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Copper-mediated oxidative difluoromethylenation of aryl boronic acids with α-silyldifluoromethylphosphonates: a new method for aryldifluorophosphonates†

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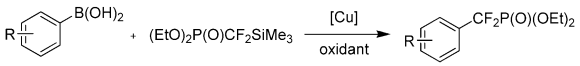
An unprecedented copper-mediated oxidative difluoromethylenation of aryl boronic acids with α-silyldifluoromethylphosphonates has been developed, allowing rapid access to a wide range of aryldifluorophosphonates containing various functional groups. This method provides a complementary and alternative method to Cu-mediated cross-couplings of aryl iodides with metalated difluoromethylphosphonates.

Introduction

Because of the unique properties of fluorinated functional groups, the incorporation of these moieties into organic molecules has a profound impact on the design of new pharmaceutical and agrochemical agents.[1] Accordingly, extensive effort has been devoted to the development of efficient and versatile methods for introducing fluorinated functional goups into various compounds. The efforts of our group in this field have focused on the development of new trifluoromethylation and fluoroalkylation reactions. Herein, we report an unprecedented copper-mediated oxidative cross-coupling reaction of aryl boronic acids with α-silyldifluoromethylphosphonates.

Over the last several years, significant achievements have been made in the transiton metal-mediated or -catalyzed aromatic difluoromethylation[2] and trifluoromethylation reactions.[3–5] Aryl halides have been typically used as electrophilic coupling parters,[2b–c,3,4a–d,f–m] however, utilizing aromatic nucleophiles for this purpose, which would broaden reaction scope and diversity, has rarely been explored until recently. In 2010, our group reported the first example of Cu-mediated oxidative trifluoromethylation of terminal alkynes with CF_3SiMe_3 (Ruppert–Prakash reagent) as a nucleophilic CF_3 source.[6] By employing this oxidative trifluoromethylation protocol, we have achieved the oxidative trifluoromethylation of various nucleophiles, such as aryl boronic acids,[5a,g] heteroarenes,[7] terminal alkenes[8] and H-phosphonates.[9] As an extension of this oxidative trifluoromethylation protocol, we also developed the analogous oxidative *gem*-difluoromethylenation protocol by achieving the first example of oxidative cross-coupling of terminal alkynes with α-silyldifluoromethylphosphonates as a nucleophilic difluoromethylenating agent.[10] We wanted to further expand this protocol to the oxidative cross-coupling of aryl boronic acids with α-silyldifluoromethylphosphonates for synthesis of aryldifluorophosphonates (Scheme 1), which are excellent mimics of phosphate esters and have been found to be potent protein tyrosine phosphatase (PTP) inhibitors.[11] To the best of our knowledge, no oxidative cross-coupling of aryl boronic acids with difluoromethylphosphonates for constructing aryl-$CF_2P(O)(OR)_2$ bonds has ever been reported, although this new method would open up a new viewpoint to prepare aryldifluorophosphonates and would provide an attractive alternative to the previously developed methods such as fluorination of phosphonates[11c,12] and copper-mediated/catalyzed cross-coupling of aryl iodides with metalated difluoromethylphosphonates.[13]



Scheme 1 Oxidative difluoromethylenation of aryl boronic acids with α-silyldifluoromethylphosphonates.

Results and discussion

We began our study by examining the reaction of phenylboronic acid **1a** with diethyl difluoro(trimethylsilyl)methylphosphonate **2a** under the optimized conditions of copper-mediated oxidative

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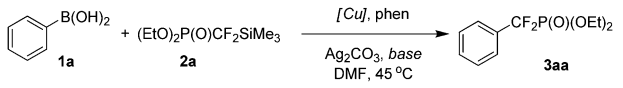
† Electronic supplementary information (ESI) available: Copies of the ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR for all products. See DOI: 10.1039/c3nj00044c

Table 1 Optimization of the reaction conditions[a]



Entry	Copper complex	Base (equiv.)	Yield of **3aa**[b] (%)
1[c]	$(CuOTf)_2{\cdot}C_6H_6$	K_3PO_4 (4.0) + KF (3.0)	7
2[c]	CuI	K_3PO_4 (4.0) + KF (3.0)	5
3[c]	$Cu(OAc)_2$	K_3PO_4 (4.0) + KF (3.0)	None
4[c]	CuTc	K_3PO_4 (4.0) + KF (3.0)	14
5	CuTc	K_3PO_4 (4.0) + KF (3.0)	19
6	CuTc	NaOH (4.0) + KF (3.0)	39
7	CuTc	Na_2CO_3 (4.0) + KF (3.0)	23
8	CuTc	Et_3N (4.0) + KF (3.0)	34
9	CuTc	DMAP (4.0) + KF (3.0)	20
10	CuTc	DIPEA (4.0) + KF (3.0)	Trace
11	CuTc	Pyridine (4.0) + KF (3.0)	38
12	CuTc	Pyridine	48
13	CuTc	NaOH	None
14[d]	CuTc	Pyridine	54
15[d,e]	CuTc	Pyridine	62
16[d,e,f]	CuTc	Pyridine	77
17[d,e,f,g]	CuTc	Pyridine	74
18[d,e,f,g,h]	CuTc	Pyridine	26

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), copper complex (0.1 mmol), phen (0.1 mmol), Ag_2CO_3 (0.1 mmol), base, DMF (2.0 mL), argon, 45 °C, 4h. [b] Yield was determined by ^{19}F NMR using fluorobenzene as an internal standard. [c] Reaction conducted at 60 °C. [d] 0.15 mmol Ag_2CO_3. [e] 1.0 mL of DMF. [f] 60 mg 4 Å MS. [g] 0.2 mmol **2a**. [h] 0.05 mmol CuTc, 0.05 mmol phen. CuTc = copper(I) thiophene-2-carboxylate; DMAP = 4-(dimethylamion)pyridine; DIPEA = *N*,*N*-diisopropylethylamine.

trifluoromethylation of boronic acids.[5a] However, only 7% yield of the desired product **3aa** was observed in this case (Table 1, entry 1). After examining the various effects of copper complexes, we found that switching to copper(I) thiophene-2-carboxylate (CuTc) afforded product **3aa** in 14% yield (entries 2–4). A slightly higher yield was observed when the reaction was conducted at 45 °C (entry 5). We next investigated the influence of bases, which are known to have a profound effect on transmetalations and coupling reactions. KF combined with NaOH or pyridine was found to be more effective than the one combined with other inorganic or organic bases (entries 5–11). Further investigation of bases revealed that the use of pyridine as a single base was more effective than the use of a combination of pyridine and KF, while NaOH was completely ineffective in the absence of KF (entries 12–13). Increasing the amount of oxidant Ag_2CO_3 (from 1.0 to 1.5 equiv.) and the concentration of substrate (from 0.05 to 0.1 M) could further improve the reaction efficiency and the product yield (entries 14–15). The highest yield of product was achieved under the conditions by using 4 Å MS as an additive (entry 16). A comparable yield of product **3aa** could be obtained with only 2.0 equiv of reagent **2a** (entry 17). Stoichiometric amounts of copper complex and 1,10-phenanthroline (phen) proved to be essential for this transformation, as the yield of **3aa** dramatically decreased in the presence of 0.5 equiv. of CuTc/phen (entry 18).

With the optimized reaction conditions in hand, we next examined the substrate scope of the Cu-mediated oxidative difluoromethylenation of aryl boronic acids **1** with α-silyldifluoromethylphosphonates **2** (Table 2). A wide range of arylboronic

Table 2 Cu-mediated oxidative difluoromethylenation of aryl boronic acids with α-silyldifluoromethylphosphonates[a]

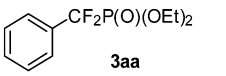
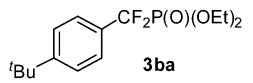
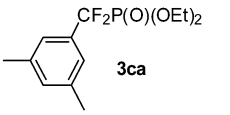
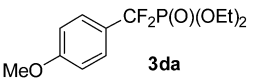
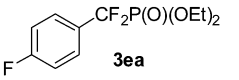
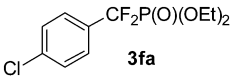
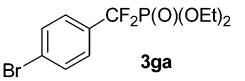
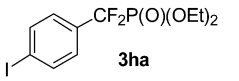
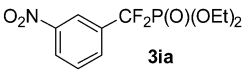
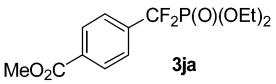
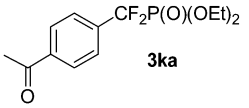
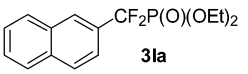
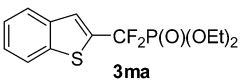
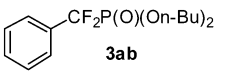
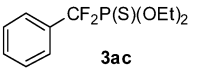
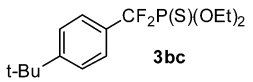
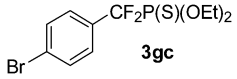
Entry	Substrate **1**, reagent **2**	Product **3**	Yield (%)
1	**1a**, **2a**	 **3aa**	72
2	**1b**, **2a**	 **3ba**	81
3	**1c**, **2a**	 **3ca**	72
4	**1d**, **2a**	 **3da**	40[b]
5	**1e**, **2a**	 **3ea**	78
6	**1f**, **2a**	 **3fa**	78
7	**1g**, **2a**	 **3ga**	76
8	**1h**, **2a**	 **3ha**	64
9	**1i**, **2a**	 **3ia**	60
10	**1j**, **2a**	 **3ja**	54
11	**1k**, **2a**	 **3ka**	56
12	**1l**, **2a**	 **3la**	79
13	**1m**, **2b**	 **3ma**	31
14	**1a**, **2b**	 **3ab**	66
15	**1a**, **2c**	 **3ac**	74
16	**1b**, **2c**	 **3bc**	69

Table 2 (*continued*)

Entry	Substrate **1**, reagent **2**	Product **3**	Yield (%)
17	**1g**, **1c**	 **3gc**	53

[a] Reaction was conducted on a 0.5 mmol scale under the optimal conditions of entry 17 in Table 1. Isolated yield. [b] Yield was determined by ^{19}F NMR by using fluorobenzene as an internal standard.

acids bearing important functional groups, including methyloxy, halides (–F, –Cl, –Br and –I), nitro, ester, and ketone, smoothly underwent the desired oxidative cross-couplings with **2a**, producing the corresponding aryldifluorophosphonates in moderate to good yields (Table 2, entries 1–12). It is remarkable that aromatic iodides, which have been reported to undergo the classical Cu-mediated/catalyzed cross-couplings with metalated difluoromethylphosphonates,[13] are also compatible with this method, and the reaction of substrate **1h** chemoselectively provided the difluoromethylenated product **3ha** in 64% yield (entry 8). The electronic properties of the substituents on the substrates have a significant influence on the reaction efficiency. The substrates bearing strongly electron-withdrawing groups (such as $-NO_2$, $-CO_2Et$, and $-COCH_3$) or strongly electron-donating groups (such as −OMe) gave relatively lower yields than less electron-rich or electron-deficient substrates (entries 1–12). Heteroaryl boronic acids proved to be viable substrates for this transformation, while the reaction of **1m** produced the desired product in a comparatively low yield (entry 13).

To further expand the potential utility of this method, other α-silyldifluoromethylphosphonates were also subjected to this system. The reactions of aryl boronic acids with **2b** or even difluoromethylphosphonothioate **2c** proceeded smoothly to furnish the corresponding aryldifluorophosphonates and aryldifluorophosphonothioates in moderate to good yields (Table 2, entries 14–17).

Conclusion

In summary, a copper-mediated oxidative difluoromethylenation of aryl boronic acids with α-silyldifluoromethylphosphonates has been developed, allowing rapid access to a wide range of aryldifluorophosphonates containing various functional groups from simple starting materials. Importantly, this method provides a complementary and alternative method to Cu-mediated cross-couplings of aryl iodides with metalated difluoromethylphosphonates. Ongoing studies will focus on the improvement and extension of the scope of this transformation.

Experimental

General experimental details

^1H NMR (TMS as the internal standard) and ^{19}F NMR spectra ($CFCl_3$ as the outside standard and low field is positive) were recorded on a Bruker AM300 or Bruker AM400 spectrometer. ^{13}C NMR and ^{31}P NMR were recorded on a Bruker AM400 spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Substrates were purchased from commercial sources (Aldrich, Alfa and Chemical Reagent Companies of China) and used as received. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Reactions were performed under an atmosphere of argon using glassware that was flame-dried under vacuum.

General procedure for copper-mediated oxidative difluoromethylenation of aryl boronic acids with α-silyldifluoromethylphosphonates

To an oven-dried tube was added CuTc (0.5 mmol), phen (0.5 mmol), Ag_2CO_3 (0.75 mmol) and 4 Å molecule sieves (300 mg). The tube was evacuated and then refilled with argon three times. Then DMF (3.0 mL), pyridine (2.0 mmol) and α-silyldifluoromethylphosphonates **2** (1.0 mmol) were added to the tube. After stirring for 5 min, the mixture was heated to 45 °C and boronic acid **1** (0.5 mmol) in DMF (2.0 mL) was added to the tube. The reaction mixture was stirred at 45 °C for 4 h, and then allowed to cool to room temperature. The resulting mixture was filtered through a celite pad, diluted with diethyl ether, washed with water and brine, dried over sodium sulfate, and concentrated. The crude products were purified by column chromatography on silica gel to give the products.

Diethyl difluoro(phenyl)methylphosphonate (3aa). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45–7.63 (m, 5H), 4.13–4.22 (m, 4H), 1.30 (t, J = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −108.5 (d, $^2J_{PF}$ = 116.5 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 132.6 (td, $^2J_{FC}$ = 22.3 Hz, $^2J_{PC}$ = 14.1 Hz), 130.8 (m), 128.5 (m), 126.3 (m), 118.1 (td, $^1J_{FC}$ = 262.0 Hz, $^1J_{PC}$ = 217.3 Hz), 64.8 (d, $^2J_{PC}$ = 6.7 Hz), 16.3 (d, $^3J_{PC}$ = 5.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 6.31 (t, $^2J_{FP}$ = 116.6 Hz). IR (thin film) ν 3069, 2988, 1452, 1274, 1046 cm^{-1}. MS (EI): m/z (%) 264 (M^+, 10.2), 127 (100). HRMS Calculated for $C_{11}H_{15}F_2O_3P$: 264.0727; Found: 264.0726.

Diethyl (4-*tert*-butylphenyl)difluoromethylphosphonate (3ba). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.54 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.11–4.26 (m, 4H), 1.29–1.33 (m, 15H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −107.7 (d, $^2J_{PF}$ = 117.3 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.1 (m), 129.6 (td, $^2J_{FC}$ = 22.4 Hz, $^2J_{PC}$ = 14.2 Hz), 126.2 (m), 125.5 (m), 118.3 (td, $^1J_{FC}$ = 261.2 Hz, $^1J_{PC}$ = 218.0 Hz), 64.7 (d, $^2J_{PC}$ = 6.7 Hz), 34.9, 31.2, 16.4 (d, $^3J_{PC}$ = 5.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 6.49 (t, $^2J_{FP}$ = 118.3 Hz). IR (thin film) ν 3046, 2967, 1614, 1273, 1020 cm^{-1}. MS (EI): m/z (%) 320 (M^+, 8.4), 183 (100). HRMS Calculated for $C_{15}H_{23}F_2O_3P$: 320.1353; Found: 320.1356.

Diethyl (3,5-dimethylphenyl)difluoromethylphosphonate (3ca). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.22 (s, 2H), 7.09 (s, 2H), 4.13–4.22 (m, 4H), 2.35 (s, 6H), 1.31 (t, J = 6.4 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −108.1 (d, $^2J_{PF}$ = 117.3 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.1, 132.4 (m), 132.5, 123.9 (m), 118.2 (td, $^1J_{FC}$ = 261.9 Hz, $^1J_{PC}$ = 217.0 Hz), 64.7 (d, $^2J_{PC}$ = 6.8 Hz), 21.3, 16.3 (d, $^3J_{PC}$ = 6.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm)

6.49 (t, $^2J_{FP}$ = 117.0 Hz). IR (thin film) ν 3057, 2983, 1724, 1273, 1018 cm^{-1}. MS (EI): *m*/*z* (%) 292 (M^+, 16.3), 155 (100). HRMS Calculated for $C_{13}H_{19}F_2O_3P$: 292.1040; Found: 292.1039.

Diethyl difluoro(4-fluorophenyl)methylphosphonate (3ea). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.62 (t, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 8.1 Hz, 2H), 4.15–4.24 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −108.3 (d, $^2J_{PF}$ = 116.7 Hz, 2F), −109.9 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.2 (d, $^1J_{FC}$ = 250.1 Hz), 128.6 (m), 117.8 (td, $^1J_{FC}$ = 262.0 Hz, $^1J_{PC}$ = 218.8 Hz), 115.8 (m), 115.5 (m), 64.9 (d, $^2J_{PC}$ = 6.7 Hz), 16.3 (d, $^3J_{PC}$ = 5.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 6.02 (t, $^2J_{FP}$ = 116.6 Hz). IR (thin film) ν 3074, 2988, 1609, 1512, 1273, 1047 cm^{-1}. MS (EI): *m*/*z* (%) 282 (M^+, 6.2), 145 (100). HRMS Calculated for $C_{11}H_{14}F_3O_3P$: 282.0633; Found: 282.0634.

Diethyl (4-chlorophenyl)difluoromethylphosphonate (3fa). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.86 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 4.16–4.24 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −108.6 (d, $^2J_{PF}$ = 115.3 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.2 (m), 131.1 (td, $^2J_{FC}$ = 22.3 Hz, $^2J_{PC}$ = 14.2 Hz), 128.8 (m), 127.8 (m), 117.7 (td, $^1J_{FC}$ = 262.8 Hz, $^1J_{PC}$ = 218.1 Hz), 64.9 (d, $^2J_{PC}$ = 6.7 Hz), 16.4 (d, $^3J_{PC}$ = 5.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 5.85 (t, $^2J_{FP}$ = 115.7 Hz). IR (thin film) ν 3078, 2986, 1602, 1492, 1273, 1018 cm^{-1}. MS (EI): *m*/*z* (%) 298 (M^+, 1.3), 161 (100). HRMS Calculated for $C_{11}H_{14}ClF_2O_3P$: 298.0337; Found: 298.0341.

Diethyl (4-bromophenyl)difluoromethylphosphonate (3ga). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 4.16–4.24 (m, 4H), 1.32 (t, *J* = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −109.2 (d, $^2J_{PF}$ = 114.8 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 131.8 (m), 131.7 (m), 128.0 (m), 125.5 (m), 117.8 (td, $^1J_{FC}$ = 262.0 Hz, $^1J_{PC}$ = 217.4 Hz), 64.9 (d, $^2J_{PC}$ = 6.7 Hz), 16.4 (d, $^3J_{PC}$ = 5.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 5.73 (t, $^2J_{FP}$ = 115.0 Hz). IR (thin film) ν 3095, 1596, 1275, 1014 cm^{-1}. MS (EI): *m*/*z* (%) 342 (M^+, 4.1), 84 (100). HRMS Calculated for $C_{11}H_{14}BrF_2O_3P$: 341.9832; Found: 341.9836.

Diethyl difluoro(4-iodophenyl)methylphosphonate (3ha). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.81 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 4.16–4.24 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −109.5 (d, $^2J_{PF}$ = 114.8 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.8 (m), 132.4 (td, $^2J_{FC}$ = 21.6 Hz, $^2J_{PC}$ = 13.4 Hz), 128.0 (m), 117.8 (td, $^1J_{FC}$ = 262.7 Hz, $^1J_{PC}$ = 217.3 Hz), 97.7 (m), 65.0 (d, $^2J_{PC}$ = 6.7 Hz), 16.4 (d, $^3J_{PC}$ = 5.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 5.72 (t, $^2J_{FP}$ = 115.2 Hz). IR (thin film) ν 3069, 2985, 1591, 1273, 1022 cm^{-1}. MS (EI): *m*/*z* (%) 390 (M^+, 7.7), 84 (100). HRMS Calculated for $C_{11}H_{14}F_2IO_3P$: 389.9693; Found: 389.9691.

Diethyl difluoro(3-nitrophenyl)methylphosphonate (3ia). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.47 (s, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 4.23–4.31 (m, 4H), 1.36 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −109.2 (d, $^2J_{PF}$ = 112.2 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.3, 134.9 (td, $^2J_{FC}$ = 23.0 Hz, $^2J_{PC}$ = 14.1 Hz), 132.5 (m), 129.9 (m), 125.7, 121.7 (m), 117.1 (td, $^1J_{FC}$ = 263.5 Hz, $^1J_{PC}$ = 217.7 Hz), 65.3 (d, $^2J_{PC}$ = 6.7 Hz), 16.4 (d, $^3J_{PC}$ = 6.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 5.04 (t, $^2J_{FP}$ = 112.1 Hz). IR (thin film) ν 3096, 2987, 1540, 1355, 1249, 1018 cm^{-1}. MS (EI): *m*/*z* (%) 309 (M^+, 3.2), 126 (100). HRMS Calculated for $C_{11}H_{14}F_2NO_5P$: 309.0578; Found: 309.0580.

Methyl 4-((diethoxyphosphoryl)difluoromethyl)benzoate (3ja). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.13 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 2H), 3.95–4.27 (m, 4H), 3.95 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −109.3 (d, $^2J_{PF}$ = 113.1 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.3, 137.0 (td, $^2J_{FC}$ = 21.6 Hz, $^2J_{PC}$ = 13.4 Hz), 132.4, 129.7, 126.5 (m), 117.8 (td, $^1J_{FC}$ = 262.7 Hz, $^1J_{PC}$ = 215.8 Hz), 65.0 (d, $^2J_{PC}$ = 6.7 Hz), 52.5, 16.4 (d, $^3J_{PC}$ = 5.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 6.37 (t, $^2J_{FP}$ = 116.6 Hz). IR (thin film) ν 3057, 2988, 1731, 1284, 1012 cm^{-1}. MS (EI): *m*/*z* (%) 322 (M^+, 5.6), 84 (100). HRMS Calculated for $C_{13}H_{17}F_2O_5P$: 322.0782; Found: 322.0781.

Diethyl (4-acetylphenyl)difluoromethylphosphonate (3ka). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.04 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 4.17–4.25 (m, 4H), 2.64 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −109.4 (d, $^2J_{PF}$ = 113.1 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.4, 138.8, 137.0 (td, $^2J_{FC}$ = 21.5 Hz, $^2J_{PC}$ = 13.4 Hz), 128.3, 126.7 (m), 117.7 (td, $^1J_{FC}$ = 262.0 Hz, $^1J_{PC}$ = 215.1 Hz), 65.0 (d, $^2J_{PC}$ = 6.7 Hz), 26.8, 16.3 (d, $^2J_{PC}$ = 5.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 5.61 (t, $^2J_{FP}$ = 113.1 Hz). IR (thin film) ν 3069, 2987, 1692, 1406, 1268, 1018 cm^{-1}. MS (EI): *m*/*z* (%) 306 (M^+, 11.5), 109 (100). HRMS Calculated for $C_{13}H_{17}F_2O_4P$: 306.0833; Found: 306.0832.

Diethyl difluoro(naphthalen-2-yl)methylphosphonate (3la). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14 (s, 1H), 7.84–7.92 (m, 3H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.50–7.55 (m, 2H), 4.14–4.23 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −107.9 (d, $^2J_{PF}$ = 115.8 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 134.2, 132.5, 129.8 (td, $^2J_{FC}$ = 21.6 Hz, $^2J_{PC}$ = 13.4 Hz), 128.8, 128.5, 127.8, 127.6, 126.8, 126.6 (m), 122.8 (m), 118.3 (td, $^1J_{FC}$ = 261.2 Hz, $^1J_{PC}$ = 216.6 Hz), 64.8 (d, $^2J_{PC}$ = 6.7 Hz), 16.4 (d, $^3J_{PC}$ = 5.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 6.37 (t, $^2J_{FP}$ = 117.1 Hz). IR (thin film) ν 3061, 2986, 1602, 1284, 1015 cm^{-1}. MS (EI): *m*/*z* (%) 314 (M^+, 10.5), 177 (100). HRMS Calculated for $C_{15}H_{17}F_2O_3P$: 314.0883; Found: 314.0885.

Diethyl benzo[*b*]thiophen-2-yldifluoromethylphosphonate (3ma). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83–7.88 (m, 2H), 7.74 (s, 1H), 7.40–7.43 (m, 2H), 4.20–4.35 (m, 4H), 1.36 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −98.4 (d, $^2J_{PF}$ = 112.0 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 140.6, 138.7, 134.4 (td, $^2J_{FC}$ = 26.0 Hz, $^2J_{PC}$ = 17.1 Hz), 126.2 (m), 126.0, 125.0, 122.6, 116.6 (td, $^1J_{FC}$ = 260.5 Hz, $^1J_{PC}$ = 221.8 Hz), 66.3 (d, $^2J_{PC}$ = 6.7 Hz), 16.5 (d, $^3J_{PC}$ = 5.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 4.80 (t, $^2J_{FP}$ = 112.6 Hz). IR (thin film) ν 3061, 2985, 1531, 1284, 1018 cm^{-1}. MS (EI): *m*/*z* (%) 320 (M^+, 12.1), 183 (100). HRMS Calculated for $C_{15}H_{23}F_2O_3P$: 320.0448; Found: 320.0451.

Dibutyl difluoro(phenyl)methylphosphonate (3ab). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45–7.63 (m, 5H), 4.03–4.18 (m, 4H), 1.59–1.66 (m, 4H), 1.31–1.40 (m, 4H), 0.90 (t, *J* = 5.4 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −108.7 (d, $^2J_{PF}$ = 117.0 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 132.8 (td, $^2J_{FC}$ = 22.3 Hz, $^2J_{PC}$ = 14.1 Hz), 130.8 (m), 126.3 (td, $^3J_{FC}$ = 6.7 Hz, $^3J_{PC}$ = 2.2 Hz), 118.2 (td, $^1J_{FC}$ = 262.0 Hz, $^1J_{PC}$ = 217.4 Hz), 68.4 (d, $^2J_{PC}$ = 6.7 Hz),

32.5 (d, $^3J_{PC}$ = 5.9 Hz), 18.6, 13.5. ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 6.40 (t, $^2J_{FP}$ = 116.0 Hz). IR (thin film) ν 3069, 2963, 1453, 1276, 1021 cm^{-1}. MS (EI): *m*/*z* (%) 320 (M^+, 1.6), 127 (100). HRMS Calculated for $C_{15}H_{23}F_2O_3P$: 320.1353; Found: 320.1349.

***O*,*O*-Diethyl difluoro(phenyl)methylphosphonothioate (3ac).** ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.41–7.60 (m, 5H), 4.07–4.24 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −107.6 (d, $^2J_{PF}$ = 122.7 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 132.3 (td, $^2J_{FC}$ = 22.3 Hz, $^2J_{PC}$ = 14.9 Hz), 130.7 (m), 128.1 (m), 126.9 (td, $^3J_{FC}$ = 6.7 Hz, $^3J_{PC}$ = 2.2 Hz), 119.1 (td, $^1J_{FC}$ = 266.5 Hz, $^1J_{PC}$ = 179.4 Hz), 64.8 (d, $^2J_{PC}$ = 7.5 Hz), 16.2 (d, $^3J_{PC}$ = 6.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 75.6 (t, $^2J_{FP}$ = 121.4 Hz). IR (thin film) ν 3066, 2984, 1451, 1259, 1016 cm^{-1}. MS (EI): *m*/*z* (%) 280 (M^+, 30.1), 127 (100). HRMS Calculated for $C_{11}H_{15}F_2O_2PS$: 280.0498; Found: 280.0497.

***O*,*O*-Diethyl (4-*tert*-butylphenyl)difluoromethylphosphonothioate (3bc).** ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.52 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 4.11–4.24 (m, 4H), 1.27–1.33 (m, 15H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −107.7 (d, $^2J_{PF}$ = 124.6 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.0, 129.4 (td, $^2J_{FC}$ = 22.3 Hz, $^2J_{PC}$ = 14.9 Hz), 126.7 (m), 125.1, 119.3 (td, $^1J_{FC}$ = 266.4 Hz, $^1J_{PC}$ = 180.8 Hz), 64.7 (d, $^2J_{PC}$ = 6.7 Hz), 34.9, 31.3, 16.2 (d, $^3J_{PC}$ = 6.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 75.9 (t, $^2J_{FP}$ = 124.1 Hz). IR (thin film) ν 3048, 2966, 1613, 1266, 1018 cm^{-1}. MS (EI): *m*/*z* (%) 336 (M^+, 13.5), 183 (100). HRMS Calculated for $C_{15}H_{23}F_2O_2PS$: 336.1124; Found: 336.1127.

***O*,*O*-Diethyl (4-bromophenyl)difluoromethylphosphonothioate (3gc).** ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.58 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 4.12–4.24 (m, 4H), 1.30 (t, *J* = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −109.0 (d, $^2J_{PF}$ = 120.7 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 131.5 (m), 131.4, 128.6 (m), 125.5, 118.8 (td, $^1J_{FC}$ = 267.2 Hz, $^1J_{PC}$ = 180.1 Hz), 64.9 (d, $^2J_{PC}$ = 6.7 Hz), 16.2 (d, $^3J_{PC}$ = 6.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 74.8 (t, $^2J_{FP}$ = 121.0 Hz). IR (thin film) ν 3074, 2983, 1595, 1488, 1257, 1066 cm^{-1}. MS (EI): *m*/*z* (%) 358 (M^+, 7.8), 153 (100). HRMS Calculated for $C_{11}H_{14}BrF_2O_3P$: 357.9604; Found: 357.9600.

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Notes and references

1 (*a*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*b*) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305; (*c*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.

2 For recent examples of aromatic difluoromethylation, see: (*a*) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 1494; (*b*) P. S. Fier and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 5524; (*c*) G. K. S. Prakash, S. K. Ganesh, J.-P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck and G. A. Olah, *Angew. Chem., Int. Ed.*, 2012, **51**, 12090; (*d*) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95.

3 For selected reviews, see: (*a*) R. J. Lundgren and M. Stradiotto, *Angew. Chem., Int. Ed.*, 2010, **49**, 9322; (*b*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (*c*) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le and S. Roy, *Tetrahedron*, 2011, **67**, 2161; (*d*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (*e*) Y. Ye and M. S. Sanford, *Synlett*, 2012, 2005; (*f*) T. Besset, C. Schneider and D. Cahard, *Angew. Chem., Int. Ed.*, 2012, **51**, 5048; (*g*) T. Liu and Q. Shen, *Eur. J. Org. Chem.*, 2012, 6679; (*h*) C. Lü, Q. Shen and D. Liu, *Chin. J. Org. Chem.*, 2012, **32**, 1380; (*i*) F. L. Qing, *Chin. J. Org. Chem.*, 2012, **32**, 815; (*j*) X.-F. Wu, H. Neumann and M. Beller, *Chem.–Asian J.*, 2012, **7**, 1744.

4 For recent examples of transition metal-mediated or -catalyzed trifluoromethylation of aryl halides or C–H bonds, see: (*a*) V. V. Grushin and W. J. Marshall, *J. Am. Chem. Soc.*, 2006, **128**, 12644; (*b*) G. G. Dubinina, H. Furutachi and D. A. Vicic, *J. Am. Chem. Soc.*, 2008, **130**, 8600; (*c*) M. Oishi, H. Kondo and H. Amii, *Chem. Commun.*, 2009, 1909; (*d*) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson and S. L. Buchwald, *Science*, 2010, **328**, 1679; (*e*) X. Wang, L. Truesdale and J. Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648; (*f*) N. D. Ball, J. B. Gary, Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 7577; (*g*) C. P. Zhang, Z. L. Wang, Q. Y. Chen, C. T. Zhang, Y. C. Gu and J. C. Xiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 1896; (*h*) H. Morimoto, T. Tsubogo, N. D. Litvinas and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2011, **50**, 3793; (*i*) O. A. Tomashenko, E. C. Escudero-Adan, M. Martinez Belmonte and V. V. Grushin, *Angew. Chem., Int. Ed.*, 2011, **50**, 7655; (*j*) Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng and K.-W. Huang, *Organometallics*, 2011, **30**, 3229; (*k*) H. Kondo, M. Oishi, K. Fujikawa and H. Amii, *Adv. Synth. Catal.*, 2011, **353**, 1247; (*l*) B. S. Samant and G. W. Kabalka, *Chem. Commun.*, 2011, **47**, 7236; (*m*) T. Knauber, F. Arikan, G. V. Roschenthaler and L. J. Gooßen, *Chem.–Eur. J.*, 2011, **17**, 2689; (*n*) X. Mu, S. Chen, X. Zhen and G. Liu, *Chem.–Eur. J.*, 2011, **17**, 6039; (*o*) Y. Ye, S. H. Lee and M. S. Sanford, *Org. Lett.*, 2011, **13**, 5464; (*p*) A. Hafner and S. Bräse, *Angew. Chem., Int. Ed.*, 2012, **51**, 3713; (*q*) X.-G. Zhang, H.-X. Dai, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 11948.

5 For recent examples of transition metal-mediated or -catalyzed trifluoromethylation of aryl boronic acids and their derivatives, see: (*a*) L. Chu and F.-L. Qing, *Org. Lett.*, 2010, **12**, 5060; (*b*) T. D. Senecal, A. T. Parsons and S. L. Buchwald, *J. Org. Chem.*, 2011, **76**, 1174; (*c*) J. Xu, D. F. Luo, B. Xiao, Z. J. Liu, T. J. Gong, Y. Fu and L. Liu, *Chem. Commun.*, 2011, **47**, 4300; (*d*) T. Liu and Q. Shen, *Org. Lett.*, 2011, **13**, 2342; (*e*) C. P. Zhang, J. Cai, C. B. Zhou, X. P. Wang, X. Zheng, Y. C. Gu and J. C. Xiao,

Chem. Commun., 2011, **47**, 9516; (*f*) B. A. Khan, A. E. Buba and L. J. Gooßen, *Chem.–Eur. J.*, 2012, **18**, 1577; (*g*) X. Jiang, L. Chu and F. L. Qing, *J. Org. Chem.*, 2012, **77**, 1251; (*h*) N. D. Litvinas, P. S. Fier and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 536; (*i*) T. Liu, X. Shao, Y. Wu and Q. Shen, *Angew. Chem., Int. Ed.*, 2012, **51**, 540; (*j*) P. Novák, A. Lishchynskyi and V. V. Grushin, *Angew. Chem., Int. Ed.*, 2012, **51**, 7767.

6 L. Chu and F.-L. Qing, *J. Am. Chem. Soc.*, 2010, **132**, 7262.

7 L. Chu and F. L. Qing, *J. Am. Chem. Soc.*, 2012, **134**, 1298.

8 L. Chu and F.-L. Qing, *Org. Lett.*, 2012, **14**, 2106.

9 L. Chu and F.-L. Qing, *Synthesis*, 2012, 1521.

10 X. Jiang, L. Chu and F.-L. Qing, *Org. Lett.*, 2012, **14**, 2870.

11 (*a*) T. R. Burke and K. Lee, *Acc. Chem. Res.*, 2003, **36**, 426; (*b*) Z.-Y. Zhang, *Acc. Chem. Res.*, 2003, **36**, 385; (*c*) V. D. Romanenko and V. P. Kukhar, *Chem. Rev.*, 2006, **106**, 3868; (*d*) X. Li, A. Bhandari, C. P. Holmes and A. K. Szardenings, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4301; (*e*) C. P. Holmes, X. Li, Y. Pan, C. Xu, A. Bhandari, C. M. Moody, J. A. Miguel, S. W. Ferla, M. N. De Francisco, B. T. Frederick, S. Zhou, N. Macher, L. Jang, J. D. Irvine and J. R. Grove, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4336; (*f*) P. K. Mandal, W. S. L. Liao and J. S. McMurray, *Org. Lett.*, 2009, **11**, 3394; (*g*) S. Zhang, S. Liu, R. Tao, D. Wei, L. Chen, W. Shen, Z.-H. Yu, L. Wang, D. R. Jones, X. C. Dong and Z.-Y. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 18116.

12 (*a*) T. R. Burke, M. S. Smyth, M. Nomizu, A. Otaka and P. R. Roller, *J. Org. Chem.*, 1993, **58**, 1336; (*b*) M. S. Smyth and T. R. Burke Jr, *Tetrahedron Lett.*, 1994, **35**, 551; (*c*) S. D. Taylor, A. N. Dinaut, A. N. Thadani and Z. Huang, *Tetrahedron Lett.*, 1996, **37**, 8089; (*d*) D. Solas, R. L. Hale and D. V. Patel, *J. Org. Chem.*, 1996, **61**, 1537; (*e*) S. D. Taylor, C. C. Kotoris, A. N. Dinaut and M.-J. Chen, *Tetrahedron*, 1998, **54**, 1691.

13 (*a*) Q. Weiming and D. J. Burton, *Tetrahedron Lett.*, 1996, **37**, 2745; (*b*) T. Yokomatsu, T. Murano, K. Suemune and S. Shibuya, *Tetrahedron*, 1997, **53**, 815; (*c*) Z. Feng, F. Chen and X. Zhang, *Org. Lett.*, 2012, **14**, 1938.