Synthesis M. V. Ivanova et al. Paper

Palladium-Catalyzed Synthesis of Aryl and Heteroaryl Difluoromethylated Phosphonates

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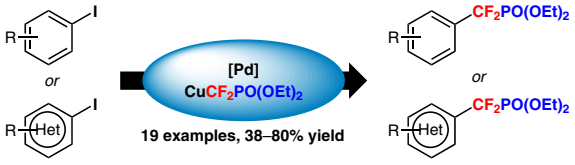

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Abstract We report the palladium-catalyzed introduction of the difluoromethylposphonate unit onto aryl and heteroaryl iodides under mild conditions. Using the $CuCF_2PO(OEt)_2$ species generated in situ, the method allows the functionalization of various otherwise reluctant substrates. In addition, this reaction permits the formation of $CF_2PO(OEt)_2$-containing heterocycles, an important class of compounds. This process broadens the current toolbox of methods available to construct $CF_2PO(OEt)_2$-containing molecules.

Key words fluorine, phosphate mimic, synthetic method, palladium, copper

Over the last years, organofluorine chemistry became a very popular research area.[1] This tremendous expansion is due to the particular properties of the fluorine atom.[2] For instance, its electronegativity (the highest of the periodic table) and its size strongly impact the physicochemical properties of the molecules. Hence, fluorinated molecules play an important role in the discovery of bioactive compounds and currently about 25% of pharmaceuticals and 40% of agrochemicals bear at least one fluorine atom.[3]

Therefore, the quest for new methods to synthesize fluorinated compounds is a blossoming research area. As part of it, the design of new tools to introduce fluorinated bioisosteres[4] is of matter of importance. In that context, the development of new methodologies to introduce the difluoromethylphosphonate residue ($CF_2PO(OR)_2$) is appealing, since this motif is widely recognized as a phosphate mimic.[5] Indeed, phosphates are involved in a plethora of biological events and the development of bioisosteres that are stable in vivo could afford metabolically stable analogues with interesting biological activities. This paradigm, developed by Blackburn in the early 1980s,[6] already afforded promising bioactive compounds (Figure 1).[7]

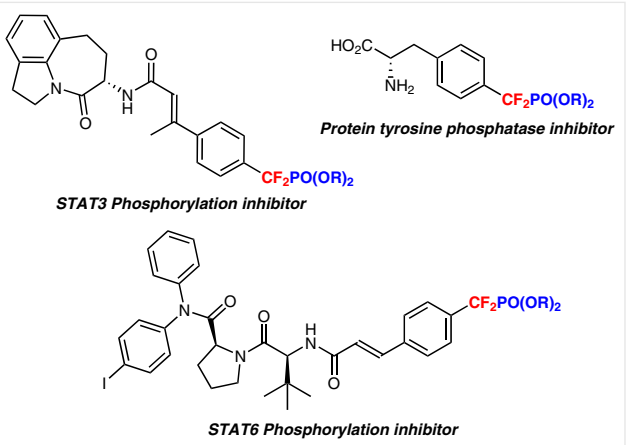
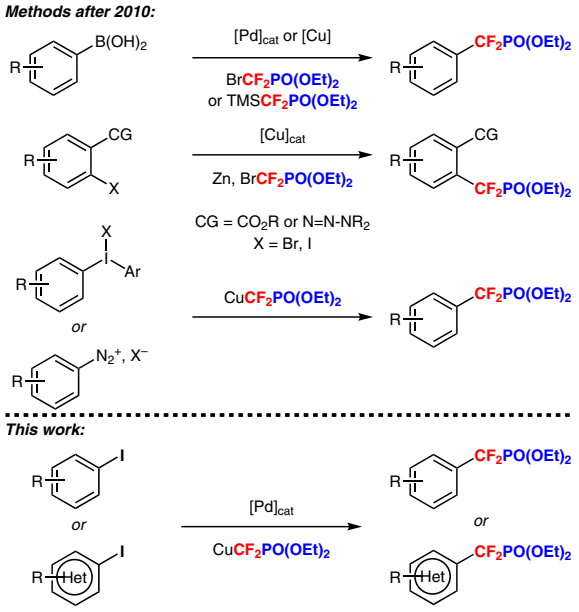


Figure 1 Biologically active molecules bearing a $CF_2PO(OR)_2$ motif

In contrast to the importance of this motif, only a few methods have been developed to introduce this fluorinated residue onto arenes prior to 2010. In 1996, Burton reported the coupling reaction of toxic $CdCF_2PO(OEt)_2$ with aryl iodides in the presence of a stoichiometric amount of CuCl.[8] The next year, Shibuya described a similar transformation using the $ZnCF_2PO(OEt)_2$ reagent under ultrasonic conditions.[9] Both of these methods suffered from the use of either a toxic reagent (Cd-derived reagent) or the use of specialized reaction conditions (ultrasound).

Recently, several alternative methods appeared that could be used to introduce this motif onto aromatic derivatives (Scheme 1). One should mention the significant contributions from the groups of Zhang[10] and Qing,[11] who developed the Suzuki and oxidative cross-coupling reactions with boronic acid derivatives to introduce the $CF_2PO(OR)_2$ motif onto arenes. Additionally, the Ullmann type coupling reaction on iodobenzoates[12] and *o*-iodo- or *o*-bromotriazenes[13] was achieved by Zhang. Recently, our group devel-

oped new approaches for the introduction of the $CF_2PO(OEt)_2$ group onto aryl diazonium salts[14] and aryl iodonium salts[15] by using a copper-mediated transformation. Quite surprisingly, no practical method was reported for the functionalization of simple halogenated aryl derivatives and the functionalization of heteroaryl compounds remained scarce, despite their high relevance in medicinal and agrochemistry.

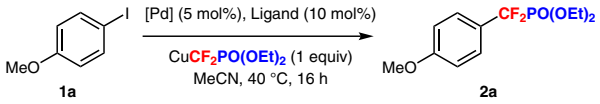


Scheme 1 State of the art and present work

To tackle this synthetic issue and to afford a straightforward access to difluoromethylphosphonate-containing molecules, we envisioned the functionalization of simple aryl and heteroaryl iodides in the presence of a palladium catalyst.

At the outset of our investigations, we studied the reaction between *p*-iodoanisole **1a** and the $CuCF_2PO(OEt)_2$ species, easily generated from $TMSCF_2PO(OEt)_2$, a copper salt and a suitable activator (Table 1).[16] First, the reaction of **1a** and the in situ generated $CuCF_2PO(OEt)_2$ species was carried out in the presence of $Pd(OAc)_2$ as a catalyst in MeCN at 40 °C and, pleasingly, traces of **2a** were detected (entry 1). Several palladium catalysts were then screened. The use of Pd_2dba_3 gave a decent 65% NMR yield (entry 2), whereas $Pd(PPh_3)_4$ and $PdCl_2$ allowed the formation of **2a** in 19% and 40% yield, respectively (entries 3 and 4). Pleasingly, the use of $PdCl_2(PPh_3)_2$ gave **2a** in 67% NMR yield and 54% isolated yield (entry 5). To improve the reaction yield, various ligands were then screened with $PdCl_2$ as catalyst. However, no improvement of the reaction yield was observed with 1,1′-bis(diphenylphosphino)ferrocene (dppf) or Xantphos (entries 6 and 7).[17] Attempts to decrease the reaction temperature or the catalyst loading did not enhance the reaction yield (entries 8 and 9). Finally, a control experiment showed that no reaction occurred in the absence of the palladium catalyst, even at a higher temperature (entries 10 and 11).

Table 1 Optimization of the Reaction Conditions with **1a**

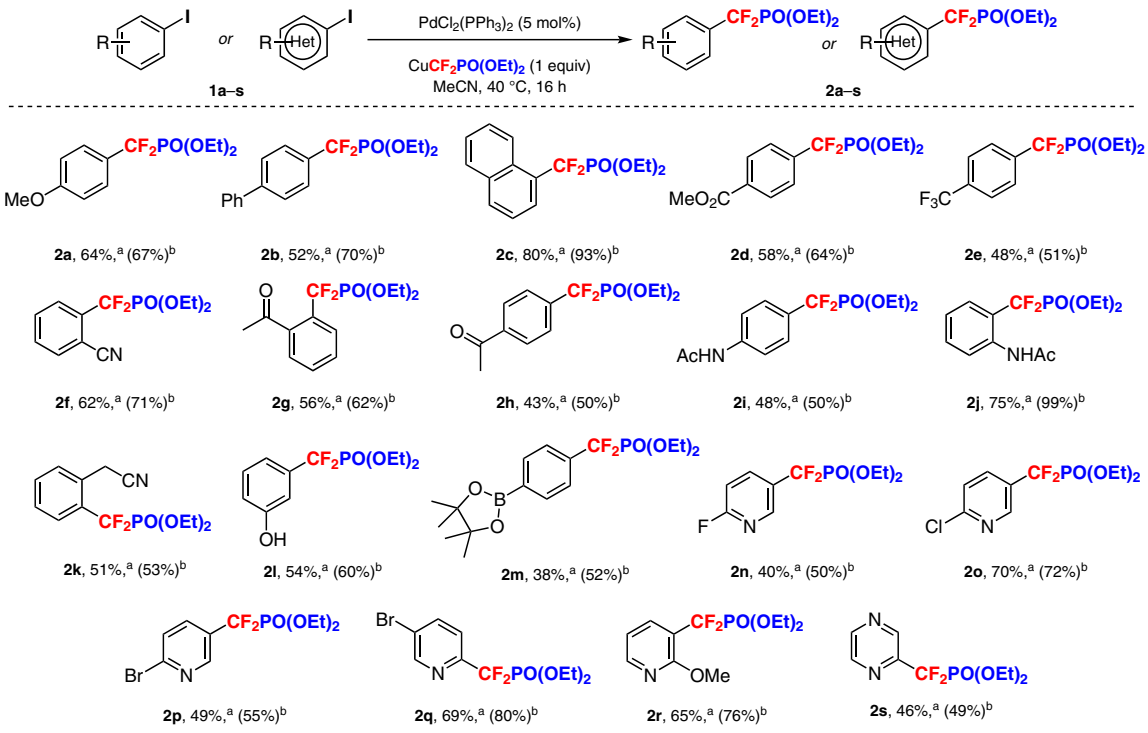


Entry	[Pd]	Ligand	Yield (%)[a]
1	$Pd(OAc)_2$	–	trace
2	Pd_2dba_3	–	65
3	$Pd(PPh_3)_4$	–	19
4	$PdCl_2$	–	40
5	$PdCl_2(PPh_3)_2$	–	67 (54)[b]
6	$PdCl_2$	dppf	11
7	$PdCl_2$	Xantphos	20
8[c]	$PdCl_2(PPh_3)_2$	–	29
9[d]	$PdCl_2(PPh_3)_2$	–	45
10	–	–	NR
11[e]	–	–	NR

[a] Yields were determined by ^{19}F NMR spectroscopic analysis using α,α,α-trifluorotoluene as internal standard. NR: no reaction.
[b] Isolated yield.
[c] Reaction was performed at 25 °C.
[d] [Pd] (2 mol%) was used.
[e] Reaction was performed at 80 °C.

Having these optimized conditions in hand, we sought to extend the scope of this transformation (Scheme 2).

First, 4-iodo-1,1′-biphenyl **1b** and 1-iodonaphthalene **1c** were tested under the optimized conditions. Pleasingly, the corresponding difluromethylphosphonates **2b** and **2c** were isolated in good yields, 52% and 80% respectively. Electron-withdrawing groups were well tolerated as substituents on the aromatic ring. Indeed, *p*-iodobenzoate and *p*-iodo-trifluorotoluene furnished the desired products **2d** and **2e** in 58% and 48% isolated yields, respectively. Notably, *o*-iodobenzonitrile **1f** was readily converted into the fluorinated compound **2f** in 62% yield. Note that this compound was reluctant under our previously reported conditions.[18] Keto-substituted iodoarenes were suitable substrates, as demonstrated with **2g** and **2h**. Iodoarenes **1i** and **1j**, bearing an acetamide group, were also readily converted into the corresponding difluoromethylphosphonates **2i** and **2j**. Note that the acetamide coordinating group was not suitable in the previously reported Ullmann type process.[18] Benzyl cyanide as well as unprotected phenol derivatives **1k** and **1l** were also functionalized in moderate yields. Interestingly, the iodo-boronate **1m** is a suitable substrate, although **2m** was isolated in a moderate 38% yield because of a difficult



Scheme 2 Scope of the transformation. [a] Isolated yields. [b] Yields determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

purification. This last example demonstrates the excellent functional group tolerance of this transformation. The presence of the boron substituent offers possibilities for a panel of post-functionalization reactions. Finally, we turned our attention to the functionalization of heterocyclic derivatives to facilitate access to $CF_2PO(OEt)_2$-containing heterocycles, which is an underexplored class of compounds.[19] First, iodopyridine derivatives **1n–q**, bearing a halogen atom at the 6- and 5-position, were tested. To our delight, the corresponding products **2n–q** were isolated in moderate to good yields. Notably, that the reaction was highly selective toward the functionalization of the iodo substituent, since chlorine and even bromine atoms were tolerated as substituents, offering room for further postfunctionalization reactions. 2-Methoxy-3-iodopyridine **1r** was also functionalized in a decent 65% yield. Finally, pyrazine **2s** was obtained in a moderate 46% yield, demonstrating the applicability of the method to diazine derivatives.

In summary, we reported herein a practical method for the functionalization of aryl and heteroaryl iodides with $CuCF_2PO(OEt)_2$ in the presence of a palladium catalyst under mild conditions. The reaction proceeded well and allowed the functionalization of various substrates that were previously reluctant, and demonstrated good functional group tolerance (phenol, boronate, ketones, nitriles, esters, etc.). In addition, the reaction proved to be an efficient way to access heteroaryl $CF_2PO(OEt)_2$-containing scaffolds. By broadening the current toolbox to build up $CF_2PO(OEt)_2$-containing molecules, we believe that this synthetic method will be useful to access new bioactive molecules.

All reactions were carried out using oven-dried glassware and magnetic stirring under an atmosphere of argon unless otherwise stated. Flash chromatography was performed with silica gel (0.040–0.060 nm). Reverse-phase chromatography was performed with a puriFlash®215 using a puriFlash® C18HP 15µm 55G Flash column. Analytical thin-layer chromatography was performed on silica gel aluminum plates with F-254 indicator and visualized with UV light (254 nm) and/or chemical staining with a $KMnO_4$ solution. ^1H NMR spectra were recorded with a Bruker DXP 300 at 300 MHz, ^{13}C NMR spectra at 75 MHz, ^{19}F NMR spectra at 282 MHz, and ^{31}P NMR at 121 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) relative to the residual solvent peak for $CDCl_3$ (δ_H = 7.26 ppm; δ_C = 77.16 ppm); or relative to external $CFCl_3$ (δ = 0 ppm). The following abbreviations are used: δ (chemical shift), *J* (coupling constant), app. (apparent), br. (broad), s (singlet), d (doublet), dd (doublet of doublets), t (triplet), td (triplet of doublets), dt (doublet of triplets), q (quartet), m (multiplet). High-resolution mass spectra (HRMS) were recorded with a Waters LCT Premier, IR spectra were recorded with a PerkinElmer Spectrum 100.

General Procedure

A tube was loaded with CuCl (50 mg, 0.50 mmol) and CsF (228 mg, 1.50 mmol) and sealed with a rubber septum. Anhydrous acetonitrile (1 mL) was added and the mixture was cooled to 0 °C. Diethyl

[(trimethylsilyl)difluoromethyl]phosphonate (neat, 325 mg, 1.25 mmol) was added and the mixture was heated at 40 °C for 1 h, cooled to 0 °C and stirred at this temperature for 1 h. $Pd(PPh_3)Cl_2$ (18 mg, 0.025 mmol) was added followed by a solution of the corresponding iodoarene **1** (0.50 mmol) in MeCN (1 mL). The suspension was stirred for 16 h at 40 °C. The reaction mixture was diluted with diethyl ether (15 mL), the organic layer was washed with water (15 mL), Na_2CO_3 (concentrated solution, 15 mL), dried over Na_2SO_4, and solvents were carefully removed under vacuum. Reverse-phase chromatography (H_2O/MeCN or MeOH, gradient: 9:1 to 0:1, rate: 1% MeCN or MeOH per minute) gave the product **2**.

Diethyl [(4-Methoxyphenyl)difluoromethyl]phosphonate (2a)

Prepared by following the general procedure from 1-iodo-4-methoxybenzene (**1a**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 64% (89 mg, 0.5 mmol scale): colorless oil.

IR (neat): 2985, 1614, 1515, 1250, 1011 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.3 Hz, 2 H), 6.94 (d, *J* = 8.6 Hz, 2 H), 4.49–3.97 (m, 4 H), 3.81 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (dd, *J* = 3.6, 1.7 Hz), 127.9 (td, *J* = 6.8, 2.4 Hz), 124.6 (td, *J* = 22.7, 14.0 Hz), 118.3 (td, *J* = 263.0, 220.9 Hz), 113.9 (d, *J* = 1.2 Hz), 64.8 (d, *J* = 6.7 Hz), 55.4, 16.4 (d, *J* = 5.6 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –107.6 (d, *J* = 119.7 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 6.6 (t, *J* = 119.8 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{18}F_2O_4P$: 295.0911; found: 295.0906 (–1.7 ppm).

Diethyl [(1,1′-Biphenyl)-4-yldifluoromethyl]phosphonate (2b)

Prepared by following the general procedure from 4-iodo-1,1′-biphenyl (**1b**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 52% (89 mg, 0.5 mmol scale); brown oil.

IR (neat): 2984, 1611, 1394, 1267, 1166, 1114, 1013, 978 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.66 (m, 4 H), 7.61 (d, *J* = 7.7 Hz, 2 H), 7.46 (t, *J* = 7.0 Hz, 2 H), 7.41–7.36 (m, 1 H), 4.32–4.12 (m, 4 H), 1.34 (t, *J* = 6.9 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7 (dt, *J* = 2.1, 1.9 Hz), 140.1, 131.5 (dt, *J* = 22.4, 13.4 Hz), 131.4, 129.0, 128.1, 127.4–127.3 (m), 126.8 (td, *J* = 6.8, 2.1 Hz), 118.2 (td, *J* = 263.9, 216.6 Hz), 64.9 (d, *J* = 6.8 Hz), 16.4 (d, *J* = 5.7 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –108.8 (d, *J* = 116.6 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 6.4 (t, *J* = 116.4 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{17}H_{23}NF_2O_3P$: 358.1384; found: 358.1383 (–0.3 ppm).

Diethyl [(Naphthen-1-yl)difluoromethyl]phosphonate (2c)

Prepared by following the general procedure from 1-iodonaphthalene (**1c**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 80% (126 mg, 0.5 mmol scale); dark orange oil.

IR (neat): 2985, 1514, 1269, 1010 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 8.5 Hz, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.81 (d, *J* = 7.4 Hz, 1 H), 7.59–7.48 (m, 3 H), 4.29–4.01 (m, 4 H), 1.25 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.1 (d, *J* = 0.9 Hz), 132.1 (dd, *J* = 3.4, 1.7 Hz), 129.9 (dd, *J* = 3.7, 1.8 Hz), 128.6 (d, *J* = 2.5 Hz), 128.4 (td, *J* = 20.1, 13.5 Hz), 126.9, 126.4 (td, *J* = 10.4, 3.6 Hz), 126.3, 126.1 (td, *J* = 5.2, 0.7 Hz), 124.4 (d, *J* = 1.7 Hz), 120.0 (td, *J* = 264.1, 216.8 Hz), 64.8 (d, *J* = 6.8 Hz), 16.3 (d, *J* = 5.6 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –102.4 (d, *J* = 114.6 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 6.7 (t, *J* = 114.7 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{21}NF_2O_3P$: 332.1227; found: 332.1233 (1.8 ppm).

Methyl 4-[(Diethoxyphosphoryl)difluoromethyl]benzoate (2d)

Prepared by following the general procedure from methyl 4-iodobenzoate (**1d**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 58% (94 mg, 0.5 mmol scale); colorless oil.

IR (neat): 2987, 2917, 2849, 1727, 1437, 1408, 1274, 1164, 1111, 1011, 941 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.2 Hz, 2 H), 7.70–7.67 (m, 2 H), 4.28–4.08 (m, 4 H), 3.93 (s, 3 H), 1.32–1.28 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 137.0 (dt, *J* = 21.9, 13.7 Hz), 132.4–132.3 (m), 129.7 (d, *J* = 1.3 Hz), 126.5 (dt, *J* = 6.7, 2.2 Hz), 117.7 (td, *J* = 263.3, 216.9 Hz), 65.0 (d, *J* = 6.8 Hz), 52.5, 16.4 (d, *J* = 5.4 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –109.8 (d, *J* = 113.3 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 5.8 (t, *J* = 112.5 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{13}H_{21}F_2O_5PN$: 340.1125; found: 340.1126 (0.3 ppm).

Diethyl [(4-{Trifluoromethyl}phenyl)difluoromethyl]phosphonate (2e)

Prepared by following the general procedure from *p*-iodotrifluorotoluene (**1e**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 48% (80 mg, 0.5 mmol scale); orange oil.

IR (neat): 2992, 1414, 1266, 1127, 1066, 1013 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.65 (m, 4 H), 4.32–4.10 (m, 4 H), 1.31 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.9–136.0 (m), 133.6–132.2 (m), 127.0 (td, *J* = 6.8, 2.3 Hz), 125.6 (qd, *J* = 3.7, 1.3 Hz), 120.1 (q, *J* = 272.7 Hz), 117.5 (td, *J* = 263.6, 217.3 Hz), 65.1 (d, *J* = 6.8 Hz), 16.4 (d, *J* = 5.5 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –63.5 (s, 3 F), –109.9 (d, *J* = 112.8 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 5.6 (t, *J* = 112.8 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{12}H_{18}NF_5O_3P$: 350.0944; found: found: 350.0938 (–1.7 ppm).

Diethyl [(2-Cyanophenyl)difluoromethyl]phosphonate (2f)

Prepared by following the general procedure from 2-iodobenzonitrile (**1f**). Reverse phase chromatography (H_2O/MeCN).

Yield: 62% (89 mg, 0.5 mmol scale); yellow oil.

IR (neat): 2987, 2234, 1445, 1271, 1240, 1129, 1070, 1010, 940 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.6 Hz, 1 H), 7.74–7.65 (m, 2 H), 7.61–7.56 (m, 1 H), 4.38–4.20 (m, 4 H), 1.35 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.3 (dt, *J* = 21.5, 13.4 Hz), 134.9, 132.6 (d, *J* = 1.1 Hz), 131.1 (d, *J* = 1.6 Hz), 128.8–128.5 (m), 117.3 (td, *J* = 265.9, 218.7 Hz), 116.8, 110.7–110.6 (m), 65.5 (d, *J* = 7.1 Hz), 16.4 (d, *J* = 5.5 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –107.4 (d, *J* = 111.9 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 4.6 (t, *J* = 112.1 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{12}H_{18}F_2N_2O_3P$: 307.1023; found: 307.1028 (1.6 ppm).

Diethyl [(2-Acetylphenyl)difluoromethyl]phosphonate (2g)

Prepared by following the general procedure from 1-(2-iodophenyl)ethan-1-one (**1g**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 56% (85 mg, 0.5 mmol scale); colorless oil.

IR (neat): 2963, 1706, 1394, 1359, 1257, 1010, 792 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.69 (m, 1 H), 7.53–7.45 (m, 2 H), 7.25–7.22 (m, 1 H), 4.28–4.14 (m, 4 H), 2.56–2.55 (m, 3 H), 1.35–1.30 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.1, 141.6 (q, *J* = 3.4 Hz), 131.0 (d, *J* = 1.6 Hz), 129.2 (d, *J* = 1.6 Hz), 128.7 (dt, *J* = 7.2, 1.2 Hz), 128.4 (dt, *J* = 21.8, 15.4 Hz), 126.0, 118.6 (td, *J* = 264.7, 217.2 Hz), 65.2 (d, *J* = 6.8 Hz), 31.8 (d, *J* = 3.3 Hz), 16.4 (d, *J* = 5.5 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –101.2 (d, *J* = 112.7 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 5.5 (t, *J* = 112.2 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}F_2O_4P$: 307.0911; found: 307.0909 (–0.7 ppm).

Diethyl [(4-Acetylphenyl)difluoromethyl]phosphonate (2h)

Prepared by following the general procedure from 1-(4-iodophenyl)ethan-1-one (**1h**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 43% (66 mg, 0.5 mmol scale); colorless oil.

IR (neat): 3670, 2988, 1689, 1613, 1407, 1264, 1011 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.1 Hz, 2 H), 7.70 (d, *J* = 7.9 Hz, 2 H), 4.28–4.09 (m, 4 H), 2.61 (s, 3 H), 1.30 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 138.9 (dd, *J* = 3.6, 1.9 Hz), 137.1 (td, *J* = 21.9, 13.6 Hz), 128.4 (d, *J* = 1.2 Hz), 126.7 (td, *J* = 6.7, 2.2 Hz), 117.7 (td, *J* = 263.6, 216.8 Hz), 65.0 (d, *J* = 6.8 Hz), 26.8, 16.4 (d, *J* = 5.5 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –105.3 (d, *J* = 115.3 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 5.9 (t, *J* = 115.0 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{13}H_{21}F_2NO_4P$: 324.1176; found: 324.1182 (1.9 ppm).

Diethyl [(4-Acetamidophenyl)difluoromethyl]phosphonate (2i)

Prepared by following the general procedure from methyl *N*-(4-iodophenyl)acetamide (**1i**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 48% (77 mg, 0.5 mmol scale); yellow oil.

IR (neat): 3283, 2984, 1694, 1601, 1534, 1408, 1369, 1317, 1258, 1118, 1018 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.50 (s, 1 H), 7.57–7.54 (m, 2 H), 7.47–7.45 (m, 2 H), 4.29–4.11 (m, 4 H), 2.14 (s, 3 H), 1.33 (t, *J* = 6.9 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 141.2, 127.0–126.8 (m), 127.3–126.5 (m), 119.4, 118.1 (td, *J* = 264.2, 219.7 Hz), 65.1 (d, *J* = 7.0 Hz), 24.4, 16.4 (d, *J* = 5.4 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –108.6 (d, *J* = 119.9 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 6.0 (t, *J* = 119.2 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{13}H_{22}F_2N_2O_4P$: 339.1285; found: 339.1284 (–0.3 ppm).

Diethyl [(2-Aacetamidophenyl)difluoromethyl]phosphonate (2j)

Prepared by following the general procedure from methyl *N*-(2-iodophenyl)acetamide (**1j**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 75% (121 mg, 0.5 mmol scale); yellow oil.

IR (neat): 3287, 2986, 2922, 1698, 1587, 1530, 1448, 1370, 1299, 1270, 1138, 1105, 1011 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.38 (s, 1 H), 7.98 (d, *J* = 8.1 Hz, 1 H), 7.48–7.42 (m, 2 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 4.26–4.03 (m, 4 H), 2.14 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 136.3–136.2 (m), 131.9 (d, *J* =1.7 Hz), 126.6 (dt, *J* = 9.9, 2.9 Hz), 126.0, 124.6, 123.2 (dt, *J* = 20.9, 13.5 Hz), 117.7 (td, *J* = 264.1, 215.5 Hz), 65.8 (d, *J* = 7.0 Hz), 24.3, 16.3 (d, *J* = 5.5 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –108.9 (d, *J* = 113.7 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 8.1 (t, *J* = 113.4 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}F_2NO_4P$: 322.1020; found: 301.1021 (0.3 ppm).

Diethyl [(2-(Cyanomethyl)phenyl)difluoromethyl]phosphonate (2k)

Prepared by following the general procedure from 2-(2-iodophenyl)acetonitrile (**1k**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 51% (78 mg, 0.5 mmol scale); colorless oil.

IR (neat): 2985, 2918, 2251, 1584, 1447, 1394, 1264, 1243, 1163, 1129, 1011, 941 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.64 (app d, 1 H), 7.59–7.51 (m, 2 H), 7.46–7.41 (m, 1 H), 4.26–4.09 (m, 6 H), 1.34–1.29 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.8–131.7 (m), 130.6 (d, *J* = 1.3 Hz), 129.7–129.6 (m), 128.2 (d, *J* = 1.2 Hz), 128.2–127.9 (m), 128.1 (d, *J* = 2.5 Hz), 119.0 (td, *J* = 266.3, 215.5 Hz), 118.1, 65.3 (d, *J* = 6.9 Hz), 22.2 (d, *J* = 5.3 Hz), 16.4 (d, *J* = 5.6 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –105.5 (d, *J* = 112.9 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 6.3 (t, *J* = 112.8 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}F_2NO_3P$: 304.0914; found: 304.0914 (0.0 ppm).

Diethyl [(3-Hydroxyphenyl)difluoromethyl]phosphonate (2l)

Prepared by following the general procedure from 3-iodophenol (**1l**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 54% (75 mg, 0.5 mmol scale); yellow oil.

IR (neat): 3259, 2986, 1772, 1607, 1593, 1481, 1455, 1296, 1240, 1163, 1122, 1013, 952 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.23–7.19 (m, 2 H), 7.02 (d, *J* = 7.7 Hz, 1 H), 6.89 (t, *J* = 8.2 Hz, 1 H), 4.24–4.01 (m, 4 H), 1.26 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (d, *J* = 1.5 Hz), 133.3 (dt, *J* = 21.8, 13.8 Hz), 129.8 (d, *J* = 1.1 Hz), 118.5 (d, *J* = 1.8 Hz), 117.8 (td, *J* = 263.9, 220.2 Hz), 117.0 (dt, *J* = 7.1, 2.8 Hz), 113.6 (dt, *J* = 6.8, 1.7 Hz), 65.5 (d, *J* = 6.8 Hz), 16.4 (d, *J* = 5.6 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –109.0 (d, *J* = 118.2 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 6.2 (t, *J* = 118.3 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{11}H_{19}NF_2O_4P$: 298.1020; found: 298.1022 (0.7 ppm).

Diethyl [(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)difluoromethyl]phosphonate (2m)

Prepared by following the general procedure from 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1m**). Reverse-phase chromatography (H_2O/MeCN).

Yield: 38% (75 mg, 0.5 mmol scale); colorless oil.

IR (neat): 2981, 2915, 2845, 1715, 1612, 1516, 1399, 1360, 1327, 1269, 1144, 1090, 1015, 857 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.8 Hz, 2 H), 7.60 (d, *J* = 7.7 Hz, 2 H), 4.24–4.08 (m, 4 H), 1.35 (s, 12 H), 1.30 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1 (dt, *J* = 21.9, 13.5 Hz), 134.8, 134.8, 125.5 (td, *J* = 6.8, 2.3 Hz), 118.0 (td, *J* = 260.0, 219.0 Hz), 84.3, 64.9 (d, *J* = 6.7 Hz), 24.9, 16.4 (d, *J* = 5.7 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –109.5 (d, *J* = 115.6 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 6.3 (t, *J* = 115.7 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{17}H_{30}BF_2NO_5P$: 408.1923; found: 408.1920 (–0.7 ppm).

Diethyl [(6-Fluoropyridin-3-yl)difluoromethyl]phosphonate (2n)

Prepared by following the general procedure from 2-fluoro-5-iodopyridine (**1n**). Reverse-phase chromatography (H_2O/MeOH).

Yield: 40% (57 mg, 0.5 mmol scale); yellow oil.

IR (neat): 2990, 1599, 1486, 1386, 1256, 1163, 1126, 1011, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.44 (s, 1 H), 8.05–8.00 (m, 1 H), 7.01 (dd, *J* = 8.5, 2.7 Hz, 1 H), 4.29–4.16 (m, 4 H), 1.32 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0 (dd, *J* = 243.7, 1.8 Hz), 146.4 (ddt, *J* = 16.3, 7.5, 2.6 Hz), 139.9 (ddt, *J* = 9.0, 6.0, 1.7 Hz), 127.4–126.5 (m), 117.0 (tdd, *J* = 264.1, 219.1, 1.4 Hz), 109.7 (dd, *J* = 37.7, 0.9 Hz), 65.3 (d, *J* = 6.8 Hz), 16.4 (d, *J* = 5.4 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –64.7 (s, 1 F), –109.5 (d, *J* = 112.5 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 5.2 (t, *J* = 112.4 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{10}H_{17}F_3N_2O_3P$: 301.0929; found: 301.0922 (–2.3 ppm).

Diethyl [(2-chloropyridin-3-yl)difluoromethyl]phosphonate (2o)

Prepared by following the general procedure from 2-chloro-5-iodopyridine (**1o**). Reverse-phase chromatography (H_2O/MeOH).

Yield: 70% (105 mg, 0.5 mmol scale; note that the product was contaminated with 10% of an unknown product); yellow oil.

IR (neat): 2986, 2917, 1591, 1461, 1372, 1263, 1107, 1012, 575 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1 H), 7.87–7.84 (m, 1 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 4.28–4.14 (m, 4 H), 1.33–1.28 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2 (dd, *J* = 4.3, 2.2 Hz), 147.7 (td, *J* = 7.4, 2.6 Hz), 137.1 (td, *J* = 6.1, 1.8 Hz), 128.0 (td, *J* = 22.9, 13.9 Hz), 124.2 (d, *J* = 1.1 Hz), 117.0 (td, *J* = 263.8, 219.1 Hz), 65.3 (d, *J* = 6.9 Hz), 16.4 (d, *J* = 5.4 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –110.4 (d, *J* = 111.8 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 5.0 (t, *J* = 111.7 Hz, 1 P).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{13}ClF_2NO_3P$: 299.0290; found: 299.0277 (–4.2 ppm).

Diethyl [(6-Bromopyridin-3-yl)difluoromethyl]phosphonate (2p)

Prepared by following the general procedure from 2-bromo-5-iodopyridine (**1p**). Reverse-phase chromatography (H_2O/MeOH).

Yield: 49% (84 mg, 0.5 mmol scale); white oil.

IR (neat): 2986, 2928, 1584, 1456, 1369, 1262, 1164, 1091, 1011 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1 H), 7.78–7.75 (m, 1 H), 7.58 (d, *J* = 8.3 Hz, 1 H), 4.29–4.16 (m, 4 H), 1.35–1.31 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.0 (td, *J* = 7.3, 2.4 Hz), 145.0 (d, *J* = 2.0 Hz), 136.7 (td, *J* = 6.2, 1.8 Hz), 128.7–128.0 (m), 128.1, 116.9 (td, *J* = 264.9, 219.2 Hz), 65.3 (d, *J* = 6.9 Hz), 16.5 (d, *J* = 5.5 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –111.1 (d, *J* = 112.0 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 4.9 (t, *J* = 111.3 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{14}BrF_2NO_3P$: 343.9863; found: 343.9866 (0.9 ppm).

Diethyl [(5-Bromopyridin-2-yl)difluoromethyl]phosphonate (2q)

Prepared by following the general procedure from 5-bromo-2-iodopyridine (**1q**). Reverse-phase chromatography (H_2O/MeOH).

Yield: 69% (119 mg, 0.5 mmol scale); yellow oil.

IR (neat): 2986, 2917, 1561, 1464, 1366, 1269, 1228, 1125, 1007, 944, 838 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.72–8.71 (m, 1 H), 7.95–7.91 (m, 1 H), 7.55 (d, *J* = 8.3 Hz, 1 H), 4.31–4.19 (m, 4 H), 1.31 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.7, 150.0 (dt, *J* = 24.3, 14.4 Hz), 139.8, 123.0–122.9 (m), 123.0, 116.0 (td, *J* = 264.6, 214.1 Hz), 65.1 (d, *J* = 6.7 Hz), 16.3 (d, *J* = 5.7 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –111.0 (d, *J* = 106.9 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 4.9 (t, *J* = 107.1 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{14}BrF_2NO_3P$: 343.9863; found: 343.9861 (–0.6 ppm).

Diethyl [(2-Methoxypyridin-3-yl)difluoromethyl]phosphonate (2r)

Prepared by following the general procedure from 3-iodo-2-methoxypyridine (**1r**). Reverse-phase chromatography (H_2O/MeOH).

Yield: 65% (66 mg, 0.5 mmol scale); white oil.

IR (neat): 2986, 2916, 1592, 1583, 1470, 1409, 1304, 1268, 1220, 1164, 1127, 1010, 936 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.24–8.22 (m, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 6.95–6.91 (m, 1 H), 4.29–4.16 (m, 4 H), 3.98 (s, 3 H), 1.33–1.29 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1–160.9 (m), 149.5 (d, *J* = 1.8 Hz), 137.7 (dt, *J* = 8.4, 2.6 Hz), 117.6 (td, *J* = 263.9, 220.8 Hz), 116.4, 115.5 (dt, *J* = 22.7, 14.2 Hz), 64.8 (d, *J* = 6.8 Hz), 53.8, 16.4 (d, *J* = 5.7 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –107.3 (d, *J* = 114.6 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 5.8 (t, *J* = 114.3 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{17}F_2NO_4P$: 296.0863; found: 296.0862 (–0.3 ppm).

Diethyl [(Pyrazin-2-yl)difluoromethyl]phosphonate (2s)

Prepared by following the general procedure from 2-iodopyrazine (**1s**). Reverse-phase chromatography (H_2O/MeOH).

Yield: 46% (61 mg, 0.5 mmol scale); colorless oil.

IR (neat): 2987, 2918, 1474, 1446, 1406, 1271, 1163, 1130, 1011, 854 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.94 (s, 1 H), 8.71–7.61 (app d, 2 H), 4.36–4.25 (m, 4 H), 1.35 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.5 (dt, *J* = 23.9, 13.8 Hz), 146.5 (d, *J* = 1.7 Hz), 143.9, 143.2 (dt, *J* = 5.4, 2.9 Hz), 115.9 (td, *J* = 264.3, 215.3 Hz), 65.3 (d, *J* = 6.6 Hz), 16.4 (d, *J* = 5.5 Hz).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz): δ = –112.4 (d, *J* = 105.4 Hz, 2 F).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 4.5 (t, *J* = 105.2 Hz, 1 P).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{14}F_2N_2O_3P$: 267.0710; found: 267.0709 (–0.4 ppm).

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