_2 = 90.8 Hz), −119.71 (ABd, J_1 = 309.8 Hz, J_2 = 104.6 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.86 (dd, J_1 = 105.1 Hz, J_2 = 91.4 Hz); IR (neat) 3326, 1714, 1504, 1476, 1271, 1073, 1045, 1012; MS (EI) 379 (M^+, 65), 197 (100), 192 (78), 225 (54), 207 (40), 226 (36), 198 (23), 182 (20); HRMS (EI) exact mass calcd for $C_{15}H_{20}F_2NO_6P$ [M^+] 379.0996, found 379.0999.

Diethyl ((7-chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-difluoromethyl)phosphonate (7g): pale yellow solid; 150.1 mg, isolated yield 98%; mp 89−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 7.5 Hz, 1H), 7.33 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 4.97 (s, br, 1H), 4.35−4.19 (m, 4H), 3.56 (s, 3H), 1.34 (t, J = 6.9 Hz, 3H), 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 172.8−172.8 (m), 141.6, 133.9, 128.5, 126.3, 124.5, 118.6 (td, J_1 = 273.4 Hz, J_2 = 205.0 Hz), 115.8, 76.5 (q, J = 20.9 Hz), 65.4 (d, J = 6.6 Hz), 65.2 (d, J = 6.7 Hz), 30.0, 16.5 (d, J = 5.5 Hz), 16.4 (d, J = 5.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −117.24 (ABd, J_1 = 309.8 Hz, J_2 = 90.0 Hz), −120.03 (ABd, J_1 = 309.4 Hz, J_2 = 104.6 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.68 (dd, J_1 = 105.3 Hz, J_2 = 90.4 Hz); IR (neat) 3312, 1730, 1610, 1466, 1258, 1168, 1072, 1015; MS (EI) 383 (M^+, 10), 229 (100), 201 (67), 231 (35), 203 (23), 196 (22), 230 (19), 232 (19); HRMS (EI) exact mass calcd for $C_{14}H_{17}{}^{35}ClF_2NO_5P$ [M^+] 383.0501, found 383.0500.

Diethyl (difluoro(3-hydroxy-1-methyl-2-oxo-7-(trifluoromethyl)indolin-3-yl)methyl)phosphonate (7h): yellow solid; 163.5 mg, isolated yield 98%; mp 93−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.68 (m, 2H), 7.22−7.17 (m, 1H), 5.05 (s, br, 1H), 4.33−4.22 (m, 4H), 3.40 (q, J = 2.1 Hz, 3H), 1.34 (t, J = 6.6 Hz, 3H), 1.32 (t, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 173.4−173.4 (m), 143.8, 131.3, 129.4 (q, J = 6.0 Hz), 128.4, 124.6 (q, J = 271.4 Hz), 123.2, 118.6 (td, J_1 = 273.7 Hz, J_2 = 205.4 Hz), 112.8 (q, J = 33.1 Hz), 75.3 (q, J = 21.0 Hz), 65.5 (d, J = 6.7 Hz), 65.2 (d, J = 6.8 Hz), 29.4 (q, J = 6.6 Hz), 16.5 (d, J = 5.7 Hz), 16.4 (d, J = 5.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −52.95 (s, 3F), −117.36 (ABd, J_1 = 309.9 Hz, J_2 = 89.4 Hz, 1F), −120.19 (ABd, J_1 = 309.4 Hz, J_2 = 104.3 Hz, 1F); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.56 (dd, J_1 = 104.9 Hz, J_2 = 90.2 Hz); IR (neat) 3236, 1738, 1599, 1460, 1260, 1174, 1080, 1018; MS (EI) 417 (M^+, 9), 263 (100), 235 (63), 215 (28), 264 (20), 230 (17), 195 (14), 236 (14); HRMS (EI) exact mass calcd for $C_{15}H_{17}F_5NO_5P$ [M^+] 417.0765, found 417.0766.

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Diethyl ((1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-difluoromethyl)phosphonate (7i): white solid; 156.4 mg, isolated yield 92%; mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.2 Hz, 1H), 7.30−7.22 (m, 6H), 7.06 (td, J_1 = 7.6 Hz, J_2 = 0.4 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.20 (s, br, 1H), 5.00 (AB, J = 16.0 Hz, 1H), 4.74 (AB, J = 16.0 Hz, 1H), 4.32−4.18 (m, 4H), 1.31 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 172.8 (d, J = 4.0 Hz), 145.0, 136.8, 131.6, 129.4, 128.3, 128.2, 127.5, 125.6, 123.4, 118.9 (td, J_1 = 272.4 Hz, J_2 = 204.6 Hz), 110.3, 77.2 (q, J = 19.5 Hz), 65.3 (d, J = 6.7 Hz), 65.1 (d, J = 6.7 Hz), 44.2, 16.5 (d, J = 5.7 Hz), 16.4 (d, J = 5.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −116.51 (ABd, J_1 = 310.8 Hz, J_2 = 90.0 Hz), −119.77 (ABd, J_1 = 310.8 Hz, J_2 = 105.2 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.86 (dd, J_1 = 106.0 Hz, J_2 = 90.4 Hz); IR (neat) 3306, 1712, 1613, 1469, 1370, 1287, 1156, 1019; MS (EI) 425 (M^+, 8), 91 (100), 271 (96), 272 (19), 243 (14), 253 (12), 109 (10), 65 (10); HRMS (EI) exact mass calcd for $C_{20}H_{22}F_2NO_5P$ [M^+] 425.1204, found 425.1206.

General Procedure for the Difluoromethylation of Reagent 5 with Ketones 8a−p. To a 10 mL Schlenk tube were added KOAc (3.9 mg, 10 mol %), 18-crown-6 (10.6 mg, 10 mol %), and anhydrous THF (1.5 mL), followed by the addition of reagent **5** (156.2 mg, 1.5 equiv) and aryl ketones **8a−p** (0.40 mmol). After the mixture was stirred at room temperature until almost full conversion of aryl ketones **8a−p** by TLC analysis, the resultant was concentrated and directly subjected to column chromatography (petroleum ether:EtOAc = 10:1) to afford the desired product **9a−p**.

Note: The weighing of 18-crown-6 and KOAc is conducted in a glovebox to avoid the absorption of moisture, which has a detrimental effect on the reaction.

Diethyl (1,1-difluoro-2-phenyl-2-((trimethylsilyl)oxy)-propyl)phosphonate (9a): yellow oil; 103.4 mg, isolated yield 68%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.52 (m, 2H), 7.38−7.30 (m, 3H), 4.24−3.97 (m, 4H), 1.95 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 141.8 (dd, J_1 = 4.4 Hz, J_2 = 2.1 Hz), 128.7, 128.5, 128.3, 120.4 (ddd, J_1 = 274.7 Hz, J_2 = 271.0 Hz, J_3 = 205.1 Hz), 79.9 (ddd, J_1 = 24.4 Hz, J_2 = 22.1 Hz, J_3 = 14.8 Hz), 64.5 (d, J = 7.0 Hz), 64.3 (d, J = 6.7 Hz), 23.6 (t, J = 3.2 Hz), 16.7 (d, J = 6.0 Hz), 16.6 (d, J = 5.6 Hz), 2.3; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.54 (d, J = 5.4 Hz), −114.91 (d, J = 5.1 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.59 (t, J = 106.3 Hz); IR (neat) 2961, 1447, 1252, 1134, 1024, 977, 840, 755; HRMS (ESI) exact mass calcd for $C_{16}H_{27}F_2O_4PSiNa$ [M + Na]$^+$ 403.1282, found 403.1276.

Diethyl (1,1-difluoro-2-(4-fluorophenyl)-2-((trimethylsilyl)-oxy)propyl)phosphonate (9b): yellow oil; 117.8 mg, isolated yield 74%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.03 (t, J = 8.7 Hz, 2H), 4.25−4.01 (m, 4H), 1.94 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 163.4 (d, J = 245.8 Hz), 138.0 (d, J = 2.2 Hz), 130.4 (d, J = 8.4 Hz), 120.3 (td, J_1 = 274.3 Hz, J_2 = 205.3 Hz), 115.0 (d, J = 21.5 Hz), 79.6 (ddd, J_1 = 24.3 Hz, J_2 = 22.4 Hz, J_3 = 15.0 Hz), 64.6 (d, J = 7.0 Hz), 64.4 (d, J = 6.8 Hz), 23.6 (t, J = 3.2 Hz), 16.7 (d, J = 5.8 Hz), 16.6 (d, J = 5.6 Hz), 2.2; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.81 (d, J = 1.7 Hz), −115.18 (d, J = 2.0 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.44 (t, J = 105.9 Hz); IR (neat) 2962, 1509, 1253, 1157, 1016, 977, 840, 756; HRMS (ESI) exact mass calcd for $C_{16}H_{26}F_3O_4PSiNa$ [M + Na]$^+$ 421.1188, found 421.1179.

Diethyl (2-(4-chlorophenyl)-1,1-difluoro-2-((trimethylsilyl)-oxy)propyl)phosphonate (9c): yellow oil; 137.4 mg, isolated yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (AB, J = 8.7 Hz, 2H), 7.32 (AB, J = 8.7 Hz, 2H), 4.24−4.02 (m, 4H), 1.93 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 140.9−140.9 (m), 134.4, 130.4, 128.4, 120.2 (td, J_1 = 274.2 Hz, J_2 = 205.5 Hz), 79.7 (td, J_1 = 24.1 Hz, J_2 = 14.8 Hz), 64.7 (d, J = 7.0 Hz), 64.5 (d, J = 6.7 Hz), 23.5 (t, J = 3.3 Hz), 16.7 (d, J = 5.8 Hz), 16.6 (d, J = 5.6 Hz), 2.2; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −115.00 (d, J = 105.2 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.34 (t, J = 105.8 Hz); IR (neat) 2962, 1492, 1399, 1253, 1162, 1135, 1013, 977; HRMS (ESI) exact mass calcd for $C_{16}H_{27}{}^{35}ClF_2O_4PSi$ [M + H]$^+$ 415.1069, found 415.1067.

Diethyl (2-(4-bromophenyl)-1,1-difluoro-2-((trimethylsilyl)-oxy)propyl)phosphonate (9d): yellow oil; 137.4 mg, isolated yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (AB, J = 8.7 Hz, 2H), 7.39 (AB, J = 8.7 Hz, 2H), 4.22−4.02 (m, 4H), 1.92 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 141.3−141.3 (m), 131.4, 130.6, 122.6, 120.1 (ddd, J_1 = 274.3 Hz, J_2 = 271.9 Hz, J_3 = 205.5 Hz), 79.7 (td, J_1 = 24.2 Hz, J_2 = 14.8 Hz), 64.6 (d, J = 6.9 Hz), 64.4 (d, J = 6.8 Hz), 23.4 (t, J = 3.3 Hz), 16.7 (d, J = 5.9 Hz), 16.6 (d, J = 5.6 Hz), 2.2; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −115.02 (d, J = 105.2 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.30 (t, J = 105.5 Hz); IR (neat) 2962, 1253, 1162, 1135, 1009, 977, 840, 754; MS (ESI) 483 (M + 2 + Na$^+$); HRMS (EI) exact mass calcd for $C_{16}H_{26}{}^{79}BrF_2O_4PSi$ [M^+] 458.0489, found 458.0481.

Diethyl (2-(4-cyanophenyl)-1,1-difluoro-2-((trimethylsilyl)-oxy)propyl)phosphonate (9e): yellow oil; 92.3 mg, isolated yield 57%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 4H), 4.23−4.04 (m, 4H), 1.94 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 6.9 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 147.4−147.3 (m), 132.2, 129.5, 120.1 (td, J_1 = 273.9 Hz, J_2 = 206.1 Hz), 119.2, 112.6, 80.0 (td, J_1 = 23.7 Hz, J_2 = 14.5 Hz), 64.8 (d, J = 7.0 Hz), 64.6 (d, J = 6.8 Hz), 23.4 (t, J = 3.3 Hz), 16.7 (d, J = 5.8 Hz), 16.6 (d, J = 5.6 Hz), 2.2; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.83 (d, J = 12.7 Hz), −115.20 (d, J = 13.0 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.76 (t, J = 104.6 Hz); IR (neat) 2967, 2230, 1254, 1164, 1135, 1052, 1017, 978; HRMS (ESI) exact mass calcd for $C_{17}H_{26}F_2NO_4PSiNa$ [M + Na]$^+$ 428.1235, found 428.1224.

Diethyl (1,1-difluoro-2-(4-(trifluoromethyl)phenyl)-2-((trimethylsilyl)oxy)propyl)phosphonate (9f): yellow oil; 134.4 mg, isolated yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (AB, J = 8.4 Hz, 2H), 7.61 (AB, J = 8.7 Hz, 2H), 4.23−4.01 (m, 4H), 1.96 (d, J = 1.8 Hz, 3H), 1.30 (t, J = 6.9 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 146.5, 130.4 (q, J = 32.3 Hz), 129.3, 125.3 (q, J = 272.3 Hz), 125.3 (q, J = 3.8 Hz), 120.2 (td, J_1 = 273.2 Hz, J_2 = 206.1 Hz), 79.9 (td, J_1 = 23.1 Hz, J_2 = 14.7 Hz), 64.8 (d, J = 7.1 Hz), 64.6 (d, J = 6.8 Hz), 23.5 (t, J = 3.1 Hz), 16.7 (d, J = 5.8 Hz), 16.6 (d, J = 5.6 Hz), 2.2; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.83 (d, J = 5.9 Hz), −115.20 (d, J = 6.2 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.09 (t, J = 105.2 Hz); IR (neat) 2963, 1327, 1254, 1164, 1110, 1015, 978, 842; HRMS (ESI) exact mass calcd for $C_{17}H_{26}F_5O_4PSiNa$ [M + Na]$^+$ 471.1156, found 471.1149.

Diethyl (1,1-difluoro-2-(4-nitrophenyl)-2-((trimethylsilyl)-oxy)propyl)phosphonate (9g):[6a] yellow oil; 105.5 mg, isolated yield 62%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (AB, J = 9.0 Hz, 2H), 7.71 (AB, J = 9.0 Hz, 2H), 4.22−4.10 (m, 4H), 1.97 (s, 3H), 1.32 (t, J = 7.5 Hz, 3H), 1.26 (t, J = 6.9 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 149.3−149.3 (m), 148.6, 129.9, 123.4, 120.1 (td, J_1 = 273.4 Hz, J_2 = 206.14 Hz), 80.0 (td, J_1 = 23.6 Hz, J_2 = 14.5 Hz), 64.8 (d, J = 7.0 Hz), 64.7 (d, J = 6.8 Hz), 23.5 (t, J = 3.2 Hz), 16.7 (d, J = 5.8 Hz), 16.6 (d, J = 5.6 Hz), 2.2; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.81 (ABd, J_1 = 302.6 Hz, J_2 = 103.8 Hz), −115.12 (ABd, J_1 = 302.7 Hz, J_2 = 103.8 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.84 (t, J = 104.3 Hz); IR (neat) 2963, 1522, 1349, 1254, 1164, 1136, 1052, 1014.

Diethyl (1,1-difluoro-2-(p-tolyl)-2-((trimethylsilyl)oxy)-propyl)phosphonate (9h): yellow oil; 61.5 mg, isolated yield 39%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (AB, J = 8.1 Hz, 2H), 7.15 (AB, J = 8.1 Hz, 2H), 4.25−3.99 (m, 4H), 2.34 (s, 3H), 1.94 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 6.9 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 138.9 (dd, J_1 = 4.5 Hz, J_2 = 2.3 Hz), 138.2, 129.0, 128.5, 120.4 (ddd, J_1 = 274.7 Hz, J_2 = 270.7 Hz, J_3 = 204.9 Hz), 79.8 (ddd, J_1 = 24.5 Hz, J_2 = 21.9 Hz, J_3 = 14.8 Hz), 64.55 (d, J = 7.1 Hz), 64.3 (d, J = 6.8 Hz), 23.6 (t, J = 3.1 Hz), 21.0, 16.7 (d, J = 6.0 Hz), 16.6 (d, J = 5.6 Hz), 2.3; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.40 (ABd, J_1 = 301.2 Hz, J_2 = 106.3 Hz), −114.86 (ABd, J_1 = 301.2 Hz, J_2 = 106.0 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.68 (t, J = 106.4 Hz); IR (neat) 2959, 1252, 1160, 1134, 1020, 976, 864, 841; HRMS (ESI) exact mass calcd for $C_{17}H_{29}F_2O_4PSiNa$ [M + Na]$^+$ 417.1439, found 417.1435.

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Diethyl (2-(2-chlorophenyl)-1,1-difluoro-2-((trimethylsilyl)-oxy)propyl)phosphonate (9i): yellow oil; 54.6 mg, isolated yield 33%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.69 (m, 1H), 7.39−7.36 (m, 1H), 7.28−7.22 (m, 2H), 4.29−4.11 (m, 4H), 2.20 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 6.9 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 138.5 (dd, J_1 = 5.8 Hz, J_2 = 2.3 Hz), 134.1, 132.8, 132.8, 130.6, 127.1, 121.2 (ddd, J_1 = 277.0 Hz, J_2 = 271.0 Hz, J_3 = 204.9 Hz), 81.3 (ddd, J_1 = 27.1 Hz, J_2 = 22.0 Hz, J_3 = 15.0 Hz), 64.9−64.8 (m), 64.6 (d, J = 6.0 Hz), 25.0 (t, J = 3.1 Hz), 16.7 (d, J = 6.5 Hz), 16.7 (d, J = 6.0 Hz), 2.1; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −111.98 (ABd, J_1 = 301.6 Hz, J_2 = 104.9 Hz), −113.10 (ABd, J_1 = 301.5 Hz, J_2 = 104.0 Hz) ; ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.09 (t, J = 105.2 Hz); IR (neat) 2964, 1428, 1252, 1138, 1023, 977, 840, 747; HRMS (ESI) exact mass calcd for $C_{16}H_{26}{}^{35}ClF_2O_4PSiNa$ $[M + Na]^+$ 437.0892, found 437.0897.

Diethyl (2-(3-chlorophenyl)-1,1-difluoro-2-((trimethylsilyl)-oxy)propyl)phosphonate (9j): yellow oil; 127.5 mg, isolated yield 77%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.42−7.40 (m, 1H), 7.29−7.27 (m, 2H), 4.25−4.02 (m, 4H), 1.93 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 114.4−144.4 (m), 134.0, 130.1, 128.8, 128.6, 127.0, 120.1 (td, J_1 = 272.2 Hz, J_2 = 205.7 Hz), 79.7 (td, J_1 = 22.6 Hz, J_2 = 14.8 Hz), 64.7 (d, J = 7.1 Hz), 64.5 (d, J = 6.8 Hz), 23.5 (t, J = 3.2 Hz), 16.7 (d, J = 5.8 Hz), 16.6 (d, J = 5.6 Hz), 2.2; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.85 (d, J = 105.2 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.26 (t, J = 105.8 Hz); IR (neat) 2960, 1573, 1267, 1253, 1163, 1137, 1023, 978; HRMS (ESI) exact mass calcd for $C_{16}H_{27}{}^{35}ClF_2O_4PSi$ $[M + H]^+$ 415.1067, found 415.1070.

Diethyl (1,1-difluoro-2-(pyridin-2-yl)-2-((trimethylsilyl)oxy)-propyl)phosphonate (9k): yellow oil; 106.7 mg, isolated yield 70%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60−8.59 (m, 1H), 7.76−7.68 (m, 2H), 7.24−7.20 (m, 1H), 4.26−4.08 (m, 4H), 2.01 (t, J = 1.8 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 160.5 (dd, J_1 = 5.4 Hz, J_2 = 2.5 Hz), 148.8, 136.6, 123.9, 123.7, 120.6 (ddd, J_1 = 274.7 Hz, J_2 = 272.3 Hz, J_3 = 206.3 Hz), 81.4 (dd, J_1 = 23.6 Hz, J_2 = 21.5 Hz, J_3 = 14.4 Hz), 64.6 (d, J = 7.0 Hz), 64.4 (d, J = 6.8 Hz), 22.7 (t, J = 3.1 Hz), 16.7 (d, J = 6.0 Hz), 16.6 (d, J = 5.6 Hz), 2.3; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.66 (ABd, J_1 = 303.3 Hz, J_2 = 104.9 Hz), −115.06 (ABd, J_1 = 303.0 Hz, J_2 = 105.5 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.40 (t, J = 105.8 Hz); IR (neat) 2959, 1588, 1433, 1253, 1167, 1139, 1016, 978; HRMS (ESI) exact mass calcd for $C_{15}H_{26}F_2NO_4PSiNa$ $[M + Na]^+$ 404.1235, found 404.1215.

Diethyl (1,1-difluoro-2-(thiophen-2-yl)-2-((trimethylsilyl)-oxy)propyl)phosphonate (9l): yellow oil; 77.2 mg, isolated yield 50%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.28 (m, 1H), 7.06−7.05 (m, 1H), 7.00−6.97 (m, 1H), 4.28−4.04 (m, 4H), 1.98 (d, J = 1.8 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 6.9 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 141.4 (dd, J_1 = 5.2 Hz, J_2 = 2.3 Hz), 127.3, 127.1, 127.0, 119.7 (ddd, J_1 = 275.5 Hz, J_2 = 271.0 Hz, J_3 = 205.0 Hz), 78.9 (ddd, J_1 = 25.4 Hz, J_2 = 22.1 Hz, J_3 = 16.6 Hz), 64.8 (d, J = 7.1 Hz), 64.5 (d, J = 6.7 Hz), 24.6 (t, J = 3.0 Hz), 16.7 (d, J = 5.8 Hz), 16.6 (d, J = 5.6 Hz), 2.0; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.77 (ABd, J_1 = 301.7 Hz, J_2 = 100.4 Hz), −114.77 (ABd, J_1 = 300.5 Hz, J_2 = 104.6 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.96 (t, J = 105.3 Hz); IR (neat) 2966, 1267, 1252, 1158, 1130, 1023, 973, 841; HRMS (ESI) exact mass calcd for $C_{14}H_{25}F_2O_4PSSiNa$ $[M + Na]^+$ 409.0846, found 409.0847.

Diethyl (2-(4-chlorophenyl)-1,1-difluoro-2-((trimethylsilyl)-oxy)butyl)phosphonate (9m): yellow oil; 78.7 mg, isolated yield 46%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (AB, J = 8.4 Hz, 2H), 7.30 (AB, J = 7.8 Hz, 2H), 4.04−3.80 (m, 4H), 2.43−2.33 (m, 1H), 2.19−2.07 (m, 1H), 1.16 (q, J = 7.2 Hz, 6H), 0.70 (t, J = 7.2 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 138.4, 134.1, 130.6, 128.4, 120.9 (td, J_1 = 274.0 Hz, J_2 = 205.1 Hz), 83.4 (td, J_1 = 20.9 Hz, J_2 = 16.6 Hz), 64.5 (d, J = 7.3 Hz), 64.4 (d, J = 7.1 Hz), 26.6 (d, J = 2.4 Hz), 16.5 (d, J = 3.8 Hz), 16.4 (d, J = 4.0 Hz), 7.8, 2.4; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −113.04 (ABd, J_1 = 300.0 Hz, J_2 = 104.0 Hz), −115.68 (ABd, J_1 = 299.9 Hz, J_2 = 104.9 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.72 (t, J = 104.8 Hz); IR (neat) 2981, 1491, 1299, 1266, 1252, 1167, 1088, 1013; HRMS (ESI) exact mass calcd for $C_{17}H_{29}{}^{35}ClF_2O_4PSi$ $[M + H]^+$ 429.1224, found 429.1226.

Diethyl (1,1,3,3,3-pentafluoro-2-phenyl-2-((trimethylsilyl)-oxy)propyl)phosphonate (9n): yellow oil; 116.3 mg, isolated yield 67%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.69 (m, 2H), 7.42−7.39 (m, 3H), 4.23−3.97 (m, 2H), 3.90−3.69 (m, 2H), 1.27 (t, J = 6.9 Hz, 3H), 1.08 (t, J = 6.9 Hz, 3H), 0.30 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 133.8 (d, J = 4.7 Hz), 130.3, 128.8, 128.5, 124.7 (qd, J_1 = 292.0 Hz, J_2 = 11.8 Hz), 119.3 (td, J_1 = 280.5 Hz, J_2 = 212.3 Hz), 81.8−81.4 (m), 65.1 (d, J = 6.8 Hz), 64.6 (d, J = 7.1 Hz), 16.6 (d, J = 5.4 Hz), 16.3 (d, J = 5.6 Hz), 1.7; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −68.78 (ddd, J_1 = 15.0 Hz, J_2 = 10.6 Hz, J_3 = 4.6 Hz, 3F), −110.60 (ABdq, J_1 = 311.0 Hz, J_2 = 97.9 Hz, J_3 = 10.6 Hz, 1F), −114.41 (ABdq, J_1 = 313.9 Hz, J_2 = 106.6 Hz, J_3 = 14.4 Hz, 1F); the ABdq is used to show that the CF_2 group in compound **9n** is first split by P atom and then by the CF_3 group; ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 3.99 (t, J = 100.8 Hz); IR (neat) 2984, 1254, 1184, 1018, 935, 846, 758, 711; MS (ESI) 457 ($M+Na^+$); HRMS (EI) exact mass calcd for $C_{16}H_{24}F_5O_4PSi$ $[M^+]$ 434.1102, found 434.1100.

Diethyl (1,1,3,3-tetrafluoro-2-phenyl-2-((trimethylsilyl)oxy)-propyl)phosphonate (9o): red oil; 121.5 mg, isolated yield 73%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.61 (m, 2H), 7.40−7.36 (m, 3H), 6.68 (dd, J_1 = 54.6 Hz, J_2 = 53.4 Hz, 1H), 4.20−4.02 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.21 (d, J = 0.6 Hz, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 134.3, 129.7, 129.0, 128.5, 119.0 (td, J_1 = 276.2 Hz, J_2 = 206.6 Hz), 115.6 (td, J_1 = 252.3 Hz, J_2 = 2.6 Hz), 81.6 (td, J_1 = 22.0 Hz, J_2 = 15.2 Hz), 65.2 (d, J = 2.4 Hz), 65.1 (d, J = 2.9 Hz), 16.6 (d, J = 5.8 Hz), 16.5 (d, J = 5.6 Hz), 1.9 (d, J = 2.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −113.65 to −113.73 (m, 1F), −114.00 to −114.09 (m, 1F), −123.87 (ABt, J_1 = 290.5 Hz, J_2 = 12.4 Hz, 1F), −126.87 (ABt, J_1 = 290.7 Hz, J_2 = 9.6 Hz, 1F); the ABt is used to show that the CF_2 group in compound **9o** is split by the CF_2H group; ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.19 (t, J = 101.6 Hz); IR (neat) 2984, 1253, 1138, 1120, 1018, 983, 872, 843; MS (ESI) 439 ($M+Na^+$); HRMS (EI) exact mass calcd for $C_{16}H_{25}F_4O_4PSi$ $[M^+]$ 416.1196, found 416.1201.

Diethyl (difluoro(1-((trimethylsilyl)oxy)-1,2,3,4-tetrahydro-naphthalen-1-yl)methyl)phosphonate (9p): yellow oil; 90.9 mg, isolated yield 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.68 (m, 1H), 7.24−7.15 (m, 2H), 7.10−7.08 (m, 1H), 4.32−4.00 (m, 4H), 2.90−2.76 (m, 3H), 2.03−2.00 (m, 2H), 1.84−1.78 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H), −0.02 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 139.9, 135.8 (dd, J_1 = 5.2 Hz, J_2 = 2.0 Hz), 130.8 (dd, J_1 = 4.7 Hz, J_2 = 2.0 Hz), 129.4, 129.0, 126.0, 120.6 (ddd, J_1 = 276.7 Hz, J_2 = 270.5 Hz, J_3 = 203.5 Hz), 77.6 (ddd, J_1 = 23.7 Hz, J_2 = 18.5 Hz, J_3 = 16.7 Hz), 64.7 (dd, J = 7.0 Hz, J = 1.2 Hz), 64.3 (d, J = 6.6 Hz), 34.4 (d, J = 3.3 Hz), 19.9, 19.8, 16.8 (d, J = 5.8 Hz), 16.6 (d, J = 5.6 Hz), 2.1; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −118.72 (ABd, J_1 = 304.6 Hz, J_2 = 105.5 Hz), −112.12 (ABd, J_1 = 304.4 Hz, J_2 = 106.6 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.07 (t, J = 106.9 Hz); IR (neat) 2959, 1251, 1142, 1017, 978, 884, 839, 741; HRMS (ESI) exact mass calcd for $C_{18}H_{29}F_2O_4PSiNa$ $[M + Na]^+$ 429.1439, found 429.1436.

General Procedure for the Difluoromethylation of Reagent 5 with Ketones 8q−w and Aldehydes 10a−d. To a 10 mL Schlenk tube were added KOAc (3.9 mg, 10 mol %), 18-crown-6 (10.6 mg, 10 mol %), and anhydrous THF (1.5 mL), followed by the addition of reagent **5** (156.2 mg, 1.5 equiv) and ketones **8q−w** (0.40 mmol) (or aldehydes **10a−d**, 0.40 mmol). After the mixture was stirred at room temperature until almost full conversion of **8** or **10** by TLC analysis, a solution of concentrated HCl in MeOH (2 M, 1 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 1 h, and then was concentrated and directly subjected to column chromatography (petroleum ether:EtOAc = 4:1) to afford the desired product **9q−w**, **11a−d**.

Note: The weighing of 18-crown-6 and KOAc is conducted in a glovebox to avoid the absorption of moisture, which has a detrimental effect on the reaction.

(*E*)-Methyl 2-((diethoxyphosphoryl)difluoromethyl)-2-hydroxy-4-phenylbut-3-enoate (9q): yellow oil; 90.7 mg, isolated

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yield 60%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 6.9 Hz, 2H), 7.36−7.26 (m, 3H), 7.04 (AB, J = 15.6 Hz, 1H), 6.43 (AB, J = 15.9 Hz, 1H), 4.32−4.23 (m, 5H), 3.91 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 170.4, 136.8, 134.1, 129.5, 129.1, 127.7, 123.3 (q, J = 3.4 Hz), 118.8 (td, J_1 = 274.5 Hz, J_2 = 206.6 Hz), 79.5 (td, J_1 = 23.1 Hz, J_2 = 14.1 Hz), 65.2, 65.1, 53.9, 16.6, 16.6 (d, J = 0.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −113.13 (ABd, J_1 = 306.8 Hz, J_2 = 101.0 Hz), −115.78 (ABd, J_1 = 306.5 Hz, J_2 = 99.3 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 5.89 (t, J = 100.6 Hz); IR (neat) 3318, 2986, 1743, 1439, 1256, 1163, 1014, 747; MS (EI) 378 (M^+, 24), 131 (100), 191 (82), 319 (71), 161 (59), 188 (51), 132 (48), 245 (47); HRMS (EI) exact mass calcd for $C_{16}H_{21}F_2O_6P$ [M^+] 378.1044, found 378.1050.

Diethyl (1,1-difluoro-2-hydroxy-2-methyl-4-phenylbut-3-yn-1-yl)phosphonate (9r): yellow oil; 108.9 mg, isolated yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2H), 7.33−7.31 (m, 3H), 4.39−4.25 (m, 5H), 1.70 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 132.4, 129.8, 129.4, 122.9, 119.3 (td, J_1 = 272.9 Hz, J_2 = 203.4 Hz), 88.6 (d, J = 4.4 Hz), 86.2, 70.9 (td, J_1 = 23.8 Hz, J_2 = 17.2 Hz), 65.2 (d, J = 6.6 Hz), 65.1 (d, J = 6.8 Hz), 24.2 (d, J = 1.6 Hz), 16.7 (d, J = 2.7 Hz), 16.6 (d, J = 2.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.30 (ABd, J_1 = 295.1 Hz, J_2 = 94.8 Hz), −120.99 (ABd, J_1 = 295.0 Hz, J_2 = 106.6 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.52 (dd, J_1 = 107.4 Hz, J_2 = 95.4 Hz); IR (neat) 3331, 2987, 1490, 1444, 1254, 1014, 757, 692; MS (EI) 332 (M^+, 16), 161 (100), 132 (83), 178 (79), 188 (68), 145 (65), 133 (30), 160 (30); HRMS (EI) exact mass calcd for $C_{15}H_{19}F_2O_4P$ [M^+] 332.0989, found 332.0994.

(*E*)-Diethyl (1,1-difluoro-2-hydroxy-2-methyl-4-phenylbut-3-en-1-yl)phosphonate (9s): yellow oil; 116.2 mg, isolated yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (AB, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 3H), 6.86 (AB, J = 16.2 Hz, 1H), 6.32 (ABd, J_1 = 15.9 Hz, J_2 = 1.8 Hz, 1H), 4.32 (quint, J = 6.9 Hz, 2H), 4.21−4.05 (m, 3H), 1.50 (s, 3H), 1.39 (t, J = 6.9 Hz, 3H), 1.21 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 137.6, 131.2, 130.4 (d, J = 2.4 Hz), 129.4, 128.6, 127.5, 120.7 (td, J_1 = 272.4 Hz, J_2 = 203.3 Hz), 75.8 (td, J_1 = 22.2 Hz, J_2 = 15.2 Hz), 65.1 (d, J = 6.6 Hz), 64.9 (d, J = 6.8 Hz), 22.3 (q, J = 2.9 Hz), 16.6 (d, J = 5.8 Hz), 16.6 (d, J = 5.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −117.64 (ABd, J_1 = 300.3 Hz, J_2 = 96.7 Hz), −120.63 (ABd, J_1 = 300.5 Hz, J_2 = 110.0 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.97 (dd, J_1 = 110.4 Hz, J_2 = 97.6 Hz); IR (neat) 3375, 2987, 1448, 1394, 1370, 1254, 1164, 1015; MS (EI) 334 (M^+, 6), 147 (100), 132 (22), 161 (21), 129 (13), 148 (11), 188 (10), 160 (8); HRMS (EI) exact mass calcd for $C_{15}H_{21}F_2O_4P$ [M^+] 334.1146, found 334.1147.

Diethyl ((3*E*,5*E*)-1,1-difluoro-2-hydroxy-2-methyl-6-phenylhexa-3,5-dien-1-yl)phosphonate (9t): yellow oil; 113.8 mg, isolated yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (AB, J = 7.2 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.22 (AB, J = 7.2 Hz, 1H), 6.79−6.61 (m, 3H), 5.92 (AB, J = 15.0 Hz, 1H), 4.36−4.13 (m, 4H), 3.96 (br, 1H), 1.47 (s, 3H), 1.39 (t, J = 6.9 Hz, 3H), 1.33 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 138.1, 134.3 (d, J = 2.2 Hz), 134.1, 131.9, 129.5, 129.1, 128.5, 127.3, 120.7 (td, J_1 = 272.4 Hz, J_2 = 203.1 Hz), 75.6 (td, J_1 = 22.2 Hz, J_2 = 15.2 Hz), 65.0 (d, J = 8.7 Hz), 64.9 (d, J = 7.2 Hz), 22.4 (d, J = 2.8 Hz), 16.7 (d, J = 1.8 Hz), 16.6 (d, J = 1.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −117.48 (ABd, J_1 = 300.0 Hz, J_2 = 97.6 Hz), −120.14 (ABd, J_1 = 300.3 Hz, J_2 = 109.1 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.82 (dd, J_1 = 109.7 Hz, J_2 = 98.2 Hz); IR (neat) 3347, 2982, 1451, 1392, 1254, 1232, 1174, 1012; MS (EI) 360 (M^+, 8), 173 (100), 91 (56), 207 (14), 132 (14), 174 (13), 128 (11), 129 (11); HRMS (EI) exact mass calcd for $C_{17}H_{23}F_2O_4P$ [M^+] 360.1302, found 360.1305.

Diethyl (1,1-difluoro-2-hydroxy-2-methyl-4-phenylbutyl)phosphonate (9u): pale yellow solid; 102.2 mg, isolated yield 76%; mp 37−38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.29 (m, 2H), 7.22−7.16 (m, 3H), 4.30 (sext, J = 7.2 Hz, 4H), 2.89−2.68 (m, 3H), 2.09−1.94 (m, 2H), 1.45 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 143.4, 129.2, 126.6, 122.1 (td, J_1 = 271.1 Hz, J_2 = 202.4 Hz), 75.2 (td, J_1 = 21.3 Hz, J_2 = 15.2 Hz), 64.8, 64.9, 38.3 (q, J = 2.9 Hz), 29.7, 20.6, 16.7, 16.6; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −118.10 (ABd, J_1 = 303.8 Hz, J_2 = 108.3 Hz), −118.85 (ABd, J_1 = 302.3 Hz, J_2 = 104.9 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.79 (t, J = 105.5 Hz); IR (neat) 3386, 2986, 1254, 1098, 1016, 796, 750, 700; MS (ESI) 359 (M+Na^+); HRMS (EI) exact mass calcd for $C_{15}H_{23}F_2O_4P$ [M^+] 336.1302, found 336.1307.

Diethyl (1,1-difluoro-2-hydroxy-2-methylpentyl)phosphonate (9v): pale yellow oil; 61.4 mg, isolated yield 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33−4.24 (m, 4H), 2.66 (s, br, 1H), 1.71−1.33 (m, 13H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.6 (td, J_1 = 272.5 Hz, J_2 = 201.5 Hz), 75.0 (td, J_1 = 21.4 Hz, J_2 = 14.1 Hz), 64.9 (t, J = 7.9 Hz), 37.5 (q, J = 2.3 Hz), 19.6 (d, J = 2.8 Hz), 16.3 (d, J = 5.6 Hz), 15.9, 14.5; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −118.02 (ABd, J_1 = 302.0 Hz, J_2 = 106.0 Hz), −118.52 (ABd, J_1 = 302.0 Hz, J_2 = 105.2 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 8.07 (t, J = 106.1 Hz); IR (neat) 3396, 2964, 1394, 1254, 1019, 979, 957, 796; HRMS (EI) exact mass calcd for $C_{10}H_{21}F_2O_4P$ [M^+] 274.1146, found 274.1142.

Diethyl ((2,2-difluoro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-inden-1-yl)difluoromethyl)phosphonate (9w): white solid; 84.4 mg, isolated yield 57%; mp 105−107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96−7.84 (m, 3H), 7.72−7.66 (m, 1H), 5.56 (s, br, 1H), 4.39−4.32 (m, 4H), 1.42 (t, J = 4.2 Hz, 3H), 1.39 (t, J = 4.2 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 188.1 (t, J = 24.4 Hz), 146.6 (d, J = 5.8 Hz), 138.0, 134.0 (t, J = 3.6 Hz), 132.8, 129.2, 124.8, 119.2 (td, J_1 = 275.0 Hz, J_2 = 205.0 Hz), 115.9 (dd, J_1 = 277.6 Hz, J_2 = 258.9 Hz), 80.1−79.0 (m), 65.6 (d, J = 6.6 Hz), 65.4 (d, J = 6.9 Hz), 16.5 (d, J = 5.8 Hz), 16.4 (d, J = 5.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −109.94 (ABdd, J_1 = 314.7 Hz, J_2 = 88.3 Hz, J_3 = 24.2 Hz, 1F), −114.01 (ABdd, J_1 = 314.6 Hz, J_2 = 104.0 Hz, J_3 = 5.9 Hz, 1F), −116.18 (AB, J = 280.9 Hz, 1F), −124.32 (ABd, J_1 = 280.9 Hz, J_2 = 24.2 Hz, 1F); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 6.80 (dd, J_1 = 104.7 Hz, J_2 = 88.3 Hz); IR (neat) 3212, 1742, 1276, 1199, 1139, 1101, 1070, 1015; MS (EI) 370 (M^+, 4), 350 (100), 132 (92), 188 (86), 161 (72), 111 (51), 138 (39), 183 (36); HRMS (EI) exact mass calcd for $C_{14}H_{15}F_4O_5P$ [M^+] 370.0593, found 370.0597.

Diethyl (2-(4-chlorophenyl)-1,1-difluoro-2-hydroxyethyl)phosphonate (11a):[4d] white solid; 110.4 mg, isolated yield 84%; mp 97−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (AB, J = 8.7 Hz, 2H), 7.36 (AB, J = 8.7 Hz, 2H), 5.08 (dq, J_1 = 20.4 Hz, J_2 = 4.8 Hz, 1H), 4.27−4.23 (m, 4H), 3.88 (d, J = 4.8 Hz, 1H), 1.37 (t, J = 6.9 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 136.4 (dd, J_1 = 5.8 Hz, J_2 = 2.8 Hz), 134.7, 130.9, 128.8, 119.4 (ddd, J_1 = 272.5 Hz, J_2 = 263.1 Hz, J_3 = 207.9 Hz), 73.1 (ddd, J_1 = 26.7 Hz, J_2 = 21.4 Hz, J_3 = 14.9 Hz), 65.2 (d, J = 6.4 Hz), 64.8 (d, J = 6.8 Hz), 16.6 (d, J = 5.7 Hz), 16.6 (d, J = 5.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.19 (ABd, J_1 = 304.7 Hz, J_2 = 98.4 Hz), −125.10 (ABd, J_1 = 304.8 Hz, J_2 = 104.6 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.30 (dd, J_1 = 105.3 Hz, J_2 = 99.1 Hz); IR (neat) 3310, 2976, 1490, 1398, 1247, 1172, 1084, 1014.

Diethyl (1,1-difluoro-2-hydroxy-2-(4-methoxyphenyl)ethyl)phosphonate (11b):[20] white solid; 118.0 mg, isolated yield 91%; mp 58−59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (AB, J = 8.7 Hz, 2H), 6.91 (AB, J = 8.7 Hz, 2H), 5.06 (dq, J_1 = 20.4 Hz, J_2 = 4.5 Hz, 1H), 4.27−4.20 (m, 4H), 3.81 (s, 3H), 3.65−3.60 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 160.9, 130.4, 129.3 (dd, J_1 = 5.9 Hz, J_2 = 2.8 Hz), 119.6 (ddd, J_1 = 272.6 Hz, J_2 = 262.8 Hz, J_3 = 207.4 Hz), 114.1, 73.4 (ddd, J = 26.8 Hz, J = 21.1 Hz, J = 14.9 Hz), 65.0 (d, J = 6.4 Hz), 64.6 (d, J = 6.7 Hz), 55.5, 16.6 (d, J = 5.2 Hz), 16.6 (d, J = 5.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −114.35 (ABd, J_1 = 303.7 Hz, J_2 = 99.8 Hz), −124.80 (ABd, J_1 = 303.7 Hz, J_2 = 105.8 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.67 (dd, J_1 = 106.0 Hz, J_2 = 100.4 Hz); IR (neat) 3316, 2985, 1611, 1511, 1246, 1170, 1085, 1012.

Diethyl (2-cyclohexyl-1,1-difluoro-2-hydroxyethyl)phosphonate (11c): yellow oil; 60.0 mg, isolated yield 50%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33−4.25 (m, 4H), 3.83−3.70 (m, 1H), 2.75 (d, J = 5.7 Hz, 1H), 1.95−1.58 (m, 6H), 1.41−1.17 (m, 11H); ^{13}C NMR (126 MHz, acetone-d_6) δ 121.8 (ddd, J_1 = 270.3 Hz, J_2 = 265.6 Hz, J_3 = 207.3 Hz), 75.3−74.9 (m), 64.9 (d, J = 6.5 Hz), 64.6 (d,

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J = 6.8 Hz), 39.1−39.1 (m), 30.9−30.8 (m), 27.8, 27.0, 26.9, 26.7, 16.7 (d, J = 1.6 Hz), 16.6 (d, J = 1.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −113.32 (ABd, J_1 = 304.4 Hz, J_2 = 102.1 Hz), −122.67 (ABd, J_1 = 304.3 Hz, J_2 = 106.6 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.93 (dd, J_1 = 107.2 Hz, J_2 = 102.5 Hz); IR (neat) 3362, 2924, 2854, 1450, 1394, 1253, 1165, 1015; MS (ESI) 301 (M +H$^+$); HRMS (EI) exact mass calcd for $C_{12}H_{23}F_2O_4P$ [M$^+$] 300.1302, found 300.1299.

Diethyl (1,1-difluoro-2-hydroxy-4-phenylbutyl)-phosphonate (11d):[4d] yellow solid; 72.2 mg, isolated yield 56%; mp 31−33 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 5H), 4.28 (quint, J = 7.5 Hz, 4H), 4.02−3.89 (m, 1H), 2.98−2.90 (m, 2H), 2.78−2.70 (m, 1H), 2.04−1.94 (m, 2H), 1.37 (t, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, acetone-d_6) δ 142.5, 129.3, 129.2, 124.4, 120.7 (ddd, J_1 = 268.2 Hz, J_2 = 265.2 Hz, J_3 = 206.4 Hz), 71.1 (ddd, J_1 = 24.4 Hz, J_2 = 22.3 Hz, J_3 = 15.2 Hz), 64.8 (d, J = 2.3 Hz), 64.7 (d, J = 2.4 Hz), 32.0, 16.7, 16.6; ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −116.75 (ABd, J_1 = 303.7 Hz, J_2 = 101.2 Hz), −124.94 (ABd, J_1 = 303.8 Hz, J_2 = 104.9 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ 7.66 (dd, J_1 = 105.5 Hz, J_2 = 102.0 Hz); IR (neat) 3365, 2985, 2932, 1251, 1164, 1015, 750, 700.

Synthesis of Product 12 by Using TBAF To Remove TMS Group. To a 10 mL Schlenk tube were added KOAc (3.9 mg, 10 mol %), 18-crown-6 (10.6 mg, 10 mol %), and anhydrous THF (1.5 mL), followed by the addition of reagent **5** (156.2 mg, 1.5 equiv) and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **8q** (0.40 mmol). After the mixture was stirred at room temperature until almost full conversion of **8q** by TLC analysis, a solution of TBAF in THF (1 M, 1 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 0.5 h, and then was concentrated and directly subjected to column chromatography (petroleum ether:EtOAc = 4:1) to afford the rearranged product **12** in 74% yield as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.45 (m, 2H), 7.44−7.31 (m, 3H), 6.94 (AB, J = 16.4 Hz, 1H), 6.48 (d, J = 16.4 Hz, 1H), 6.24 (t, J = 54.8 Hz, 1H), 4.25−4.13 (m, 4H), 3.91 (s, 3H), 1.37−1.31 (m, 6H); ^{13}C NMR (126 MHz, acetone-d_6) δ 167.4−167.3 (m), 136.8, 136.3, 129.7, 129.6, 127.8, 120.6−120.6 (m), 114.5 (td, J_1 = 250.4 Hz, J_2 = 7.7 Hz), 83.1 (td, J_1 = 23.2 Hz, J_2 = 5.5 Hz), 64.8, 64.8, 53.7, 16.3 (d, J = 4.4 Hz), 16.3 (d, J = 4.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −127.61 (AB, J = 284.0 Hz), −129.16 (AB, J = 284.0 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ −4.32 (s); IR (neat) 2986, 1722, 1441, 1218, 1164, 1025, 757, 698; MS (EI) 378 (M$^+$, 9), 165 (100), 155 (60), 209 (58), 204 (45), 224 (39), 115 (38), 127 (36); HRMS (EI) exact mass calcd for $C_{16}H_{21}F_2O_6P$ [M$^+$] 378.1044, found 378.1050.

Rearrangement Reaction of Product 7a. To a solution of **7a** (139.6 mg, 0.4 mmol) in 2.0 mL of anhydrous THF at room temperature was added NaH (48 mg, 5 equiv, washed with anhydrous hexane prior to use) in portions. After full conversion of **7a** by TLC analysis, water was added cautiously at −10 °C. The mixture was extracted with ethyl acetate three times, and the combined organic layers were dried over anhydrous Na_2SO_4. After concentration, the crude material was purified by column chromatography (petroleum ether:EtOAc = 4:1) to afford the rearrangement product **13** in 66% yield as brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.06 (dd, J_1 = 56.5 Hz, J_2 = 54.3 Hz, 1H), 4.14 (quint, 2H), 3.96−3.86 (m, 2H), 3.24 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 170.5 (d, J = 5.9 Hz), 146.7, 132.8, 127.4, 123.4, 121.6, 114.8 (ddd, J_1 = 252.2 Hz, J_2 = 243.0 Hz, J_3 = 16.2 Hz), 110.0, 79.4 (ddd, J_1 = 31.1 Hz, J_2 = 22.4 Hz, J_3 = 4.8 Hz), 64.9 (d, J = 6.2 Hz), 64.7 (d, J = 5.5 Hz), 26.8, 16.2 (d, J = 4.4 Hz), 16.1 (d, J = 4.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $PhCF_3$) δ −129.49 (ABd, J_1 = 289.9 Hz, J_2 = 4.5 Hz), −133.56 (AB, J = 290.3 Hz); ^{31}P NMR (122 MHz, $CDCl_3$, 85% H_3PO_4) δ −4.00 (d, J = 3.8 Hz); IR (neat) 2998, 1733, 1614, 1473, 1370, 1287, 1093, 1016; MS (EI) 349 (M$^+$, 24), 195 (100), 167 (53), 162 (45), 196 (24), 168 (15), 127 (12), 148 (9); HRMS (EI) exact mass calcd for $C_{14}H_{18}F_2NO_5P$ [M$^+$] 349.0891, found 349.0893.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01457.

^{1}H, ^{19}F, ^{31}P, and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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