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Copper-Mediated Synthesis of Aryldifluoromethylphosphonates: A Sandmeyer Approach

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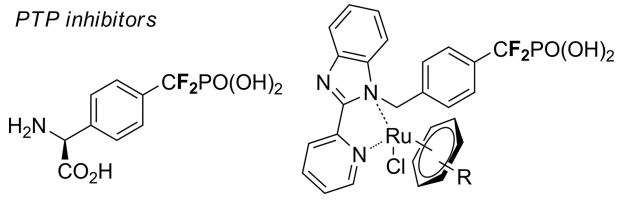
Difluoromethylated arenes are scaffolds of great interest. We report herein a mild and general method for the introduction of the $CF_2PO(OEt)_2$ moiety into arenes. The $CuCF_2PO(OEt)_2$ species, which is generated in situ from the corresponding silylated derivatives, in combination with aryl diazonium salts furnished the highly valuable aryl difluoromethylphosphonates in moderate to good yields. This represents the first general method to introduce difluoromethylphosphonates under mild conditions.

Introduction

Fluorinated molecules, particularly fluorinated arenes, are an important class of compounds as they are present in a plethora of bioactive molecules, pharmaceuticals, agrochemicals, and materials.[1] Indeed, because of its size and electronegativity, the fluorine atom has the remarkable ability to strongly modify the chemical, physical, and biological properties of a molecule.[2] As a result, organofluorine chemistry has become a field of widespread interest with the development of new approaches to these versatile fluorinated skeletons, recently culminating in new, innovative, and elegant methodologies.[3] However, all recent efforts have mostly focused on the introduction of the fluorine atom and the CF_3 group. Less attention has been paid to the introduction of functionalized fluorinated building blocks and, particularly, those that contain a difluoromethylene moiety.[4] With regard to the high value of the CF_2 group as a bioisostere of the oxygen atom, its introduction into a molecule, particularly an arene moiety, is of great interest. Moreover, the concomitant introduction of the CF_2 moiety along with a functional group might allow for further postfunctionalizations and, thus, lead to more elaborate fluorinated molecules.

Among fluorinated motifs, the difluoromethylphosphonate residue is of great interest as an in vivo stable phosphate mimic, as proposed by Blackburn 30 years ago.[5] In fact, the replacement of an oxygen atom by a difluoromethylene substituent suppresses the metabolic hydrolysis of the phosphate moiety as a result of the higher energy of the C–P bond. Although much effort has been devoted to the introduction of the $CF_2PO(OR)_2$ motif into carbonyl derivatives and α,β-unsaturated systems,[6] less attention has been paid to the incorporation of such a phosphate mimic into aromatic derivatives, despite the huge biological interest of these compounds (Scheme 1).[7]



Scheme 1. Selected examples of protein tyrosine phosphatase (PTP) inhibitors with the aryl difluromethylphosphonic motif.

To date, since Shibuya's pioneering work regarding the copper-mediated Negishi cross-coupling reaction of vinyl halide with $BrZnCF_2PO(OEt)_2$,[8] the introduction of the $CF_2PO(OR)_2$ unit into arenes has focused on: (1) the addition of fluorinated radicals to arenes,[9] (2) the copper-catalyzed cross-coupling reaction of the iodoarenes, iodobenzoate and haloaryl triazenes, with in situ prepared $MCF_2PO(OEt)_2$ (M = ZnX or CdX),[10] (3) the palladium-catalyzed Suzuki cross-coupling reaction with $BrCF_2PO(OEt)_2$,[11] and (4) the copper-mediated oxidative addition of the $TMSCF_2PO(OR)_2$ (TMS = trimethylsilyl) reagent to an aryl boronic acid.[12a] In the same vein, the recent report by Qing and co-workers regarding the copper-mediated oxidative introduction of the difluoromethylphosphonate moiety into alkynes uses a similar approach.[12b] In this com-

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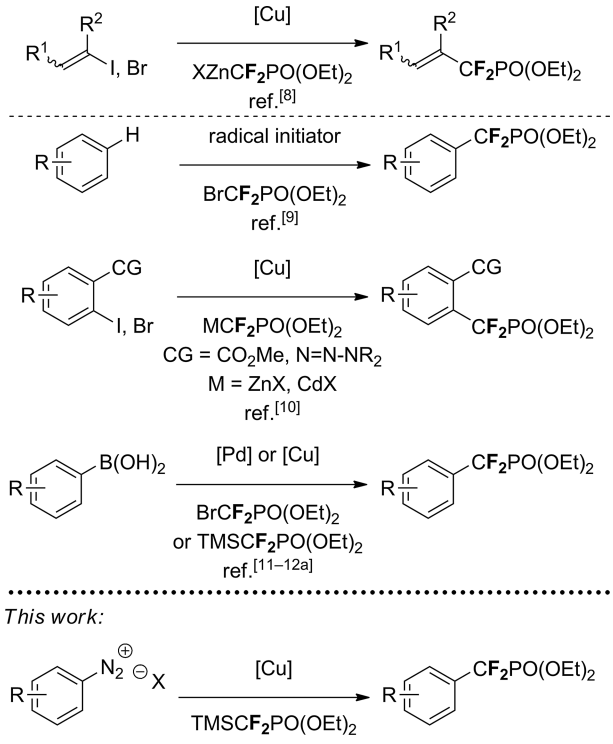
munication and as part of our research program devoted to the development of new synthetic pathways to access fluorinated building blocks,[13] we report a mild and practical method to introduce the $CF_2PO(OEt)_2$ residue into arenes at room temperature by starting from readily available aromatic amines through their corresponding aryl diazonium salts. This strategy, which employs a Sandmeyer approach,[14] represents a straightforward alternative to the use of harsh reaction conditions and expensive organoboron or iodoarene derivatives (Scheme 2).[15]

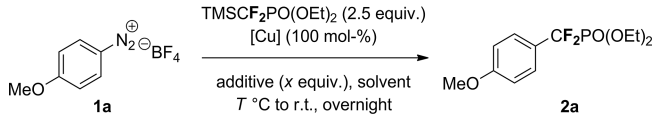


Scheme 2. State-of-the-art and proposed strategy (CG = coordinating group).

Results and Discussion

At the outset of the project, we chose aryl diazonium salt **1a** as the model substrate and $TMSCF_2PO(OEt)_2$ as the fluorinated reagent to demonstrate the feasibility of the method. Initial attempts were performed by treating the preformed copper species (generated from the silylated reagent, a Lewis base activator, and a copper source in MeCN) with aryl diazonium salt **1** (Table 1). Pleasingly, the use of CuI as the copper source and CsF as the activator furnished the desired aryldifluoromethylphosphonate **2a** in 30% yield. We then examined the nature of the copper source and observed a significant enhancement in the yield by using CuSCN (Table 1, Entry 2), whereas lower yields were obtained by using CuBr and CuOAc (Table 1, Entries 3 and 4). Screening for the best solvent revealed that MeCN was the most adequate. Indeed, *N*,*N*-dimethylformamide (DMF) was less efficient, despite its wide use in the formation of hypervalent silicon species, and a mixture of tetrahydrofuran (THF)/MeCN did not afford any improvement (Table 1, Entries 5 and 6). Next, we examined the nature of the Lewis base. Cs_2CO_3 gave a lower yield of **2a** (23%; Table 1, Entry 7), whereas KOAc and KF did not promote the reaction (Table 1, Entries 8 and 9), probably as a result

Table 1. Optimization of the reaction conditions.[a]

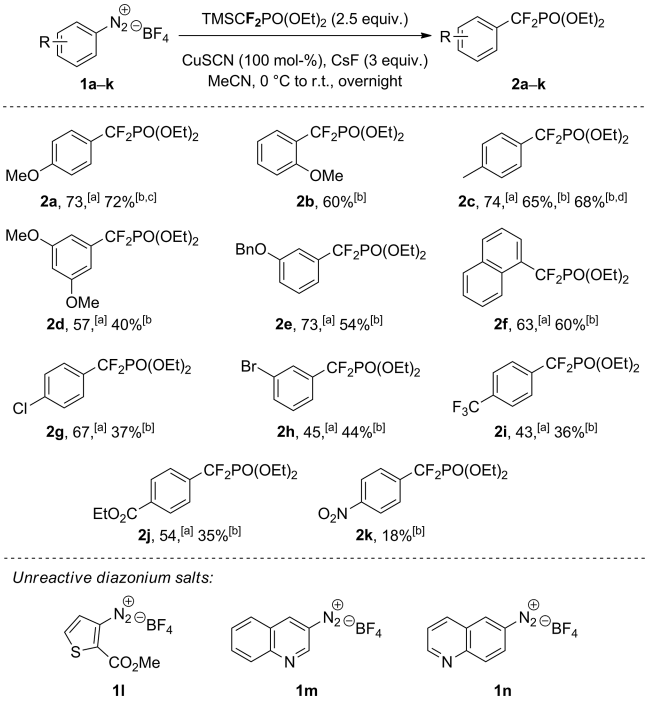


Entry	[Cu]	Additive	*x*	Solvent	*T*	Yield [%][b]
1	CuI	CsF	3	MeCN	room temp.	30
2	CuSCN	CsF	3	MeCN	room temp.	55
3	CuBr	CsF	3	MeCN	room temp.	27
4	CuOAc	CsF	3	MeCN	room temp.	26
5	CuSCN	CsF	3	DMF	room temp.	24
6	CuSCN	CsF	3	THF/MeCN	room temp.	37
7	CuSCN	Cs_2CO_3	3	MeCN	room temp.	23
8	CuSCN	KOAc	3	MeCN	room temp.	n.r.
9	CuSCN	KF	3	MeCN	room temp.	n.r.
10	CuSCN	TMAF	3	MeCN	room temp.	n.r.
11	CuSCN	TBAF	3	MeCN	room temp.	trace
12	CuSCN	CsF	3	MeCN	0 °C	73 (72)[c,d]
13	CuSCN	CsF	3	MeCN	–10 °C	70
14	CuSCN	CsF	3	MeCN	–20 °C	69
15[e]	CuSCN	CsF	3	MeCN	0 °C	53
16	CuSCN	CsF	2	MeCN	0 °C	57
17	CuSCN	CsF	1	MeCN	0 °C	50

[a] $TMSCF_2PO(OEt)_2$ (1.25 mmol), CsF (1.5 mmol), and CuSCN (0.5 mmol) in MeCN (1 mL) were stirred at 40 °C for 1 h, and then **1a** (0.5 mmol) was added to this solution at the reported temperature. The mixture was then warmed to room temp. [b] Yields were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard; n.r.: no reaction. [c] Isolated yield. [d] The product was contaminated with 7% of $HCF_2PO(OEt)_2$. [e] Reaction was performed with 1.5 equiv. of $TMSCF_2PO(OEt)_2$.

of their poor solubility in MeCN. Surprisingly, tetramethylammonium fluoride (TMAF) and tetra-*n*-butylammonium fluoride (TBAF) were inefficient and did not promote the formation of the copper species (Table 1, Entries 10 and 11). We then examined the temperature of the addition of **1a** to the copper species. Pleasingly, decreasing the temperature from room temperature to 0 °C resulted in a significant increase of the reaction yield (73% NMR yield), and **2a** was isolated in 72% yield (Table 1, Entry 12). It is noteworthy that the addition of aryl diazonium salt **1a** to the in situ prepared Cu species at either –10 or –20 °C did not improve the reaction yield (Table 1, Entries 13 and 14). Finally, all attempts to increase the yield by decreasing the amount of $TMSCF_2PO(OEt)_2$ or the additive to less than 3 equiv. were unsuccessful (Table 1, Entries 15, 16, and 17).

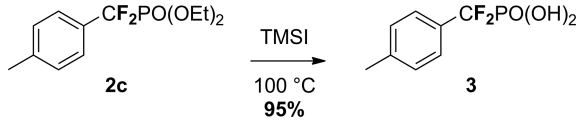
With these optimized conditions in hand, we turned our attention to extending the scope of the reaction to other aryl diazonium salts (Scheme 3). First, aryl diazonium salts that contained an electron-donating group were studied. Pleasingly, the 2-OMe-substituted derivative **1b** provided the desired difluoromethylated phosphonate **2b** in good isolated yield, which reveals that an *ortho* substituent did not affect the outcome of the reaction. Aryl diazonium salt **1c**, which was derived from *para*-toluidine, gave the corresponding difluoromethylated compound **2c** in a fairly decent yield of 65%, and pleasingly a gram-scale reaction furnished **2c** in 68% yield, highlighting the versatility of the method. In contrast, 3,5-disubstituted diazonium salt **1d** gave a lower yield of difluoromethylphosphonate **2d**, which



Scheme 3. Scope and limitations of the reaction. See Experimental Section for details. [a] Yield was determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard. [b] Isolated yield. [c] The product was contaminated with 7% of $HCF_2PO(OEt)_2$. [d] Reaction performed on gram scale.

was isolated in 40% yield, and 3-*O*-benzyl derivative **1e** furnished the desired product **2e** in a 54% isolated yield because of the difficulty separating the product from the fluorinated impurities. Naphthyl diazonium salt **1f** underwent the reaction smoothly to afford phosphonate **2f** in 60% isolated yield. Then, we screened aryl diazonium salts with halide substituents. The chloro group on aryl diazonium salt **1g** was well-tolerated under the reaction conditions, and the corresponding phosphonate **2g** was produced in 67% NMR yield and a lower isolated yield (37%) because of the difficulty with purification. The bromo substituent was also suited for the reaction, and difluoromethylated phosphonate **2h** was isolated in 44% yield. Throughout these reactions, no alteration to the carbon-halogen bond was observed, which also highlights the versatility of the method. Aryl diazonium salts that contained an electron-withdrawing group such as $–CF_3$ in **1i** or $–CO_2Et$ in **1j** were examined, and the corresponding difluoromethylated arenes **2i** and **2j** were obtained in the moderate yields of 36 and 35%, respectively. Finally, nitro-substituted aryl diazonium salt **1k** was engaged under our reaction conditions and furnished product **2k** in a poor 18% yield. Unfortunately, heteroaromatic diazonium salts, **1l**–**1n**, were unreactive as a result of their low solubility in the reaction media. All of our attempts to tackle this issue were unsuccessful.

Finally, we demonstrated the easy conversion of the diethylphosphonates into the corresponding phosphonic acids by using TMSI (Scheme 4). Phosphonic acid **3** was readily obtained in 95% yield.



Scheme 4. Access to the phophonic acid **3**.

Conclusions

In summary, we reported herein a versatile and straightforward approach to prepare aryl difluoromethylphosphonates under mild conditions by starting from readily available aryl diazonium salts. The corresponding products were obtained in good to moderate yields, and the reaction scope proved to be tolerant of a broad range of functional groups. This methodology represents a convenient alternative to the use of expensive boronic acids or iodoarenes, and it avoids the need for harsh reaction conditions.

Experimental Section

General Methods: All reactions were performed with oven-dried glassware and by magnetic stirring under argon, unless otherwise stated. Flash chromatography was performed on silica gel (0.040–0.060 nm). Reverse phase chromatography was performed on a puriFlash®215 system by using a puriFlash® C18HP 15 µm 55G flash column. Analytical thin layer chromatography was performed on silica gel aluminium plates with F-254 indicator and visualized

by UV light (254 nm) and/or chemical staining with a $KMnO_4$ solution. The ^1H NMR spectroscopic data were recorded with a Bruker DXP 300 spectrometer. The ^{13}C, ^{19}F, and ^{31}P NMR spectroscopic data were recorded at 75, 282, and 121 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to the solvent signal ($CHCl_3$: δ = 7.26 ppm for ^1H NMR, $CDCl_3$: δ = 77.16 ppm for ^{13}C NMR, or relative to external $CFCl_3$: δ = 0 ppm for ^{19}F NMR). The following abbreviations are used: δ (chemical shift), J (coupling constant), app. (apparent), br. (broad), s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), q (quartet), and m (multiplet). High resolution mass spectra were recorded on a Waters LCT Premier instrument, and IR spectra were recorded on a PerkinElmer Spectrum 100 spectrometer. Dry acetonitrile (sure-sealed bottle) was purchased from Acros Organics, and CsF was purchased from Apollo Scientific Ltd. CuSCN was obtained from Sigma–Aldrich Ltd. Diethyl (bromodifluoromethyl)phosphonate was purchased from Apollo Scientific Ltd and Fluorochem Ltd and used as received. Chlorotrimethylsilane was acquired from Sigma–Aldrich Ltd. and freshly distilled from CaH_2. All starting materials were distilled or recrystallized prior to use. Diethyl [difluoro(trimethylsilyl)methyl]phosphonate and the diazonium salts were prepared according to reported methods.[14,16]

General Procedure for the Copper-Mediated Synthesis of Difluoromethylphosphonates 2: In a glove box, a sealed tube was loaded with CuSCN (61 mg, 0.50 mmol) and CsF (228 mg, 1.50 mmol) and then capped with a rubber septum. Dry acetonitrile (1 mL) was added, and the mixture was cooled to 0 °C. Diethyl [difluoro(trimethylsilyl)methyl]phosphonate (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. Unless otherwise noted, the corresponding diazonium salt (0.50 mmol) was added dropwise as a solution in acetonitrile (1 mL). The rubber septum was removed, and the tube was sealed. The suspension was then stirred for 16 h, and the reaction mixture was diluted with diethyl ether (30 mL). The resulting mixture was filtered through a plug of Celite®. The filtrate was washed with water (4× 10 mL) and brine (2× 10 mL) and then dried with $MgSO_4$. The solvents were carefully removed. Unless otherwise noted, purification by chromatography on silica gel gave the pure desired product.

Diethyl [Difluoro(4-methoxyphenyl)methyl]phosphonate (2a): The difluoromethylphosphonate was prepared by following the general procedure and using 4-methoxybenzenediazonium tetrafluoroborate (0.5 mmol scale). Reverse phase chromatography (H_2O/MeCN) afforded **2a** (72% yield) as a yellow oil. ^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) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (dd, J = 3.6 and 1.7 Hz), 127.9 (td, J = 6.8 and 2.4 Hz), 124.6 (td, J = 22.7 and 14.0 Hz), 118.3 (td, J = 263.0 and 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) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –107.6 (d, J = 119.7 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 6.6 (t, J = 119.8 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2985, 1614, 1515, 1250, 1011 cm^{-1}. HRMS (ESI+): calcd. for $[M + H]^+$ $C_{12}H_{18}F_2O_4P$ 295.0911; found 295.0906 (–1.7 ppm).

Diethyl [Difluoro(2-methoxyphenyl)methyl]phosphonate (2b): The difluoromethylphosphonate was prepared by following the general procedure and using 2-methoxybenzenediazonium tetrafluoroborate (0.5 mmol scale) to afford **2b** (60% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 7.8 Hz, 1 H), 7.41 (app. t, J = 7.9 Hz, 1 H), 6.97 (m, 2 H), 4.32–4.05 (m, 4 H), 3.85 (s, 3 H), 1.29 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8 (td, J = 3.3 and 2.0 Hz), 132.4 (dd, J = 3.2 and 1.6 Hz), 128.2 (td, J = 9.1 and 2.7 Hz), 120.9 (td, J = 21.7 and 13.7 Hz), 120.4 (d, J = 0.8 Hz), 118.6 (td, J = 264.1 and 219.4 Hz), 112.2 (d, J = 0.9 Hz), 64.6 (d, J = 6.7 Hz), 55.9, 16.4 (d, J = 5.8 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –105.2 (d, J = 116.5 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 6.7 (t, J = 116.3 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2919, 1603, 1495, 1257, 1036, 1017 cm^{-1}. HRMS (ESI+): calcd. for $C_{12}H_{18}F_2O_4P$ $[M + H]^+$ 295.0911; found 295.0914 (1 ppm).

Diethyl [Difluoro(*p*-tolyl)methyl]phosphonate (2c): The difluoromethylphosphonate was prepared by following the general procedure and using *p*-tolyldiazonium tetrafluoroborate (0.5 mmol scale) to afford **2c** (65% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, J = 7.7 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H), 4.28–4.05 (m, 4 H), 2.37 (s, 3 H), 1.29 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5 (dd, J = 4.1 and 2.1 Hz), 129.7 (td, J = 22.2 and 13.8 Hz), 129.2 (d, J = 1.3 Hz), 118.3 (td, J = 262.9 and 219.1 Hz), 64.8 (d, J = 6.7 Hz), 21.4, 16.4 (d, J = 5.6 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –108.5 (d, J = 118.0 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 6.5 (t, J = 118.0 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2985, 1617, 1515, 1260, 101 cm^{-1}. HRMS (ESI+): calcd. for $[M + H]^+$ $C_{12}H_{18}F_2O_3P$ 279.0962; found 279.0957 (–1.8 ppm).

Diethyl [Difluoro(3,5-dimethoxyphenyl)methyl]phosphonate (2d): The difluoromethylphosphonate was prepared by following the general procedure and using 3,5-dimethoxybenzenediazonium tetrafluoroborate (0.5 mmol scale). Reverse phase chromatography (H_2O/MeOH) afforded **2d** (40% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.74 (s, 2 H), 6.53 (s, 1 H), 4.27–4.07 (m, 4 H), 3.79 (s, 6 H), 1.31 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8 (d, J = 1.2 Hz), 134.6 (td, J = 22.1 and 14.1 Hz), 117.9 (td, J = 263.8 and 217.8 Hz), 104.3 (td, J = 7.1 and 2.3 Hz), 103.0 (dd, J = 3.4 and 1.7 Hz), 64.9 (d, J = 6.7 Hz), 55.6, 16.4 (d, J = 5.6 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –108.5 (d, J = 115.5 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 6.2 (t, J = 115.6 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2985, 1597, 1460, 1270, 1205, 1157, 1011 cm^{-1}. HRMS (ESI+): calcd. for $[M + NH_4]^+$ $C_{13}H_{23}NF_2O_5P$ 342.1282; found 342.1274 (–2.3 ppm).

Diethyl [3-Benzyloxyphenyldifluoromethyl]phosphonate (2e): The difluoromethylphosphonate was prepared by following the general procedure and using 3-benzyloxybenzenediazonium tetrafluoroborate (0.5 mmol scale). Reverse phase chromatography (H_2O/MeCN) afforded **2e** (54% yield) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 (m, 5 H), 7.15 (m, 3 H), 6.99 (d, J = 8.1 Hz, 1 H), 5.00 (s, 2 H), 4.18–3.97 (m, 4 H), 1.21 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7 (d, J = 1.2 Hz), 136.6, 134.0 (td, J = 22.0 and 13.8 Hz), 129.7 (d, J = 1.2 Hz), 128.7, 128.2, 127.6, 118.8 (td, J = 6.9 and 2.3 Hz), 117.9 (td, J = 263.5 and 217.8 Hz), 112.6 (td, J = 7.1 and 2.3 Hz), 70.2, 64.9 (d, J = 6.7 Hz), 16.4 (d, J = 5.5 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –108.6 (d, J = 115.7 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 6.3 (t, J = 115.7 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2985, 1587, 1442, 1268, 1012 cm^{-1}. HRMS (ESI+): calcd. for $[M + NH_4]^+$ $C_{18}H_{25}NF_2O_4P$ 388.1489; found 388.1487 (–0.5 ppm).

Diethyl [Difluoro(naphthalen-1-yl)methyl]phosphonate (2f): The difluoromethylphosphonate was prepared by following the general procedure and using naphthalene-1-diazonium tetrafluoroborate (0.5 mmol scale) to afford **2f** (60% yield) as a dark orange oil. ^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) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.1 (d, J = 0.9 Hz), 132.1 (dd, J = 3.4 and 1.7 Hz), 129.9 (dd, J = 3.7 and 1.8 Hz), 128.6 (d, J = 2.5 Hz), 128.4 (td, J = 20.1 and 13.5 Hz), 126.9, 126.4 (td, J = 10.4 and 3.6 Hz), 126.3, 126.1 (td, J = 5.2 and 0.7 Hz), 124.4 (d, J = 1.7 Hz), 120.0 (td, J = 264.1 and 216.8 Hz), 64.8 (d, J = 6.8 Hz), 16.3 (d, J = 5.6 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –102.4 (d, J = 114.6 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 6.7 (t, J = 114.7 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2985, 1514, 1269, 1010 cm^{-1}. HRMS (ESI+): calcd. for $[M + NH_4]^+$ $C_{15}H_{21}NF_2O_3P$ 332.1227; found 332.1233 (1.8 ppm).

Diethyl [(4-Chlorophenyl)difluoromethyl]phosphonate (2g): The difluoromethylphosphonate was prepared by following the general procedure and using 4-chlorobenzenediazonium tetrafluoroborate (0.5 mmol scale) to afford **2g** (37% yield) as a dark yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, J = 7.9 Hz, 2 H), 7.42 (d, J = 8.5 Hz, 2 H), 4.29–4.08 (m, 4 H), 1.30 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.2 (dd, J = 4.7 and 2.4 Hz), 131.2 (td, J = 22.5 and 14.0 Hz), 128.9 (d, J = 1.3 Hz), 127.8 (td, J = 6.8 and 2.3 Hz), 117.8 (td, J = 263.5 and 218.8 Hz), 65.0 (d, J = 6.8 Hz), 16.4 (d, J = 5.5 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –109.1 (d, J = 115.1 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 5.9 (t, J = 115.2 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2986, 1602, 1492, 1270, 1256, 1012 cm^{-1}. HRMS (ESI+): calcd. for $[M + NH_4]^+$ $C_{11}H_{18}NF_2O_3PCl$ 316.0681; found 316.0675 (–1.9 ppm).

Diethyl [(3-Bromophenyl)difluoromethyl]phosphonate (2h): The difluoromethylphosphonate was prepared by following the general procedure and using 3-bromobenzenediazonium tetrafluoroborate (0.5 mmol scale) to afford **2h** (44% yield) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.54 (d, J = 7.7 Hz, 1 H), 7.32 (app. t, J = 7.9 Hz, 1 H), 4.32–4.09 (m, 4 H), 1.31 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.7 (td, J = 22.3 and 13.9 Hz), 134.0 (dd, J = 3.6 and 1.7 Hz), 130.2 (d, J = 1.3 Hz), 129.4 (td, J = 7.1 and 2.4 Hz), 125.1 (td, J = 6.7 and 2.2 Hz), 117.3 (td, J = 264.1 and 218.0 Hz), 65.1 (d, J = 6.8 Hz), 16.4 (d, J = 5.5 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –109.4 (d, J = 113.9 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 5.7 (t, J = 114.0 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2985, 1574, 1476, 1270, 1242, 1012 cm^{-1}. HRMS (ESI+): calcd. for $[M^{79}Br + NH_4]^+$ $C_{11}H_{18}NF_2O_3P^{79}Br$ 360.0176; found 360.0170 (–1.7 ppm).

Diethyl [Difluoro(4-{trifluoromethyl}phenyl)methyl]phosphonate (2i): The difluoromethylphosphonate was prepared by following the general procedure and using 4-(trifluoromethyl)benzenediazonium tetrafluoroborate (0.5 mmol scale) to afford **2i** (36% yield) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.69 (m, 4 H), 4.32–4.10 (m, 4 H), 1.31 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.9–136.0 (m), 133.6–132.2 (m), 127.0 (td, J = 6.8 and 2.3 Hz), 125.6 (qd, J = 3.7 and 1.3 Hz), 120.1 (q, J = 272.7 Hz), 117.5 (td, J = 263.6 and 217.3 Hz), 65.1 (d, J = 6.8 Hz), 16.4 (d, J = 5.5 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –63.5 (s, 3 F), –109.9 (d, J = 112.8 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 5.6 (t, J = 112.8 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2992, 1414, 1266, 1127, 1066, 1013 cm^{-1}. HRMS (ESI+): calcd. for $[M + NH_4]^+$ $C_{12}H_{18}NF_5O_3P$ 350.0944; found 350.0938 (–1.7 ppm).

Ethyl 4-[(Diethoxyphosphoryl)difluoromethyl]benzoate (2j): The difluoromethylphosphonate was prepared by following the general procedure and using 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (0.5 mmol scale). Reverse phase chromatography (H_2O/MeOH) afforded **2j** (35% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.2 Hz, 2 H), 7.68 (d, J = 8.0 Hz, 2 H), 4.38 (q, J = 7.1 Hz, 2 H), 4.27–4.07 (m, 4 H), 1.39 (t, J = 7.1 Hz, 3 H), 1.30 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 136.9 (td, J = 21.9 and 13.6 Hz), 132.8 (dd, J = 3.6 and 1.7 Hz), 129.7 (d, J = 1.3 Hz), 126.5 (td, J = 6.8 and 2.3 Hz), 117.8 (td, J = 263.6 and 216.9 Hz), 65.0 (d, J = 6.8 Hz), 61.5, 16.4 (d, J = 5.5 Hz), 14.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –109.9 (d, J = 113.5 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 5.8 (t, J = 113.4 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2985, 1719, 1270, 1107, 1011 cm^{-1}. HRMS (ESI+): calcd. for $[M + NH_4]^+$ $C_{14}H_{23}NF_2O_5P$ 354.1282; found 354.1291 (2.5 ppm).

Diethyl [Difluoro(4-nitrophenyl)methyl]phosphonate (2k): The difluoromethylphosphonate was prepared by following the general procedure and using 4-nitrobenzenediazonium tetrafluoroborate (0.5 mmol scale). Reverse phase chromatography (H_2O/MeOH) afforded **2k** (18% yield) as an orange foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.6 Hz, 2 H), 7.81 (d, J = 7.9 Hz, 2 H), 4.32–4.13 (m, 4 H), 1.33 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.5, 139.1 (td, J = 22.3 and 13.8 Hz), 127.8 (td, J = 6.7 and 2.2 Hz), 123.7 (d, J = 1.2 Hz), 117.3 (td, J = 264.3 and 216.3 Hz), 65.3 (d, J = 6.9 Hz), 16.5 (d, J = 5.4 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –110.1 (d, J = 110.8 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, $CFCl_3$): δ = 5.1 (t, J = 110.9 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2919, 1522, 1343, 1270, 1253, 1014 cm^{-1}. HRMS (ESI+): calcd. for $[M + NH_4]^+$ $C_{11}H_{18}N_2F_2O_5P$ 327.0921; found 327.0920 (–0.3 ppm).

[Difluoro(*p*-tolyl)methyl]phosphonic Acid (3): In a tube, iodotrimethylsilane (160 μL, 1.15 mmol) was added to diethyl [difluoro(*p*-tolyl)methyl]phosphonate (**2c**, 212 mg, 0.77 mmol). The tube was sealed, and the mixture was heated at 100 °C overnight, cooled to room temperature, and then diluted with diethyl ether (10 mL). Activated zinc dust was added to decolorize the mixture and then removed by filtration. The organic layer was washed with an aqueous solution of NaOH (1 M, 10 mL), and the two phases were separated. Concentrated HCl was added to the aqueous layer until it reached pH = 1. The aqueous layer was extracted with chloroform (3 × 15 mL), and the combined extracts were concentrated in vacuo to give **3** (95% yield) as a gummy brown solid. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 10.30 (s, 2 H), 7.31 (d, J = 7.8 Hz, 2 H), 7.11 (d, J = 7.9 Hz, 2 H), 2.18 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 140.5 (dd, J = 3.9 and 2.0 Hz), 130.1 (td, J = 22.2 and 13.7 Hz), 128.7 (d, J = 1.1 Hz), 118.2 (td, J = 260.4 and 218.6 Hz), 20.3 ppm. ^{19}F NMR (282 MHz, [D$_6$]acetone, $CFCl_3$): δ = –108.7 (d, J = 118.2 Hz, 2 F) ppm. ^{31}P NMR (121 MHz, [D$_6$]acetone, $CFCl_3$): δ = 6.0 (t, J = 118.2 Hz, 1 P) ppm. IR (neat): $\tilde{\nu}$ = 2985, 2146, 1687, 1617, 1513, 1261, 1043, 1024 cm^{-1}.

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