Facile syntheses of building blocks for the construction of phosphotyrosine mimetics

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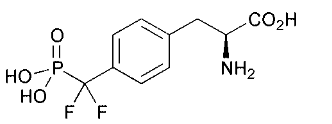
The copper-catalysed zinc phosphonate chemistry described by Yokomatsu and Shibuya can be used to enter the classical organometallic coupling repertoire *via* Stille and Suzuki–Miyaura couplings. 1,4-Diiodobenzene underwent coupling with the organozinc reagent derived from diethyl bromodifluoromethylphosphonate with copper(I) catalysis to afford diethyl (4-iodophenyl)difluoromethylphosphonate. Higher yielding couplings were run with (4-trifluoromethylsulfonyloxy)- and (4-nonafluorobutylsulfonyloxy)-iodobenzenes. The iodide and the triflate coupled under palladium-catalysed conditions with a range of stannanes and boronic acids in moderate to excellent yields. Shibuya–Yokomatsu couplings were also successful with more functionalised iodoarenes and heteroarenes presenting the important phosphate mimic on a range of scaffolds.

Non-hydrolysable phosphotyrosine mimics including (difluorophosphonomethyl)phenylalanine **1** have aroused the interest



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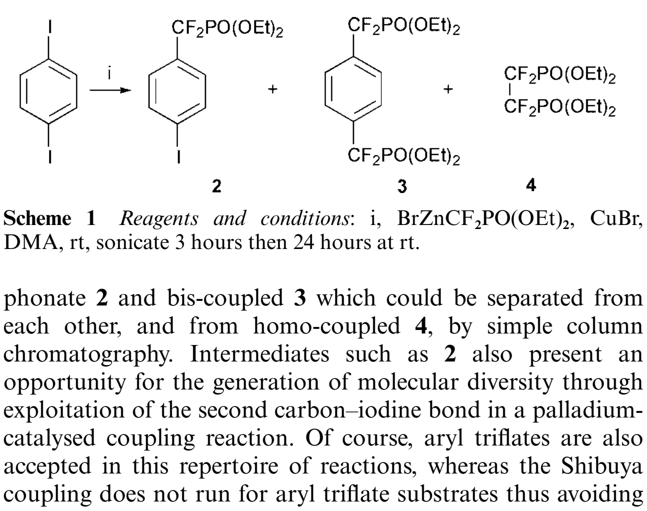
of many groups concerned with the role of transient protein phosphorylation in disease (notably cancer) and the possible importance of the process as a target for the development of new therapeutic agents and strategies.[1,2] The current literature burgeons as (particularly industrial) groups define the selectivity of binding events and bases for molecular recognition of *inter alia* Grb-2,[3–5] Lck SH-2,[6,7] Src-SH2,[8–12] and p-85 C-SH2[13] receptor sites. The fruitful collaboration between Burke and Barford has yielded profound insight into small molecule ligand–large molecule receptor interactions based upon a number of key crystal structures,[14] providing a solid basis for molecular design of ligands.[15] Mimesis responds to a number of imperatives; as the binding site recognises a tetrahedral phosphate monoester dianion within a hydrogen bonding array to two arginine residues, charge and shape are critical. Difluorophosphonates confer hydrolytic stability while preserving the correct charge and geometry. Other mimetics were described recently by Fretz ($ArOCF_2CO_2H$)[16] and Burke *et al.* ($ArCF_2COOH$);[17] they share the advantage of lower charge (an asset for potential *in vivo* applications) but offer different geometries to the recognition array. These mimetics are also straightforward to synthesise;[18–20] carbene chemistry is effective in the former case, while the recent coupling approach to the latter described by Kumadaki[21] and co-workers represents a significant advance. Malonates (OMt and FOMt) also have a role to play and have been effective probes and inhibitors in certain cases.[22,23]

Modern methods for the generation of molecular diversity have not to our knowledge been deployed extensively in this area of chemistry—the attempts by Ganesan[24] and Bergnes[25] to synthesise libraries of phosphate mimetics as potential phosphatase inhibitors provide rare examples and illustrate the need for readily-available functionalised scaffolds bearing phosphate mimetics. Following our recent communication in this area,[26] we wish to describe the scope, generality and limitations of palladium-catalysed coupling reactions investigated in our laboratory.

As described by Shibuya,[27,28] 1,4-diiodobenzene underwent smooth coupling (Scheme 1) to afford the iodophenyl phos-

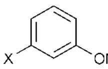
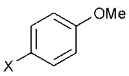
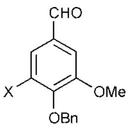
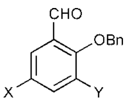
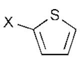
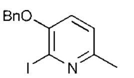


Scheme 1 *Reagents and conditions*: i, $BrZnCF_2PO(OEt)_2$, CuBr, DMA, rt, sonicate 3 hours then 24 hours at rt.

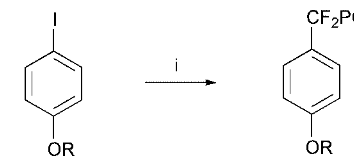
phonate **2** and bis-coupled **3** which could be separated from each other, and from homo-coupled **4**, by simple column chromatography. Intermediates such as **2** also present an opportunity for the generation of molecular diversity through exploitation of the second carbon–iodine bond in a palladium-catalysed coupling reaction. Of course, aryl triflates are also accepted in this repertoire of reactions, whereas the Shibuya coupling does not run for aryl triflate substrates thus avoiding the formation of bis-coupled **3**, so we decided to explore the behaviour of (iodoaryl)perfluoroalkanesulfonates under the Shibuya conditions.

Consistent with the reactivity described by Shibuya, iodotriflate **5a**, prepared from 4-iodophenol on a 50 g scale under standard conditions (triflic anhydride, pyridine, 0 °C, 95%)[29] underwent efficient coupling under sonication conditions to afford **6a** in a pleasing 66% isolated, purified yield (Scheme 2). Typically, 2 equivalents of the copper–zinc reagent were used for these couplings. Intermediate **6a** could be stored for extended periods in the freezer without decomposition. The nonaflate (nonafluorobutanesulfonate) **5b** was prepared following a literature procedure[30] and coupled in a similar way affording **6b** in 75% yield. Short periods of sonication were required in both cases. The more bulky diisopropyl phosphonate **7** could be

Table 1 Shibuya–Yokomatsu couplings on electron-rich, functionalised benzenoid and heteroaromatic templates

Template	X = I	X = $CF_2PO(OEt)_2$	Yield (%)
		**8**	32
		**9**	17
	**14**	**16**	25
	**15**[a]	**17a**[b] **17b**	19 21
	**18**	**19**	62
	**20**		0

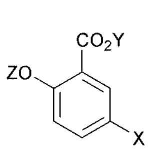
[a] **15**, Y = I. [b] **17a**, X = $CF_2PO(OEt)_2$, Y = I; **17b**, X = I, Y = $CF_2PO(OEt)_2$.



5a, R = SO_2CF_3; **5b**, R = $SO_2C_4F_9$. **6a**, R = SO_2CF_3, R′ = Et; 66% **6b**, R = $SO_2C_4F_9$, R′ = Et; 75% **6c**, R = SO_2CF_3, R′ = *i*-Pr; 31%. **7**

Scheme 2 *Reagents and conditions*: i, $BrZnCF_2PO(OR')_2$, CuBr, DMA, rt, sonicate 3 hours then 24 hours at rt.

coupled *via* the corresponding organozinc reagent with iodotriflate under similar conditions to afford **6c** though in rather lower (31%) yield. Table 1 summarises additional results with a range of aromatic templates. Contrasting results were obtained when *m*- and *p*-iodoanisole were exposed to 1.5 equivalents of the coupling reagent; educts **8** and **9** were obtained in 32 and 17% yields respectively suggesting that the rate-determining step in the coupling sequence is oxidative addition of an organometallic reagent into the C–I bond.[31] Similar behaviour was observed in the efficient coupling of activated substrate **12** (67%) derived from commercial **10** (Scheme 3). Substrates **14**

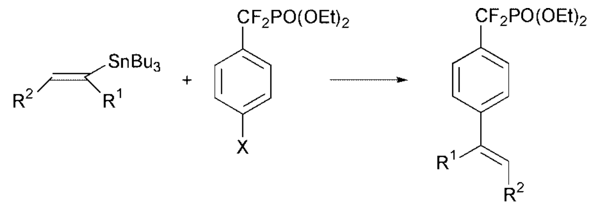


i: **10**, X = I, Y = Z = H; → **11**, X = I, Y = Bn, Z = H;
ii: → **12**, X = I, Y = Bn, Z = SO_2CF_3;
iii: → **13**, X = $CF_2PO(OEt)_2$, Y = Bn, Z = SO_2CF_3.

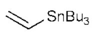
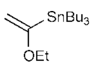
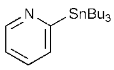
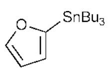
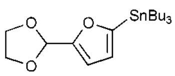
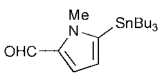
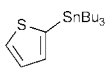
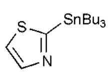
Scheme 3 *Reagents and conditions*: i, BnBr, KF, DMF, rt; ii, Tf_2O, pyridine, 0 °C; iii, $BrZnCF_2PO(OEt)_2$, CuBr, DMA, rt, sonicate 3 hours then 24 hours at rt.

and **15** coupled rather sluggishly to afford **16** (25%), and **17a** (19%) and **17b** (21%) respectively. In **15**, the two C–I bonds appear rather similar electronically and the two insertions occur at almost identical rates despite a difference in steric hindrance. However, in the original report of the coupling reaction by

Table 2 Stille couplings of **6a**[a]



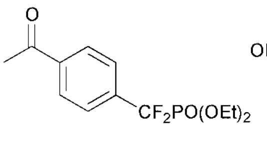
21 + **2** X = I / **6a** X = OSO_2CF_3 → **22**

Stannane **21**		Time/h	Product	Yield (%)
	**21a**	5 1	**22a**	51 84[b]
	**21b**	6	(**22b**)[c] **23**	(–) 52
	**21c**	6	**22c**	52
	**21d**	6	**22d**	79 90[d]
	**21e**	6	(**22e**)[e] **24**	60 30[b]
	**21f**	1	**22f**	53 57[b]
	**21g**	6	**22g**	64
	**21h**	6	**22h**	52 49[b]

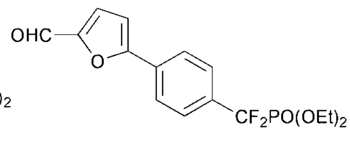
[a] 1.0 equiv. **6a**, 1.0 equiv. stannane, 5% $Pd(PPh_3)_2Cl_2$, DMF, 60 °C. [b] Yield from **2** under these conditions. [c] The methyl ketone **23** was isolated after hydrolysis. [d] 5% Pd_2dba_3·$CHCl_3$, 10% CuI, 20% PPh_3, DMF, 60 °C. [e] The aldehyde **24** was isolated after hydrolysis.

Yokomatsu and co-workers,[28] methyl 2-iodo- and 4-iodobenzoate coupled in identical (99%) yields suggesting that the steric hindrance provided, at least, by an sp^2 hybridised array, is minimal. Commercial heteroaryl 2-iodothiophene **18** displayed the expected high reactivity and underwent Shibuya–Yokomatsu coupling to **19** in 62% yield. Coupling failed completely with **20** in which a benzyloxy group flanks the coupling site and in which a pyridyl nitrogen is also present. From these results, we conclude that protection of phenolic hydroxy groups may be best undertaken using electron withdrawing sulfonate esters rather than ethers.[32]

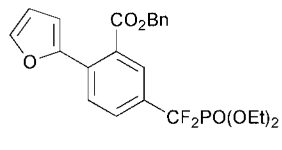
Stille coupling reactions of **2** and **6a** with a range of aliphatic, aryl and heteroaryl tributylstannanes **21a**–**h** afforded coupling products **22a**–**h** in moderate to high yields, thus presenting the phosphate mimicking group on a wide range of biaryl scaffolds (Table 2), in clear contrast to the results reported by the Tokyo group who found the triflate an inefficient precursor for coupled products. Coupling conditions were not optimised exhaustively but our best results were achieved in hot (60 °C) DMF with either $Pd(PPh_3)_2Cl_2$ (5 mol%) or Pd_2dba_3·$CHCl_3$ complex (2.5 mol%); tetrakis(triphenylphosphino)palladium(0) and (dppb)$PdCl_2$ were ineffective catalysts for the reaction in our hands. The addition of lithium chloride to the Stille reactions either inhibited the coupling, or resulted in decomposition of **2** or **6a**. Lower yields were obtained when couplings were attempted in 1,4-dioxane either at room temperature or at reflux, but Stille couplings with **2** proceeded in moderate yield in THF, suggesting that oxidative addition is indeed the slow step in the sequence and that nucleophilic attack at phosphorus (or elsewhere) competes when this initial step becomes laboured. Triflate **6a** performed as well as, if not better than iodide **2** in most cases. Bulkier alkoxy groups at phosphorus have been used traditionally to solve the problem of nucleophilic attack but we did not explore this possibility in view of the success of most of the couplings. Increases in yield (up to 90% for **21d**) were obtained under one set of Farina–Liebeskind conditions[33] in which copper(I) iodide (10 mol%) and Ph_3P (20 mol%) were added. We were also able to use **13** efficiently in Stille coupling with (tributylstannyl)furan; product **25** was afforded under the CuI–Ph_3P conditions in good



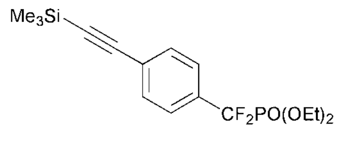
23



24



25



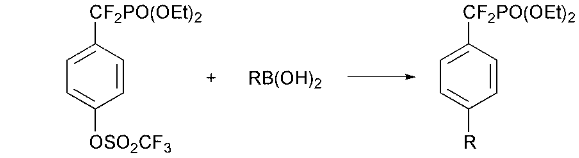
26

(70%) yield. Direct coupling with (trimethylsilyl)ethyne also proceeded well to afford **26** (80% yield) under the palladium-catalysed conditions described by Chen and Yang.[34]

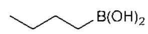
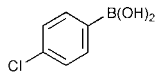
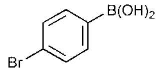
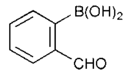
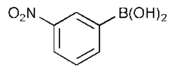
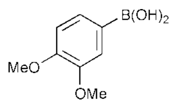
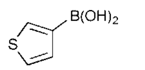
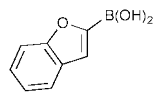
Suzuki coupling conditions were based on the findings of Shieh and Carlson.[35] For the reaction between **6a** and 2,3-dimethoxyphenylboronic acid, the heterogeneous conditions ($Pd(PPh_3)_4$, K_2CO_3, PhMe, 90 °C) afforded none of the desired biaryl but the homogeneous conditions which use the same catalyst and triethylamine base in DMF were more successful and the biaryl was formed. Table 3 shows the scope of the chemistry. The acceptable yield of the 4-bromo biaryl **27c** is of note, as is the successful coupling with the alkylboronic acid in the absence of any activating additive (to form the ate-complex).

These results show tolerance by the difluoromethylphosphoryl group of non-nucleophilic coupling conditions, and the availability of aryl phosphonate building blocks of different levels and types of reactivity. These and related species could be of some use in combinatorial solid and solution phase approaches to the development of PTK ligands and inhibitors with *in vitro* applications at least. The recent publication of a series of 3-PGK inhibitors by the Sheffield group[36] signifies continuing interest in the area.

Table 3 Suzuki couplings of **6a**[a]



6a **27** **28**

Boronic acid		Time/h	Product	Yield (%)
	**27a**	1.3	**28a**	63
	**27b**	1.3	28b	72
	**27c**	2	**28c**	47
	**27d**	1	**28d**	63
	**27e**	1	**28e**	86
	**27f**	2	**28f**	45
	**27g**	1.3	**28g**	75
	**27h**	1	**28h**	66

[a] 1.0 equiv. **6a**, 2.0 equiv. boronic acid, 5% $Pd(PPh_3)_4$, 4.0 equiv. Et_3N, DMF, 90 °C.

Experimental

All NMR spectra were obtained in $CDCl_3$ and were recorded relative to tetramethylsilane as the internal standard. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 (300.13 and 75.47 MHz respectively) spectrometer. ^{13}C NMR spectra were recorded using the JMOD pulse sequence. ^{31}P NMR spectra were also recorded on a Bruker AC-300 (121.50 MHz) spectrometer using orthophosphoric acid as the internal standard. ^{19}F NMR spectra were recorded on a Bruker AC-300 (282.41 MHz) relative to chlorotrifluoromethane as the internal standard. Chemical ionisation (CI) and electron impact (EI) mass spectra were recorded on a VG ProSpec mass spectrometer, a Kratos Profile mass spectrometer or a VG Zabspec mass spectrometer. Chemical ionisation (CI) methods used ammonia as the reagent gas. LC/MS were performed at room temperature using an HP1050 HPLC (5 µl injection volume; 3 µm ABZ+PLUS column with 3.3 cm × 4.6 mm internal diameter) and a Platform Series II mass spectrometer. The HPLC ran a 5.50 minute solvent gradient (time taken to change from one solvent to another at the quoted flow rate) from formic acid to 10 mM ammonium nitrate–acetonitrile–formic acid (10:85:5) with a flow rate of 3 ml min^{-1}. A Micromass LCT mass spectrometer was used for both low resolution (ES-TOF) mass spectra and HRMS measurements (using a lockmass incorporated into the mobile phase). Elemental analyses were performed at the University of North London. For TLC, precoated aluminium-backed silica gel plates were supplied by E. Merck, A.G. Darmstadt, Germany (silica gel 60 F254, thickness 0.2 mm, Art. 5554). Visualisation was achieved by UV light and/or an anisaldehyde–sulfuric acid or potassium permanganate stain. Flash column chromatography was performed using an air compressor on silica gel (E. Merck A.G. Kieselgel 60, Art. 9385). THF was dried by refluxing with benzophenone over sodium wire until a deep purple colour developed, then distilled and collected by dry syringe as required. Dimethylacetamide (DMA) was dried overnight with barium oxide then distilled under reduced pressure, and the distillate stored over calcium hydride under an atmosphere of nitrogen. Diisopropylamine and triethylamine were distilled from calcium hydride and each stored under an atmosphere of nitrogen over calcium hydride. Dimethylformamide was distilled from calcium hydride and stored over 4 Å molecular sieves under an atmosphere of nitrogen.

Tetrakis(triphenylphosphino)palladium(0) and bis(triphenylphosphino)palladium(II) chloride were used as supplied by the Aldrich Chemical Co. Ltd. Zinc activation was achieved by heating the desired quantity of Aldrich 325 mesh zinc dust to 260 °C under vacuum (0.01 mmHg) for two hours. Sonication reactions were performed using a Kerry BE3118 ultrasonic bath operating at 50 Hz. Iodotriflate **5a** was prepared by a known method and gave spectral data in agreement with those reported.[29]

Boronic acids were purchased from Aldrich or Lancaster Synthesis; stannanes **21b**–**21h** were generously provided by GlaxoWellcome. Copper bromide was prepared according to Vogel.[37]

4-[(Diethoxyphosphoryl)difluoromethyl]phenyl trifluoromethanesulfonate 6a

Diethyl bromodifluoromethylphosphonate (28.4 mmol, 7.59 g) in DMA (7 ml) was added dropwise under nitrogen to a stirred solution of activated zinc dust (28.4 mmol, 1.85 g) in DMA (7 ml) at 50–60 °C. After stirring the suspension at room temperature for 3 hours, CuBr (28.4 mmol, 4.06 g) was added in one portion and stirring was continued for a further thirty minutes. A solution of **5a** (14.2 mmol, 5.0 g) in DMA (7 ml) was added dropwise and the reaction was sonicated for three hours, before being stirred at room temperature for a further 24 hours. The mixture was diluted with diethyl ether (50 ml) and water (30 ml), filtered through Celite® and extracted with diethyl ether (3 × 30 ml). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (5 × 20 ml) and brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a pale yellow oil (7.50 g) which was purified by column chromatography (30% ethyl acetate in light petroleum) to afford **6a** (3.91 g, 66%) as a colourless oil; R_f (30% ethyl acetate in light petroleum) 0.53 (Found: C, 34.99; H, 3.47. $C_{12}H_{14}F_5O_6PS$ requires: C, 34.96; H, 3.42%); ν_{max}(film)/cm^{-1} 2989m, 1604w, 1504m, 1428s, 1274s (P=O), 1252s, 1217br vs, 1142vs, 1020br vs, 889s, 844m, 757m; δ_H (300 MHz, $CDCl_3$) 7.70 (2 H, d, *J* 8, *H*-2, *H*-6), 7.36 (2 H, d, *J* 8, *H*-3, *H*-5), 4.28–4.09 (4 H, m, -OCH_2), 1.31 (6 H, t, *J* 7.4, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 151.0, 133.1 (dt, $^2J_{C-F}$ 22.3, $^2J_{C-P}$ 13.6), 128.6, 121.5, 118.9 (q, $^1J_{C-F}$ 320.4), 117.5 (dt, $^1J_{C-F}$ 263.9, $^1J_{C-P}$ 218.1), 65.0, 16.2; δ_F (282 MHz, $CDCl_3$) −72.9 (3 F, s), −108.9 (2 F, d, $^2J_{F-P}$ 112.5); δ_P (121 MHz, $CDCl_3$) 5.83 (t, $^2J_{F-P}$ 112.5) [HRMS (CI, M[NH_4]$^+$) Found: 430.051264. Calc. for $C_{12}H_{18}F_5NO_6PS$: 430.052407]; *m*/*z* (CI) 430 (100%, M[NH_4]$^+$), 413 (15, M + 1), 282 (75), 265 (55).

4-[(Diethoxyphosphoryl)difluoromethyl]phenyl nonafluorobutanesulfonate 6b

Activated zinc dust (1.30 g, 19.9 mmol) in DMA (5 ml), diethyl bromodifluoromethylphosphonate (5.32 g, 19.9 mmol) in DMA (5 ml), copper bromide (2.86 g, 19.9 mmol) and nonaflate **5b** (5.00 g, 10.0 mmol) in DMA (3 ml) were treated and worked up as described above. Concentration *in vacuo* afforded a yellow oil which was purified by column chromatography (light petroleum) to afford **6b** (4.21 g, 75%) as a colourless oil (purity by GC 97%); R_f (light petroleum) 0.42 (Found: C, 32.01; H, 2.51. $C_{15}H_{14}F_{11}O_6PS$ requires: C, 32.04; H, 2.51%); ν_{max}(film)/cm^{-1} 2989w, 1503m, 1430s, 1354m, 1242br vs (P=O), 1205vs, 1147vs, 1020br vs, 894s, 844m, 736m; δ_H (300 MHz, $CDCl_3$) 7.72 (2 H, d, *J* 8.6, *H*-2, *H*-6), 7.37 (2 H, d, *J* 8.6, *H*-3, *H*-5), 4.30–4.10 (4 H, m, -OCH_2), 1.30 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 151.1, 133.0 (td, $^2J_{C-F}$ 22.6, $^2J_{C-P}$ 14.1), 128.4 (td, $^3J_{C-F}$ 6.8, $^3J_{C-P}$ 2.3), 121.3, 119.2–118.1 (m), 117.2 (td, $^1J_{C-F}$ 263.5, $^1J_{C-P}$ 217.6), 115.7–112.8 (m), 112.2–108.0 (m), 106.5–105.6 (m), 65.0 (d, $^2J_{C-P}$ 7.4), 15.7 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −72.8 (3 F, t, $^3J_{F-F}$ 9.5), −108.7 (2 F, t, $^2J_{F-F}$ 12.7), −108.8 (2 F, d, $^2J_{F-P}$ 112.0), −120.86 to −120.9 (2 F, m), −125.8 to −125.9 (2 F, m); δ_P (121 MHz, $CDCl_3$) 5.87 (t, $^2J_{P-F}$ 112.0) [HRMS (ES, M[Na]$^+$) Found: 584.9987. Calc. for $C_{15}H_{14}O_6F_{11}NaPS$: 584.9971]; *m*/*z* (CI) 580 (61%, M[NH_4]$^+$) 563 (100, M + 1), 425 (7), 279 (7), 109 (7).

4-[(Diisopropoxyphosphoryl)difluoromethyl]phenyl trifluoromethanesulfonate 6c

Activated zinc dust (1.30 g, 20 mmol) in DMF (10 ml), diisopropyl bromodifluoromethylphosphonate (5.90 g, 20 mmol) in DMF (10 ml), copper bromide (2.86 g, 20 mmol) and triflate **5a** (3.52 g, 10.0 mmol) in DMF (2 ml) were treated and worked up as described above. Concentration *in vacuo* afforded a pale yellow oil which was purified by column chromatography (30% diethyl ether in light petroleum) to afford **6c** (1.36 g, 31%) as a colourless oil (purity by GC 96%); R_f (30% ether in light petroleum) 0.17; ν_{max}(film)/cm^{-1} 2986m, 1604w, 1502m, 1428s, 1252m (P=O), 1215s, 1143s, 999s, 887m; δ_H (300 MHz, $CDCl_3$) 7.71 (2 H, d, *J* 8.5, Ar-*H*), 7.34 (2 H, d, *J* 8.5, Ar-*H*), 4.83–4.69 (2 H, m, -C*H*(CH_3)$_2$), 1.33 (6 H, d, *J* 6.2, -CH(CH_3)$_2$), 1.23 (6 H, d, *J* 6.2, -CH(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 150.9, 133.4 (dt, $^2J_{C-F}$ 22.6, $^2J_{C-P}$ 14.1), 128.8, 121.4, 118.7 (q, $^1J_{C-F}$ 320.5), 117.1 (dt, $^1J_{C-F}$ 263.9, $^1J_{C-P}$ 219.3), 74.3, 74.2, 24.1, 24.0, 23.5, 23.4; δ_F (282 MHz, $CDCl_3$) −72.9 (3 F, s), −109.4 (2 F, d, $^2J_{F-P}$ 112.5); δ_P (121 MHz, $CDCl_3$) 4.07 (t, $^2J_{F-P}$ 112.5) [HRMS (ES, M[Na]$^+$) Found: 463.0376. Calc. for $C_{14}H_{18}F_5NaO_6PS$: 463.0380]; *m*/*z* (ES$^+$) 463 (90%, M[Na]$^+$), 421 (82), 379 (100).

3-[(Diethoxyphosphoryl)difluoromethyl]-1-methoxybenzene 8

From diethyl bromodifluoromethylphosphonate (6.41 mmol, 1.71 g) in DMA (2 ml), activated zinc dust (6.41 mmol, 0.42 g) in DMA (2 ml), CuBr (6.41 mmol, 0.92 g), 3-iodoanisole (4.27 mmol, 1.00 g) in DMA (2 ml) which were reacted and worked up as described above. Concentration *in vacuo* afforded a yellow oil (2.30 g) which was purified by column chromatography (20% ethyl acetate in light petroleum) to afford **8** (0.40 g, 32%) as a colourless oil; R_f (20% ethyl acetate in light petroleum) 0.2 (Found: C, 49.11; H, 5.76. $C_{12}H_{17}F_2O_4P$ requires: C, 48.99; H, 5.82%); ν_{max}(film)/cm^{-1} 2985s, 1604s, 1588s, 1488s, 1454s, 1438s, 1275vs (P=O), 1211s, 1043br vs, 794s, 749m, 698s, 682m; δ_H (300 MHz, $CDCl_3$) 7.32 (1 H, dd, *J* 8.1, 7.7, *H*-5), 7.16 (1 H, d, *J* 7.7, *H*-4), 7.09 (1 H, s, *H*-2), 6.97 (1 H, d, *J* 8.1, *H*-6), 4.25–4.03 (4 H, m, -OCH_2), 3.78 (3 H, s, -OCH_3), 1.27 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 159.7, 134.2 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 14.1), 129.8, 118.7 (dt, *J* 7.3, $^3J_{C-P}$ 2.8), 118.5, 118.2 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 218.1), 111.8 (dt, $^3J_{C-F}$ 7.4, $^3J_{C-P}$ 2.3), 65.0 (d, $^2J_{C-P}$ 6.4), 55.5, 16.5 (d, $^3J_{C-P}$ 5.0); δ_F (282 MHz, $CDCl_3$) −108.2 (2 F, d, $^2J_{F-P}$ 116.9); δ_P (121 MHz, $CDCl_3$) 5.31 (t, $^2J_{F-P}$ 116.9) [HRMS (CI, M + 1) Found: 295.090726. Calc. for $C_{12}H_{18}F_2O_4P$: 295.091079]; *m*/*z* (CI) 312 (72%, M[NH_4]$^+$), 295 (100, M + 1), 157 (20).

4-[(Diethoxyphosphoryl)difluoromethyl]-1-methoxybenzene 9

Aryl difluorophosphonate **9** was prepared under identical conditions to **8** from 4-iodoanisole (4.27 mmol, 1.00 g) and diethyl bromodifluoromethylphosphonate (6.41 mmol, 1.71 g) to leave a yellow oil (2.30 g) which was purified by column chromatography (20% ethyl acetate in light petroleum) to afford **9** (0.21 g, 17%) as a colourless oil; R_f (20% ethyl acetate in light petroleum) 0.21 (Found: C, 48.99; H, 5.75. $C_{12}H_{17}F_2O_4P$ requires: C, 48.99; H, 5.82%); ν_{max}(film)/cm^{-1} 2985m, 1614s, 1516s, 1254s (P=O), 1019br s, 835m; δ_H (300 MHz, $CDCl_3$) 7.51 (2 H, d, *J* 8.5, *H*-3, *H*-5), 6.91 (2 H, d, *J* 8.5, *H*-2, *H*-6), 4.24–4.01 (4 H, m, -OCH_2), 3.78 (3 H, s, -OCH_3), 1.26 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 161.4, 127.8, 124.5 (dt, $^2J_{C-F}$ 22.6, $^2J_{C-P}$ 14.1), 118.2 (dt, $^1J_{C-F}$ 262.8, $^1J_{C-P}$ 221.0), 113.8, 64.7 (d, $^2J_{C-P}$ 6.4), 55.3, 16.4 (d, $^3J_{C-P}$ 5.0); δ_F (282 MHz, $CDCl_3$) −107.1 (d, $^2J_{F-P}$ 119.5); δ_P (121 MHz, $CDCl_3$) 6.95 (t, $^2J_{P-F}$ 119.5) [HRMS (CI, M + 1) Found: 295.091284. Calc. for $C_{12}H_{18}F_2O_4P$: 295.091079]; *m*/*z* (CI) 295 (39%, M + 1), 275 (10), 221 (7), 157 (100).

Benzyl (2-hydroxy-5-iodo)benzoate 11

Benzyl bromide (4.5 ml, 37.9 mmol) and potassium fluoride (4.84 g, 83.3 mmol) were dissolved in DMF (50 ml) with stirring at room temperature. After 5 minutes, 5-iodosalicylic acid **10** (10.00 g, 37.9 mmol) was added in one portion and the mixture was heated to 100 °C and stirred at that temperature for 2 hours under an atmosphere of nitrogen. The mixture was cooled to room temperature, quenched with water (50 ml) and extracted with diethyl ether (3 × 75 ml). The combined organic extracts were washed with water (3 × 100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a light pink solid (13.62 g) which was recrystallised from light petroleum to afford **11** as a white solid (11.04 g, 82%); mp 50–53 °C (light petroleum); R_f (40% diethyl ether in light petroleum) 0.77 (Found: C, 47.38; H, 2.98. $C_{14}H_{11}IO_3$ requires: C, 47.48; H, 3.13%); ν_{max}(KBr)/cm^{-1} 3462m, 1675s, 1602m, 1470m, 1286s, 1201s, 1091m, 694m; δ_H (300 MHz, $CDCl_3$) 8.14 (1 H, d, *J* 2.2, *H*-6), 7.74 (1 H, dd, *J* 8.8, *J* 2.2, *H*-4), 7.46–7.36 (5 H, m, Ph-*H*), 6.77 (1 H, d, *J* 8.8, *H*-3), 5.38 (2 H, s, -OCH_2Ph); δ_C (75 MHz, $CDCl_3$) 168.8, 161.4, 144.2, 138.2, 134.9, 128.8, 128.5, 120.0, 114.6, 80.1, 67.5; *m/z* (EI) 354 (20%, [M]$^+$), 91 (100). The phenolic O–H was not observed in the ^{1}H NMR spectrum.

Benzyl (5-iodo-2-trifluoromethylsulfonyloxy)benzoate 12

Trifluoromethanesulfonic anhydride (5.3 ml, 31.5 mmol) was added dropwise to a cooled (ice–water bath) solution of benzyl (2-hydroxy-5-iodo)benzoate **11** (10.14 g, 28.6 mmol) in pyridine (20 ml). The reaction mixture was stirred for 18 hours at 0 °C. The resulting yellow mixture was diluted with water (50 ml) and extracted with diethyl ether (3 × 50 ml). The combined organic extracts were washed with water (3 × 100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to recover a yellow oil which was purified by column chromatography (15% diethyl ether in light petroleum) to afford **12** (11.01 g, 79%) as a pale yellow liquid (purity by GC 99%); R_f (15% diethyl ether in light petroleum) 0.39 (Found: C, 37.19; H, 1.98. $C_{15}H_{10}O_5F_3SI$ requires: C, 37.06; H, 2.07%); ν_{max}(film)/cm^{-1} 3034w, 1731vs (C=O), 1594m, 1474s, 1428vs, 1286vs, 1250vs (P=O), 1213vs, 1170vs, 1140vs, 1072s, 889s, 832s, 749s, 609s; δ_H (300 MHz, $CDCl_3$) 8.36 (1 H, d, *J* 2.2, *H*-6), 7.91 (1 H, dd, *J* 8.8, 2.2, *H*-4), 7.47–7.36 (5 H, m, Ph*H*), 7.03 (1 H, d, *J* 8.8, *H*-3), 5.40 (2 H, s, -OCH_2Ph); δ_C (75 MHz, $CDCl_3$) 162.2, 148.2, 143.2, 141.4, 134.9, 129.0, 128.7, 126.1, 124.6, 118.7 (q, $^1J_{C-F}$ 320.8), 92.9, 68.1; δ_F (282 MHz, $CDCl_3$) −73.1 (s) [HRMS (FAB, M + Na$^+$) Found: 508.9159. Calc. for $C_{15}H_{10}O_5F_3SINa$: 508.9144]; *m/z* (EI) 486 (44%, [M]$^+$), 379 (80), 359 (66) 247 (53), 91 (100).

Benzyl 5-[(diethoxyphosphoryl)difluoromethyl]-2-(trifluoromethylsulfonyloxy)benzoate 13

From diethyl bromodifluoromethylphosphonate (0.55 g, 2.1 mmol) in DMA (2 ml), activated zinc dust (0.13 g, 2.1 mmol) in dry DMA (2 ml), freshly prepared copper(I) bromide (0.30 g, 2.1 mmol), **12** (0.50 g, 1.0 mmol) in DMA (2 ml), reacted and worked up as described above. Concentration *in vacuo* afforded a yellow oil (0.81 g) which was purified by column chromatography (60% diethyl ether in light petroleum) to afford **13** (0.37 g, 67%) as a pale yellow oil (purity by GC 100%); ν_{max}(film)/cm^{-1} 2986m, 1735 (C=O), 1431vs, 1276vs (P=O), 1224vs, 1140vs, 1070vs, 1022vs, 893s, 752s, 699m; δ_H (300 MHz, $CDCl_3$) 8.29 (1 H, s, *H*-6), 7.87 (1 H, d, *J* 8.8, *H*-3), 7.47–7.34 (6 H, m), 5.42 (2 H, s, -OCH_2Ph), 4.28–4.15 (4 H, m, -OCH_2), 1.29 (6 H, t, *J* 7.2, -CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 162.8, 149.8, 134.9, 133.4 (td, $^2J_{C-F}$ 23.2, $^2J_{C-P}$ 14.1), 132.4 (td, $^3J_{C-F}$ 6.8, $^3J_{C-P}$ 2.3), 130.8 (td, $^3J_{C-F}$ 6.8, $^3J_{C-P}$ 2.3), 128.9, 128.7, 124.9, 123.3, 118.7 (q, $^1J_{C-F}$ 320.4), 116.9 (td, $^1J_{C-F}$ 264.3, $^1J_{C-P}$ 218.0), 68.0, 65.2 (d, $^2J_{C-P}$ 6.8), 16.3 (d, $^3J_{C-P}$ 5.7); δ_F (121 MHz, $CDCl_3$) −73.1 (3 F, s), −109.1 (2 F, d, $^2J_{F-P}$ 111.6); δ_P (121 MHz, $CDCl_3$) 5.38 (t, $^2J_{P-F}$ 111.6) [HRMS (FAB, M + Na$^+$) Found: 569.0429. Calc. for $C_{19}H_{20}F_5O_8PNa$: 569.0434]; *m/z* (EI) 546 (16%, [M]$^+$), 439 (35), 412 (85), 307 (64), 91 (100).

4-Benzyloxy-3-iodo-5-methoxybenzaldehyde 14

A solution of 5-iodovanillin (5.65 mmol, 1.57 g) in DMF (2 ml) was added dropwise under an atmosphere of nitrogen to a stirred suspension of potassium carbonate (5.65 mmol, 0.78 g) in DMF (2 ml) at 0 °C. The suspension was stirred at 0 °C for 50 minutes. Benzyl bromide (5.65 mmol, 0.67 ml) was added dropwise and after stirring at 0 °C for a further 30 minutes, the reaction was allowed to warm to room temperature and stirred for four hours. Water (10 ml) was added and the mixture was extracted with diethyl ether (3 × 15 ml). The combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil (2.46 g) which was purified by column chromatography (20% diethyl ether in light petroleum) to afford **14** (1.85 g, 89%) as an off white solid; mp 54–56 °C; R_f (20% diethyl ether in light petroleum) 0.24; ν_{max}(KBr)/cm^{-1} 2984m, 1694s (C=O), 1583s, 1560s, 1464s, 1275s (P=O), 1143s, 1042s, 954s, 738m, 692s, 671m; δ_H (300 MHz, $CDCl_3$) 9.82 (1 H, s, C*H*O), 7.84 (1 H, d, *J* 1.8, Ar-*H*), 7.58–7.51 (2 H, m, Ar-*H*), 7.44–7.30 (4 H, m, Ar-*H*), 5.14 (2 H, s, -OCH_2Ph), 3.93 (3 H, s, -OCH_3); δ_C (75 MHz, $CDCl_3$) 189.8, 153.1, 152.9, 136.5, 134.9, 134.0, 128.7, 128.5, 111.0, 92.8, 74.8, 56.2. This material was used directly without further purification or characterisation.

4-Benzyloxy-3-[(diethoxyphosphoryl)difluoromethyl]-5-methoxybenzaldehyde 16

From diethyl bromodifluoromethylphosphonate (3.05 mmol, 0.82 g) in DMA (2 ml), activated zinc dust (3.05 mmol, 0.20 g) in DMA (2 ml), freshly prepared CuBr (3.05 mmol, 0.44 g), **14** (2.04 mmol, 0.75 g) in DMA (2 ml), reacted for 40 hours and worked up as described above. Concentration *in vacuo* afforded a yellow oil (1.76 g) which was purified by column chromatography (40% ethyl acetate in light petroleum) to afford **16** (0.22 g, 25%) as a colourless oil; R_f (40% ethyl acetate in light petroleum) 0.33; ν_{max}(film)/cm^{-1} 2984m, 1698s (C=O), 1586m, 1291br s (P=O), 1020br s; δ_H (300 MHz, $CDCl_3$) 9.91 (1 H, s, C*H*O), 7.65 (1 H, s, *H*-2), 7.58 (1 H, s, *H*-6), 7.52 (2 H, d, *J* 6.6, Ar-*H*), 7.41–7.29 (3 H, m, Ar-*H*), 5.15 (2 H, s, -OCH_2Ph), 4.30–4.04 (4 H, m, -OCH_2CH$_3$), 3.96 (3 H, s, -OCH_3), 1.20 (6 H, t, *J* 7.7, -CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 190.6, 154.3, 151.9, 136.9, 132.2, 128.5, 128.3, 128.2, 127.9–127.4 (m), 124.6 (t, $^3J_{C-F}$ 8.2), 118.0 (dt, $^1J_{C-F}$ 264.5, $^1J_{C-P}$ 218.7), 112.2, 75.8, 65.0 (d, $^2J_{C-P}$ 6.2), 56.2, 16.3 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −105.1 (d, $^2J_{F-P}$ 113.2); δ_P (121 MHz, $CDCl_3$) 5.93 (t, $^2J_{P-F}$ 113.2) [HRMS (CI, M[H]$^+$) Found: 429.126534. Calc. for $C_{20}H_{24}F_2O_6P$: 429.127859]; *m/z* (CI) 429 (24%, M$^+$), 401 (13), 339 (9), 262 (8), 245 (100).

2-Benzyloxy-3,5-diiodobenzaldehyde 15

Benzyl ether **15** was prepared under identical conditions to **14** from 3,5-diiodosalicylaldehyde (8.02 mmol, 3.00 g) and benzyl bromide (8.02 mmol, 0.95 ml) to afford a yellow solid which was recrystallised from diethyl ether–light petroleum to afford **15** (3.71 g, 100%) as an off white solid; mp 98–101 °C; δ_H (300 MHz, $CDCl_3$) 9.91 (1 H, s, C*H*O), 8.37 (1 H, d, *J* 2.1, *H*-6), 8.06 (1 H, d, *J* 2.1, *H*-4), 7.47–7.36 (5 H, m, Ar-*H*), 5.05 (2 H, s); δ_C (75 MHz, $CDCl_3$) 187.7, 160.7, 152.7, 137.7, 134.7, 132.0, 129.2, 129.0, 128.9, 94.9, 89.6, 78.6. The material was used directly without further purification or characterisation.

2-Benzyloxy-3-[(diethoxyphosphoryl)difluoromethyl]-5-iodobenzaldehyde 17a and 2-benzyloxy-5-[(diethoxyphosphoryl)difluoromethyl]-3-iodobenzaldehyde 17b

From diethyl bromodifluoromethylphosphonate (4.85 mmol, 1.30 g) in DMA (2 ml), activated zinc dust (4.85 mmol, 0.32 g) in DMA (2 ml), freshly prepared CuBr (4.85 mmol, 0.69 g), and **16** (3.23 mmol, 1.50 g) in DMA (2 ml) which were reacted and worked up as described above. Concentration *in vacuo* afforded a yellow oil (2.87 g) which was purified by column chromatography (30% ethyl acetate in light petroleum) to afford the aryl phosphonates **17a** (0.32 g, 19%) and **17b** (0.35 g, 21%) as colourless oils; for **17a** R_f (30% ethyl acetate in light petroleum) 0.30; ν_{max}(film)/cm^{-1} 2984s, 1693vs (C=O), 1571s, 1445s, 1372s, 1272vs (P=O), 1234vs, 1021br vs, 736s, 699s, 660m; δ_H (300 MHz, $CDCl_3$) 10.05 (1 H, s, C*H*O), 8.29 (1 H, s, *H*-6), 8.01 (1 H, s, *H*-4), 7.49–7.35 (5 H, m, CH_2*Ph*), 5.10 (2 H, s, OCH_2Ph), 4.34–4.16 (4 H, m, -OCH_2), 1.34 (6 H, t, $^3J_{H-H}$ 7.0 Hz, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 188.1, 162.6, 143.1 (t, $^3J_{C-F}$ 5.6), 134.7, 131.2 (dt, $^2J_{C-F}$ 23.2, $^2J_{C-P}$ 14.1), 130.4, 129.2, 129.0, 128.9, 127.2 (t, $^3J_{C-F}$ 5.1), 116.6 (dt, $^1J_{C-F}$ 265.6, $^1J_{C-P}$ 218.7), 93.6, 78.5, 64.5 (d, $^2J_{C-P}$ 6.8), 16.4 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.7 (d, $^2J_{F-P}$ 113.5); δ_P (121 MHz, $CDCl_3$) 5.57 (t, $^2J_{P-F}$ 113.5) [HRMS (FAB$^+$) Found: 546.993790. Calc. for $C_{19}H_{20}F_2INaO_5P$: 546.995891]; *m*/*z* (EI) 524 (19%, M$^+$), 496 (9), 433 (26), 397 (9), 91 (100); for **17b** R_f (30% ethyl acetate in light petroleum) 0.40; δ_H (300 MHz, $CDCl_3$) 10.06 (1 H, s, C*H*O), 8.22 (1 H, s, *H*-6), 8.07 (1 H, s, *H*-4), 7.45–7.32 (5 H, m, CH_2*Ph*), 5.04 (2 H, s, -OCH_2Ph), 4.24–4.06 (4 H, m, -OCH_2), 1.20 (6 H, t, $^3J_{H-H}$ 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 187.0, 159.6, 142.8 (t, $^3J_{C-F}$ 8.2), 140.5, 135.0, 132.5, 129.6 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.0), 128.8, 128.6, 128.5, 117.1 (dt, $^1J_{C-F}$ 266.5, $^1J_{C-P}$ 218.7), 88.0, 81.7, 65.1 (d, $^2J_{C-P}$ 6.8), 16.2 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −105.7 (d, $^2J_{F-P}$ 111.6); δ_P (121 MHz, $CDCl_3$) 5.44 (t, $^2J_{P-F}$ 111.6) [HRMS (FAB$^+$) Found: 546.994831. Calc. for $C_{19}H_{20}F_2INaO_5P$: 546.995891]; *m*/*z* (FAB$^+$) 547 (100%, M[Na]$^+$), 392 (6).

2-[(Diethoxyphosphoryl)difluoromethyl]thiophene 19

From diethyl bromodifluoromethylphosphonate (7.14 mmol, 1.91 g) in DMA (3 ml), activated zinc dust (7.14 mmol, 0.46 g) in DMA (3 ml), freshly prepared CuBr (7.14 mmol, 1.05 g) and 2-iodothiophene (4.76 mmol, 0.53 ml) in DMA (3 ml) which were reacted and worked up as described above. Concentration *in vacuo* afforded a yellow oil (1.95 g) which was purified by column chromatography (40% diethyl ether in light petroleum) to afford **19** (0.79 g, 62%) as a colourless oil; R_f (40% diethyl ether in light petroleum) 0.48 (Found: C, 40.09; H, 5.00. $C_9H_{13}F_2O_3PS$ requires: C, 40.00; H, 4.85%); ν_{max}(film)/cm^{-1} 2987m, 1431m, 1272s (P=O), 1242s, 1036br vs, 717m; δ_H (300 MHz, $CDCl_3$) 7.53–7.39 (2 H, m, *H*-2, *H*-4), 7.10–7.04 (1 H, m, *H*-3), 4.30–4.12 (4 H, m, -OCH_2), 1.31 (6 H, t, $^3J_{H-H}$ 7.0 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 133.7 (dt, $^2J_{C-F}$ 26.0, $^2J_{C-P}$ 17.0), 128.9, 128.8, 127.2, 97.9 (dt, $^1J_{C-F}$ 261.1, $^1J_{C-P}$ 225.5), 65.0 (d, $^2J_{C-P}$ 6.4), 16.2 (d, $^3J_{C-P}$ 4.8); δ_F (282 MHz, $CDCl_3$) −96.9 (2 F, d, $^2J_{F-P}$ 114.4); δ_P (121 MHz, $CDCl_3$) 5.41 (t, $^2J_{F-P}$ 114.4) [HRMS (CI) Found: 271.038054. Calc. for $C_9H_{14}F_2O_3PS$: 271.036936]; *m*/*z* (CI) 288 (10%, M[NH_4]$^+$), 271 (82, M + 1), 270 (9), 251 (14), 155 (25), 133 (100).

General procedure for Stille couplings from iodide 2 or triflate 6a: 1-{4′-[(diethoxyphosphoryl)difluoromethyl]phenyl}ethene 22a

$PdCl_2(PPh_3)_2$ (0.4 mmol, 0.27 g) was added to a stirred solution of iodide **2** (7.69 mmol, 3.0 g) and tributylstannylethene **21a** (8.07 mmol, 2.56 g) in DMF (15 ml) and the mixture was heated to 60 °C for one hour. After cooling, the black suspension was diluted with water (15 ml) and ether (25 ml), and filtered through a pad of Harbolite®. The mixture was extracted with ether (3 × 20 ml), and the combined organic extracts were washed with brine (20 ml). After drying ($MgSO_4$), the solvent was removed *in vacuo* to leave a brown oil (3.24 g) which was purified by flash chromatography (30% ethyl acetate in light petroleum) to afford alkene **22a** (1.87 g, 84%) as a colourless oil; R_F (40% ethyl acetate in light petroleum) 0.57 (Found: C, 53.72; H, 6.03. Calc. for $C_{13}H_{17}F_2O_3P$: C, 53.80; H, 5.90%); ν_{max}(film)/cm^{-1} 2985m, 1261s (P=O), 1017s, 843m; δ_H (300 MHz, $CDCl_3$) 7.56 (2 H, d, *J* 8.1, *H*-2′, *H*-6′), 7.47 (2 H, d, *J* 8.1, *H*-3′, *H*-5′), 6.72 (1 H, dd, *J* 17.3, 11.0, *H*-1), 5.81 (1 H, d, J_{trans} 17.3, *H*-2), 5.33 (1 H, d, J_{cis} 11.0, *H*-2), 4.28–4.06 (4 H, m, -OCH_2), 1.30 (6 H, t, $^3J_{H-H}$ 7.0, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 140.7, 135.9, 131.7 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 126.5 (dt, $^3J_{C-F}$ 5.9, $^3J_{C-P}$ 1.7), 126.2, 118.1 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 218.7), 115.9, 64.8 (d, $^2J_{C-P}$ 6.8), 16.4 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.3 (d, $^2J_{F-P}$ 117.0); δ_P (121 MHz, $CDCl_3$) 6.70 (t, $^2J_{P-F}$ 117.0); *m*/*z* (CI) 308 (100%, M[NH_4]$^+$), 291 (21, M + 1).

1-{4′-[(Diethoxyphosphoryl)difluoromethyl]phenyl}-1-ethoxyethene 22b and 1-{4′-[(diethoxyphosphoryl)difluoromethyl]phenyl}ethanone 23. As above from **6a** (1 mmol, 0.41 g) and 1-(tributylstannyl)-1-ethoxyethene **21b** (1 mmol, 0.36 g). Following the usual work up, the residue (crude **22b**) was redissolved in THF (6 ml). Dilute HCl (3 ml of 1 M solution) was added and the mixture was stirred at room temperature for 3 hours. After extraction with ether (3 × 10 ml), the combined organic extracts were washed with $NaHCO_3$ (2 × 7 ml) and brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil (0.23 g) which was purified by flash column chromatography (30% ethyl acetate in light petroleum) to afford the aryl ketone **23** (0.16 g, 52%) as a colourless oil; R_f (40% ethyl acetate in light petroleum) 0.39 (Found: C, 51.26; H, 5.50. $C_{13}H_{17}F_2O_4P$ requires: C, 50.99; H, 5.59%); δ_H (300 MHz, $CDCl_3$) 7.98 (2 H, d, *J* 8.1, *H*-2′, *H*-6′), 7.67 (2 H, d, *J* 8.1, *H*-3′, *H*-5′), 4.27–4.0 (4 H, m, -OCH_2), 2.59 (3 H, s, CH_3CO), 1.27 (6 H, t, $^3J_{H-H}$ 7.0, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 197.2, 138.6, 136.7 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 128.6, 126.5 (dt, $^3J_{C-F}$ 5.7), 117.5 (dt, $^1J_{C-F}$ 263.9, $^1J_{C-P}$ 217.0), 64.8 (d, $^2J_{C-P}$ 6.8), 26.6, 16.4 (d, $^3J_{C-P}$ 5.1); δ_F (282 MHz, $CDCl_3$) −109.4 (d, $^2J_{F-P}$ 113.5); δ_P (121 MHz, $CDCl_3$) 6.02 (t, $^2J_{P-F}$ 113.5) [HRMS (CI, M[NH_4]$^+$) Found: 324.117480. Calc. for $C_{13}H_{21}F_2NO_4P$: 324.117628]; *m*/*z* (EI) 306 (25%, M$^+$), 291 (27), 264 (31), 169 (97), 155 (100), 141 (47), 126 (80), 109 (94).

4-(2′-Pyridyl)-1-[(diethoxyphosphoryl)difluoromethyl]benzene 22c. As above from **6a** (1 mmol, 0.41 g) and 2-(tributylstannyl)pyridine **21c** (1 mmol, 0.37 g). Following the usual work up, purification by flash chromatography (40% ethyl acetate in light petroleum) afforded **22c** (0.18 g, 52%) as a colourless oil; R_f (40% ethyl acetate in light petroleum) 0.25; ν_{max}(film)/cm^{-1} 2959m, 1702w, 1587m, 1467s, 1436s, 1259vs (P=O), 1019vs, 783s; δ_H (300 MHz, $CDCl_3$) 8.69 (1 H, d, *J* 4.8, *H*-6′), 8.07 (2 H, d, *J* 8.1, *H*-2, *H*-6), 7.79–7.64 (4 H, m, *H*-3, *H*-5, *H*-4′), 7.30–7.23 (1 H, m, *H*-5), 4.30–4.10 (4 H, m, -OCH_2), 1.31 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 150.1, 149.7, 141.5, 136.8, 132.8 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 126.8, 126.6 (t, $^3J_{C-F}$ 5.1), 122.6, 120.7, 117.9 (dt, $^1J_{C-F}$ 262.8, $^1J_{C-P}$ 218.1), 64.7 (d, $^2J_{C-P}$ 6.8), 16.2 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.5 (d, $^2J_{F-P}$ 117.0); δ_P (121 MHz, $CDCl_3$) 6.61 (t, $^2J_{P-F}$ 117.0) [HRMS (ES, M[Na]$^+$) Found: 364.0883. Calc. for $C_{16}H_{18}F_2NNaO_3P$: 364.0890]; *m*/*z* (LCMS, CI, 4.30 min) 342 (100%, M + 1), 322 (3), 314 (23).

4-(2′-Furyl)-1-[(diethoxyphosphoryl)difluoromethyl]benzene 22d. As above from **6a** (1 mmol, 0.41 g) and 2-(tributylstannyl)furan **21d** (1 mmol, 0.36 g). Following the usual work up, purification by flash chromatography (30% ethyl acetate in light petroleum) afforded the furyl benzene derivative **22d** (0.26 g, 79%) as a colourless oil; R_f (40% ethyl acetate in light petroleum) 0.50; ν_{max}(film)/cm^{-1} 2987m, 1770m, 1731m, 1693m, 1409m, 1258s (P=O), 1022br s, 839m, 794m, 750m; δ_H (300 MHz, $CDCl_3$) 7.70 (2 H, d, *J* 8.1, *H*-2, *H*-6), 7.58 (2 H, d, *J* 8.1, *H*-3, *H*-5), 7.44 (1 H, d, *J* 1.8, *H*-5′), 6.69 (1 H, d, *J* 3.7, *H*-3′), 6.44 (1 H, dd, *J* 3.7, 1.8, *H*-4′), 4.26–4.11 (4 H, m, -OCH_2), 1.26 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 152.8, 142.9, 133.0, 131.0 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 126.7 (dt, $^3J_{C-F}$ 5.4, $^3J_{C-P}$ 1.7), 123.6, 118.0 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 219.3), 111.9, 106.6, 64.8 (d, $^2J_{C-P}$ 6.2), 16.3 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.4 (d, $^2J_{F-P}$ 117.0); δ_P (121 MHz, $CDCl_3$) 6.64 (t, $^2J_{P-F}$ 117.0) [HRMS (ES, M[Na]$^+$) Found: 353.0718. Calc. for $C_{15}H_{17}F_2NaO_4P$: 353.0730]; *m*/*z* (LCMS, CI, 4.62 min) 331 (28%, M + 1), 311 (100), 283 (12), 219 (27).

2-{4′-[(Diethoxyphosphoryl)difluoromethyl]phenyl}-5-(1,3-dioxolan-2-yl)furan 22e. As above from triflate **6a** (1 mmol, 0.41 g) and 2-(tributylstannyl)-5-(1,3-dioxolan-2-yl)furan **21e** (1 mmol, 0.43 g). Following the usual work up, purification by flash chromatography (40% ethyl acetate in light petroleum) afforded **22e** (0.24 g, 60%) as a yellow oil; R_f (40% ethyl acetate in light petroleum) 0.21; δ_H (300 MHz, $CDCl_3$) 7.71 (2 H, d, *J* 8.1, *H*-3′, *H*-5′), 7.58 (2 H, d, *J* 8.1, *H*-2′, *H*-6′), 6.67 (1 H, d, *J* 3.3, *H*-4), 6.67 (1 H, d, *J* 3.3, *H*-3), 5.95 (1 H, s, C*H*O_2), 4.28–3.90 (8 H, m, -OCH_2CH$_3$, -OCH_2CH_2), 1.29 (6 H, t, *J* 7.0, -CH$_2$$CH_3$); δ_C (75 MHz, $CDCl_3$) 153.3, 151.6, 133.3 (dt, $^2J_{C-F}$ 22.6, $^2J_{C-P}$ 13.6), 132.7, 126.6 (t, $^3J_{C-F}$ 4.5), 123.8, 117.9 (dt, $^1J_{C-F}$ 262.8, $^1J_{C-P}$ 218.1), 110.8, 107.0, 97.7, 65.2, 65.0 (d, $^2J_{C-P}$ 6.8), 16.3 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.6 (d, $^2J_{F-P}$ 117.0); δ_P (121 MHz, $CDCl_3$) 6.59 (t, $^2J_{P-F}$ 117.0); *m*/*z* (LCMS, CI, 4.48 min) 403 (100%, M + 1), 383 (75), 291 (27), 243 (37). The acetal was hydrolysed without further characterisation.

2-{4′-[(Diethoxyphosphoryl)difluoromethyl]phenyl}-5-furancarbaldehyde 24. Aqueous HCl (2.0 ml of a 2 M solution) was added to a stirred solution of acetal **22e** (0.97 mmol, 0.39 g) in THF (6 ml). After stirring at room temperature for twenty minutes the mixture was diluted with water (3 ml), and extracted with ether (3 × 6 ml). The combined organic extracts were washed with $NaHCO_3$ (2 × 5 ml) and brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil (0.36 g) which was purified by column chromatography (40% diethyl ether in isohexane to 100% ether) to afford aldehyde **24** (0.25 g, 77%) as a yellow solid; mp 67–69 °C; R_f (40% ethyl acetate in isohexane) 0.13 (Found: C, 53.54; H, 4.76. $C_{16}H_{17}F_2O_5P$ requires: C, 53.64; H, 4.78%); ν_{max}(KBr)/cm^{-1} 2958m, 1725m, 1678vs (C=O), 1668s, 1485m, 1254vs (P=O), 1024br vs, 807m, 773m; δ_H (300 MHz, $CDCl_3$) 9.67 (1 H, s, C*H*O), 7.89 (2 H, d, *J* 8.5, *H*-3′, *H*-5′), 7.65 (2 H, d, *J* 8.5, *H*-2′, *H*-6′), 7.33 (1 H, d, *J* 3.7, *H*-4), 6.92 (1 H, d, *J* 3.7, *H*-3), 4.30–4.08 (4 H, m, -OCH_2), 1.31 (6 H, t, *J* 7.0, -CH$_2$$CH_3$); δ_C (75 MHz, $CDCl_3$) 177.4, 157.8, 152.3, 133.4 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 131.1, 126.9 (t, $^3J_{C-F}$ 5.9), 125.1, 123.3, 117.7 (dt, $^1J_{C-F}$ 263.6, $^1J_{C-P}$ 218.1), 108.9, 64.9 (d, $^2J_{C-P}$ 6.8), 16.3 (d, $^3J_{C-P}$ 5.1); δ_F (282 MHz, $CDCl_3$) −109.0 (d, $^2J_{F-P}$ 114.4); δ_P (121 MHz, $CDCl_3$) 6.30 (t, $^2J_{P-F}$ 114.4) [HRMS (CI, M + 1) Found: 359.086402. Calc. for $C_{16}H_{18}F_2O_5P$: 359.085994]; *m*/*z* (LCMS, CI, 4.30 min) 376 (30%, M[NH_4]$^+$), 359 (100, M + 1), 339 (36).

2-{4′-[(Diethoxyphosphoryl)difluoromethyl]phenyl}-1-methylpyrrole-5-carbaldehyde 22f. As above from triflate **6a** (1 mmol, 0.41 g) and *N*-methyl-5-tributylstannylpyrrole-2-carbaldehyde **21f** (1 mmol, 0.40 g). Following the usual work up, purification by flash chromatography (30% ethyl acetate in light petroleum) afforded aldehyde **22f** as a brown solid which recrystallised from ether–light petroleum as light brown prisms (0.20 g, 53%); mp 71–73 °C; R_f (40% ethyl acetate in light petroleum) 0.23 (Found: C, 54.83; H, 5.25; N, 3.74. $C_{17}H_{20}F_2NO_4P$ requires: C, 54.99; H, 5.43; N, 3.77%); ν_{max}(KBr)/cm^{-1} 3470m, 1661vs (C=O), 1464m, 1279m (P=O), 1116s, 1052s, 1026s, 788m, 568m; δ_H (300 MHz, $CDCl_3$) 9.59 (1 H, s, C*H*O), 7.70 (2 H, d, *J* 8.1, *H*-3′, *H*-5′), 7.50 (2 H, d, *J* 8.1, *H*-2′, *H*-6′), 7.0 (1 H, d, *J* 4.0, *H*-4), 6.33 (1 H, d, *J* 4.0, *H*-3), 4.31–4.15 (4 H, m, -OCH_2), 1.33 (6 H, t, *J* 7.0, -CH$_2$$CH_3$); δ_C (75 MHz, $CDCl_3$) 179.8, 142.8, 133.6, 133.4, 132.7 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 14.1), 129.2, 126.7 (t, $^3J_{C-F}$ 5.7), 124.4, 117.9 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 218.2), 111.2, 65.0 (d, $^2J_{C-P}$ 6.8), 34.5, 16.4 (d, $^3J_{C-P}$ 5.1); δ_F (282 MHz, $CDCl_3$) −108.6 (d, $^2J_{F-P}$ 114.4); δ_P (121 MHz, $CDCl_3$) 6.34 (t, $^2J_{P-F}$ 114.4) [HRMS (CI, M[H]$^+$) Found: 372.117437. Calc. for $C_{17}H_{21}F_2NO_4P$: 372.117628]; *m*/*z* (LCMS, CI, 4.41) 372 (100%, M[NH_4]$^+$), 359 (100, M + 1), 352 (22), 260 (12), 232 (22).

4-(2′-Thienyl)-1-[(diethoxyphosphoryl)difluoromethyl]benzene 22g. As above from triflate **6a** and 2-(tributylstannyl)thiophene **21g**. Following the usual work up, purification by flash chromatography (30% ethyl acetate in light petroleum) afforded a white solid which recrystallised from ether–light petroleum to afford **22g** (0.22 g, 64%) as white needles; mp 59–60 °C; R_f (40% ethyl acetate in light petroleum) 0.57 (Found: C, 51.97; H, 5.15. $C_{15}H_{17}F_2O_3PS$ requires: C, 52.02; H, 4.95%); ν_{max}(KBr)/cm^{-1} 1609w, 1265s (P=O), 1050s, 1014vs, 822m, 566m; δ_H (300 MHz, $CDCl_3$) 7.68 (2 H, d, *J* 8.5, *H*-3′, *H*-5′), 7.61 (2 H, d, $^3J_{Ha-Hb}$ 8.5 Hz, *H*-2′, *H*-6′), 7.37 (1 H, d, *J* 3.3, *H*-3), 7.32 (1 H, d, *J* 5.2, *H*-5), 7.01 (1 H, dd, *J* 5.2, 3.3, *H*-4), 4.31–4.08 (4 H, m, -OCH_2), 1.32 (6 H, t, $^3J_{H-H}$ 7.0, -CH$_2$$CH_3$); δ_C (75 MHz, $CDCl_3$) 143.0, 136.8, 131.3 (dt, $^2J_{C-F}$ 22.1, $^2J_{C-P}$ 14.1), 128.3, 126.9 (t, $^3J_{C-F}$ 5.1), 125.9, 125.8, 124.2, 118.0 (dt, $^1J_{C-F}$ 262.8, $^1J_{C-P}$ 219.3), 64.8 (d, $^2J_{C-P}$ 6.8), 16.4 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.4 (d, $^2J_{F-P}$ 115.7); δ_P (121 MHz, $CDCl_3$) 6.77 (t, $^2J_{P-F}$ 115.7) [HRMS (CI, M[NH_4]$^+$) Found: 364.095758. Calc. for $C_{15}H_{21}F_2NO_3PS$: 364.094785]; *m*/*z* (CI) 347 (46%, M + 1), 210 (100), 352 (22).

4-Thiazol-2-yl-1-[(diethoxyphosphoryl)difluoromethyl]benzene 22h. As above from triflate **6a** (1 mmol, 0.41 g) and 2-(tributylstannyl)thiazole **21h** (1 mmol, 0.36 g). Following the usual work up, purification by flash chromatography (30% ethyl acetate in light petroleum) afforded biaryl **22h** (0.18 g, 52%) as a colourless oil; R_f (40% ethyl acetate in light petroleum) 0.36 (Found: C, 48.50; H, 4.83; N, 3.97. $C_{14}H_{16}F_2NO_3PS$ requires: C, 48.41; H, 4.64; N, 4.03%); ν_{max}(film)/cm^{-1} 2956m, 1480w, 1262s, 1021s, 834m, 755m; δ_H (300 MHz, $CDCl_3$) 8.02 (2 H, d, *J* 8.1, *H*-3′, *H*-5′), 7.86 (1 H, d, *J* 3.3, *H*-5), 7.67 (2 H, d, *J* 8.1, *H*-2′, *H*-6′), 7.36 (1 H, d, *J* 3.3, *H*-4), 4.28–4.05 (4 H, m, -OCH_2), 1.29 (6 H, t, *J* 7.0, CH$_2$$CH_3$); δ_C (75 MHz, $CDCl_3$) 167.8, 144.1, 135.7, 134.1 (dt, $^2J_{C-F}$ 22.1, $^2J_{C-P}$ 13.6), 127.0 (t, $^3J_{C-F}$ 5.1), 126.5, 119.8, 117.8 (dt, $^1J_{C-F}$ 263.9, $^1J_{C-P}$ 218.1), 64.9 (d, $^2J_{C-P}$ 6.8), 16.4 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.4 (d, $^2J_{F-P}$ 115.7); δ_P (121 MHz, $CDCl_3$) 6.36 (t, $^2J_{P-F}$ 115.7) [HRMS (CI, M + 1) Found: 348.063507. Calc. for $C_{14}H_{17}F_2NO_3PS$: 348.063485]; *m*/*z* (LCMS, CI, 4.37 min) 348 (100%, M + 1), 320 (6), 188 (11).

Benzyl 5-[(diethoxyphosphoryl)difluoromethyl]-2-(2′-furyl)-benzoate 25

A solution of triflate **13** (0.546 g, 1 mmol), 2-(tributylstannyl)furan **21d** (0.357 g, 1 mmol), Pd_2dba_3·$CHCl_3$ (0.026 g, 2.5 mol%), copper(I) iodide (0.019 g, 0.1 mmol) and triphenylphosphine (0.0525 g, 0.2 mmol) in dry degassed DMF (1 ml) was heated at 80 °C for 6 hours. The mixture was cooled, partitioned between water (10 ml) and ethyl ether (10 ml) and filtered through Celite. The aqueous phase was separated and extracted with ethyl ether (3 × 10 ml) then the combined organic extracts were dried and concentrated *in vacuo* to afford a yellow oil. Column chromatography (40% ethyl acetate in light petroleum) afforded **25** (0.324 g, 70%) as a yellow oil; R_f (40% ethyl acetate in light petroleum) 0.12; ν_{max}(film)/cm^{-1} 2981m, 1732vs (C=O), 1614m, 1273vs (P=O), 1225vs, 1020br vs, 739s, 698m; δ_H (300 MHz, $CDCl_3$) 7.86 (1 H, s, *H*-6), 7.75–7.68 (2 H, m, *H*-5′, *H*-4), 7.34–7.33 (6 H, m, *H*-3, CH$_2$Ph), 6.61 (1 H, d, *J* 3.3, *H*-3′), 6.42 (1 H, dd, *J* 3.3, 1.7, *H*-4′), 5.31 (2 H, s, -OCH_2Ph), 4.27–4.15 (4 H, m, -OCH_2CH$_3$), 1.33–1.28 (6 H, m, -OCH$_2$$CH_3$); δ_C (75 MHz, $CDCl_3$) 168.1, 151.2, 143.4, 135.3, 131.9, 131.8 (td, $^2J_{C-F}$ 22.6, $^2J_{C-P}$ 14.1), 131.8, 128.7 (td, $^3J_{C-F}$ 6.8, $^3J_{C-P}$ 2.3), 128.7, 128.6, 128.4, 127.9, 127.2 (td, $^3J_{C-F}$ 7.4, $^3J_{C-P}$ 2.8), 117.5 (td, $^1J_{C-F}$ 263.9, $^1J_{C-P}$ 218.2), 111.8, 109.5, 67.5, 65.0 (d, $^3J_{C-P}$ 6.8), 16.3 (d, $^3J_{C-P}$ 5.6); δ_F (282 MHz, $CDCl_3$) −108.9 (d, $^2J_{F-P}$ 114.7); δ_P (121 MHz, $CDCl_3$) 6.13 (t, $^2J_{P-F}$ 114.7) [HRMS (ES, M + 1) Found: 487.1095. Calc. for $C_{23}H_{23}F_2NaO_6P$: 487.1098]; *m*/*z* (ES) 487 (100%, M[Na]$^+$).

1-{4′-[(Diethoxyphosphoryl)difluoromethyl]phenyl}-2-(trimethylsilyl)ethyne 26

$PdCl_2(PPh_3)_2$ (5 mol%, 0.02 g) was added under an atmosphere of nitrogen to a stirred solution of triflate **6a** (0.24 mmol, 0.1 g), trimethylsilylethyne (0.34 g, 0.05 ml) and triethylamine (0.15 ml) in DMF (1 ml) and the mixture was heated to 90 °C for one hour. After cooling, the black suspension was diluted with ethyl acetate (10 ml) and filtered through a pad of Harbolite®. The mixture was washed with brine (2 ml), dried ($MgSO_4$), and concentrated *in vacuo* to leave a yellow oil (0.12 g) which was purified by column chromatography (20% ethyl acetate in isohexane) to afford alkyne **26** (0.07 g, 81%) as a pale yellow oil; R_f (20% ethyl acetate in isohexane) 0.20; δ_H (300 MHz, $CDCl_3$) 7.58–7.48 (4 H, m, Ar-H), 4.28–4.0 (4 H, m, -OCH_2), 1.29 (6 H, t, *J* 7.0, -CH_2CH_3), 0.25 (9 H, s, -SiCH_3); δ_C (75 MHz, $CDCl_3$) 132.5 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 14.1), 132.0, 126.3 (t, $^3J_{C-F}$ 5.6), 126.2, 117.9 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 218.1), 104.0, 96.7, 65.0 (d, $^2J_{C-P}$ 6.8), 16.3 (d, $^3J_{C-P}$ 5.1), 0.0; δ_F (282 MHz, $CDCl_3$) −108.9 (d, $^2J_{F-P}$ 115.7); δ_P (121 MHz, $CDCl_3$) 6.44 (t, $^2J_{P-F}$ 115.7) [HRMS (CI, M + 1) Found: 361.120399. Calc. for $C_{16}H_{24}F_2O_3PSi$: 361.120043]; *m*/*z* (LCMS, CI, 5.11 min) 361 (50%, M + 1), 341 (72), 313 (20), 249 (46), 201 (100).

General procedure for Suzuki coupling reactions: 1-{4′-[(diethoxyphosphoryl)difluoromethyl]phenyl}butane 28a

$PdCl_2(PPh_3)_2$ (5 mol%) was added under an atmosphere of nitrogen to a stirred solution of triflate **6a** (1.0 mmol), boronic acid **27a** (2.0 mmol) and triethylamine (4.0 mmol, 0.56 ml) in DMF (3 ml) and the mixture was heated to 90 °C for the time indicated (consumption of the triflate as shown by TLC). After cooling, the black suspension was diluted with ethyl acetate, and washed sequentially with aqueous solutions of $NaHCO_3$ (3 ml), water (3 ml), 2 M citric acid (3 ml) and brine (3 ml). After drying ($MgSO_4$), the solvent was removed *in vacuo*. Purification by flash chromatography (20% ethyl acetate in isohexane) afforded **28a** (0.20 g, 63%) as a colourless oil; R_f (20% ethyl acetate in isohexane) 0.19 (Found: C, 55.92; H, 7.29. $C_{15}H_{23}F_2O_3P$ requires: C, 56.25; H, 7.24%); ν_{max}(film)/cm^{-1} 2932w, 1271s (P=O), 1048s, 1019s; δ_H (300 MHz, $CDCl_3$) 7.49 (2 H, d, *J* 7.7, *H*-3′, *H*-5′), 7.24 (2 H, d, *J* 7.7, *H*-2′, *H*-6′), 4.27–4.0 (4 H, m, -OCH_2), 2.62 (2 H, *J* 7.7, ArCH_2-), 1.65–1.52 (2 H, m, -CH_2Et), 1.37–1.21 (8 H, m, -$CH_2CH_2CH_3$, -OCH_2CH_3), 0.90 (3 H, t, *J* 7.2, -$CH_2CH_2CH_3$); δ_C (75 MHz, $CDCl_3$) 145.9, 129.8 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 128.5, 126.1 (dt, $^3J_{C-F}$ 6.5, $^3J_{C-P}$ 2.3), 118.3 (dt, $^1J_{C-F}$ 262.8, $^1J_{C-P}$ 219.3), 64.7 (d, $^2J_{C-P}$ 6.8), 35.5, 33.4, 22.3, 16.3 (d, $^3J_{C-P}$ 5.7), 13.9; δ_F (282 MHz, $CDCl_3$) −107.8 (d, $^2J_{F-P}$ 118.3); δ_P (121 MHz, $CDCl_3$) 6.95 (t, $^2J_{P-F}$ 118.3) [HRMS (CI, M + 1) Found: 321.142830. Calc. for $C_{15}H_{24}F_2O_3P$: 321.143115]; *m*/*z* (LCMS, CI, 4.93 min) 321 (34%, M + 1), 301 (33), 273 (8), 209 (21), 181 (25), 161 (100).

4-Chloro-1-{4′-[(diethoxyphosphoryl)difluoromethyl]phenyl}-benzene 28b. Aryl triflate **6a** and 4-chlorophenylboronic acid were treated as described above for 80 minutes. Following the usual work up, purification by flash chromatography (30% ethyl acetate in isohexane) afforded the biaryl chloride **28b** (0.27 g, 72%) as a pale yellow oil; R_f (40% ethyl acetate in isohexane) 0.39 (Found: C, 54.67; H, 5.00. $C_{17}H_{18}ClF_2O_3P$ requires: C, 54.49; H, 4.84%); ν_{max}(film)/cm^{-1} 2985w, 1613w, 1487m, 1260s (P=O), 1018s, 817s; δ_H (300 MHz, $CDCl_3$) 7.68 (2 H, d, *J* 8.5, *H*-3′, *H*-5′), 7.62 (2 H, d, *J* 8.5, *H*-2′, *H*-6′), 7.52 (2 H, d, *J* 8.5, *H*-3, *H*-5), 7.42 (2 H, d, *J* 8.5, *H*-2, *H*-6), 4.32–4.10 (4 H, m, -OCH_2), 1.33 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 142.7, 138.2, 134.2, 131.7 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 129.1, 128.5, 127.0, 126.9 (t, $^3J_{C-F}$ 6.2), 118.1 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 218.7), 64.9 (d, $^2J_{C-P}$ 6.8), 16.4 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.3 (d, $^2J_{F-P}$ 115.7); δ_P (121 MHz, $CDCl_3$) 6.62 (t, $^2J_{P-F}$ 115.7); [HRMS (CI, M + 1) Found: 375.072243. Calc. for $C_{17}H_{19}ClF_2O_3P$: 375.072842]; *m*/*z* (LCMS, CI, 4.98 min) 394 (9%, ^{37}M[NH_4]$^+$), 392 (29%, ^{35}M[NH_4]$^+$), 377 (29, ^{37}M + 1), 375 (100, ^{35}M + 1), 355 (34).

4-Bromo-1-{4′-[(diethoxyphosphoryl)difluoromethyl]phenyl}-benzene 28c. Aryl triflate **6a** and 4-bromophenylboronic acid were treated as described above for 80 minutes. Following the usual work up, purification by flash chromatography (40% ether in isohexane) afforded biaryl **28c** (0.20 g, 48%) as a pale yellow oil; R_f (40% ethyl acetate in isohexane) 0.20; ν_{max}(film)/cm^{-1} 2933m, 1613m, 1588m, 1483s, 1390m, 1260s (P=O), 1020br s, 813s; δ_H (300 MHz, $CDCl_3$) 7.68 (2 H, d, *J* 8.1, *H*-3′, *H*-5′), 7.62 (2 H, d, *J* 8.1, *H*-4′, *H*-6′), 7.58 (2 H, d, *J* 8.5, *H*-3, *H*-5), 7.45 (2 H, d, *J* 8.5, *H*-4′, *H*-6′), 4.33–4.11 (4 H, m, -OCH_2), 1.33 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 142.4, 138.9, 132.1, 131.7 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 128.9, 127.0, 126.9 (t, $^3J_{C-F}$ 6.2), 122.4, 118.5 (dt, $^1J_{C-F}$ 263.9, $^1J_{C-P}$ 218.5), 64.9 (d, $^2J_{C-P}$ 6.8), 16.4 (d, $^3J_{C-P}$ 5.1); δ_F (282 MHz, $CDCl_3$) −108.4 (d, $^2J_{F-P}$ 116.4); δ_P (121 MHz, $CDCl_3$) 6.60 (t, $^2J_{P-F}$ 116.4) [HRMS (CI, M + 1) Found: 419.0223. Calc. for $C_{17}H_{19}BrF_2O_3P$: 419.0209]; *m*/*z* (CI) 438 (100%, ^{81}M[NH_4]$^+$), 436 (100, ^{79}M[NH_4]$^+$), 421 (31, ^{81}M + 1), 420 (17, ^{81}M), 419 (31, ^{79}M + 1), 418 (12, ^{79}M), 358 (14).

2-{4′-[(Diethoxyphosphoryl)difluoromethyl]phenyl}benzaldehyde 28d. Aryl triflate **6a** and 2-formylphenylboronic acid were treated as described above for 1 hour. Following the usual work up, purification by flash chromatography (20% ethyl acetate in isohexane) afforded biaryl **28d** (0.23 g, 63%) as a yellow oil; R_f (40% ethyl acetate in isohexane) 0.13 (Found: C, 58.68; H, 4.99. $C_{18}H_{19}F_2O_4P$ requires: C, 58.70; H, 5.20%); δ_H (300 MHz, $CDCl_3$) 9.91 (1 H, s, *CHO*), 7.98 (1 H, d, *J* 7.4, *H*-3), 7.69 (2 H, d, *J* 7.7, *H*-3′, *H*-5′), 7.66–7.58 (1 H, m, *H*-5), 7.53–7.36 (4 H, m, *H*-4, *H*-6, *H*-2′, *H*-6′), 4.31–4.10 (4 H, m, -OCH_2), 1.30 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 191.8, 144.6, 140.4, 133.7, 133.6, 132.5 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 14.1), 130.7, 130.1, 128.4, 127.9, 126.4 (t, $^3J_{C-F}$ 5.1), 118.0 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 218.7), 64.0 (d, $^2J_{C-P}$ 6.8), 16.4 (d, $^3J_{C-P}$ 5.1); δ_F (282 MHz, $CDCl_3$) −108.4 (d, $^2J_{F-P}$ 115.7); δ_P (121 MHz, $CDCl_3$) 6.40 (t, $^2J_{P-F}$ 115.7) [HRMS (CI, M + 1) Found: 369.107004. Calc. for $C_{18}H_{20}F_2O_4P$: 369.106729]; *m*/*z* (LCMS, CI, 4.55 min) 386 (8%, M[NH_4]$^+$), 369 (100, M + 1), 341 (19).

1-{4′-[(Diethoxyphosphoryl)difluoromethyl]phenyl}-3-nitrobenzene 28e. Aryl triflate **6a** and 3-nitrophenylboronic acid were treated as described above for 1 hour. Following the usual work up, purification by flash chromatography (30% ethyl acetate in isohexane) afforded an off white solid which crystallised from ether–isohexane to yield biaryl **28e** (0.33 g, 86%) as white needles, mp 65–67 °C; R_f (40% ethyl acetate in isohexane) 0.23 (Found: C, 53.07; H, 4.51; N, 3.59. $C_{17}H_{18}F_2NO_5P$ requires: C, 52.99; H, 4.71; N, 3.64%); δ_H (300 MHz, $CDCl_3$) 8.42 (1 H, s, *H*-2), 8.20 (1 H, d, *J* 8.1, *H*-4), 7.90 (1 H, d, *J* 7.7, *H*-6), 7.72 (2 H, d, *J* 8.8, *H*-3′, *H*-5′), 7.68 (2 H, d, *J* 8.8, *H*-4′, *H*-6′), 7.61 (1 H, dd, *J* 8.1, 7.7, *H*-5), 4.32–4.10 (4 H, m, -OCH_2), 1.33 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 148.8, 141.7, 141.1, 133.2, 132.8 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 14.1), 130.0, 127.3, 127.2, 122.7, 122.1, 118.0 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 218.2), 64.9 (d, $^2J_{C-P}$ 6.8), 16.2 (d, $^3J_{C-P}$ 5.1); δ_F (282 MHz, $CDCl_3$) −108.5 (d, $^2J_{F-P}$ 115.7); δ_P (121 MHz, $CDCl_3$) 6.41 (t, $^2J_{P-F}$ 115.7) [HRMS (CI, M + 1) Found: 386.096478. Calc. for $C_{17}H_{19}F_2NO_5P$: 386.096893]; *m*/*z* (LCMS, CI, 4.72 min) 403 (59%, M[NH_4]$^+$), 386 (100, M + 1), 366 (10), 274 (9).

1-{4′-[(Diethoxyphosphoryl)difluoromethyl]phenyl}-3,4-dimethoxybenzene 28f. Aryl triflate **6a** and 3,4-dimethoxyphenylboronic acid were treated as described above for 2 hours. Following the usual work up, purification by flash chromatography (80% ether in isohexane) afforded the biaryl **28f** (0.18 g, 45%) as a pale yellow semi-solid; R_f (40% ethyl acetate in isohexane) 0.29 (Found: C, 57.05; H, 5.75. $C_{19}H_{23}F_2O_5P$ requires: C, 57.00; H, 5.79%); ν_{max}(KBr)/cm^{-1} 1611m, 1526m, 1504m, 1266s (P=O), 1029s, 805m, 576m; δ_H (300 MHz, $CDCl_3$) 7.66 (2 H, d, *J* 9.4, *H*-3′, *H*-5′), 7.62 (2 H, d, *J* 9.4, *H*-4′, *H*-6′), 7.16 (1 H, dd, *J* 8.5, 1.2, *H*-6), 7.10 (1 H, d, *J* 1.2, *H*-2), 6.95 (1 H, d, *J* 8.5, *H*-5), 4.29–4.10 (4 H, m, -OCH_2), 3.94 (3 H, s, -OCH_3), 3.92 (3 H, s, -OCH_3), 1.33 (6 H, t, *J* 7.0 Hz,

-CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 149.1, 149.0, 143.3, 132.7, 130.6 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 126.6, 126.5 (t, $^3J_{C-F}$ 6.2), 119.4, 118.0 (dt, $^1J_{C-F}$ 263.4, $^1J_{C-P}$ 219.3), 111.3, 110.1, 64.6 (d, $^2J_{C-P}$ 6.8), 55.8, 16.2 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.2 (d, $^2J_{F-P}$ 116.9); δ_P (121 MHz, $CDCl_3$) 6.77 (t, $^2J_{P-F}$ 116.9) [HRMS (CI, M + 1) Found: 401.132944. Calc. for $C_{19}H_{24}F_2O_5P$: 401.132944]; *m/z* (LCMS, CI, 4.53 min) 418 (100%, $M[NH_4]^+$), 401 (67, M + 1), 381 (54).

4-(3′-Thienyl)-1-[(diethoxyphosphoryl)difluoromethyl]benzene 28g. Aryl triflate **6a** and 3-thienyl boronic acid were treated as described above for 80 minutes. Following the usual work up, purification by flash chromatography (30% ethyl acetate in isohexane) afforded a light brown solid which crystallised from ether–isohexane to yield biaryl **28g** (0.26 g, 75%) as off-white prisms, mp 60–62 °C; R_f (40% ethyl acetate in isohexane) 0.39 (Found: C, 52.12; H, 4.79. $C_{15}H_{17}F_2O_3PS$ requires: C, 52.02; H, 4.95%); ν_{max}(KBr)/cm^{-1} 1611w, 1265s (P=O), 1014s, 786s, 567s; δ_H (300 MHz, $CDCl_3$) 7.67 (2 H, d, *J* 8.8, *H*-3, *H*-5), 7.63 (2 H, d, *J* 8.8, *H*-2, *H*-6), 7.54–7.50 (1 H, m, *H*-4′), 7.43–7.39 (2 H, m, *H*-2′, *H*-5′), 4.30–4.09 (4 H, m, -OCH_2), 1.32 (6 H, t, *J* 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 141.2, 138.2, 131.1 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 126.8 (t, $^3J_{C-F}$ 6.2), 126.7, 126.4, 126.2, 121.5, 118.1 (dt, $^1J_{C-F}$ 262.8, $^1J_{C-P}$ 219.3), 64.9 (d, $^2J_{C-P}$ 6.2), 16.4 (d, $^3J_{C-P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −108.3 (d, $^2J_{F-P}$ 117.0); δ_P (121 MHz, $CDCl_3$) 6.74 (t, $^2J_{P-F}$ 117.0) [HRMS (CI, M + 1) Found: 347.067978. Calc. for $C_{15}H_{18}F_2O_3PS$: 347.068236]; *m/z* (LCMS, CI, 4.69 min) 364 (13%, $M[NH_4]^+$), 347 (72, M + 1), 327 (97), 299 (12), 235 (59), 187 (100).

4-(1-Benzofuran-2-yl)-1-[(diethoxyphosphoryl)difluoromethyl]-benzene 28h. Aryl triflate **6a** and 1-benzofuran-2-ylboronic acid were treated as described above for 1 hour. Following the usual work up, purification by flash chromatography (20% ethyl acetate in isohexane) afforded an off white solid which crystallised from ether–isohexane to afford biaryl **28h** (0.25 g, 66%) as white plates, mp 104–106 °C; R_f (40% ethyl acetate in isohexane) 0.33 (Found: C, 59.72; H, 4.88. $C_{19}H_{19}F_2O_4P$ requires: C, 60.00; H, 5.04%); ν_{max}(KBr)/cm^{-1} 1269s, 1014s, 809m, 753m; δ_H (300 MHz, $CDCl_3$) 7.93 (2 H, d, *J* 8.1, *H*-3, *H*-5), 7.69 (2 H, d, *J* 8.1, *H*-2, *H*-6), 7.59 (1 H, d, *J* 7.0, *H*-7′), 7.53 (1 H, d, *J* 8.1, *H*-4′), 7.53–7.20 (2 H, m, *H*-4′, *H*-6′), 7.10 (1 H, s, *H*-3′), 4.31–4.10 (4 H, m, -OCH_2), 1.32 (6 H, t, $^3J_{H-H}$ 7.0, -CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 155.1, 154.6, 132.8, 132.3 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.6), 129.0, 126.8 (t, $^3J_{C-F}$ 5.6), 124.9, 124.8, 123.2, 121.3, 118.0 (dt, $^1J_{C-F}$ 262.8, $^1J_{C-P}$ 218.7), 111.3, 102.9, 64.9 (d, $^2J_{C-P}$ 6.8), 16.4 (d, $^3J_{C-P}$ 5.1); δ_F (282 MHz, $CDCl_3$) −108.5 (d, $^2J_{F-P}$ 115.4); δ_P (121 MHz, $CDCl_3$) 6.60 (t, $^2J_{P-F}$ 115.4) [HRMS (CI, M + 1) Found: 381.106867. Calc. for $C_{19}H_{20}F_2O_4P$: 381.106729]; *m/z* (LCMS, CI, 5.00 min) 398 (50%, $M[NH_4]^+$), 381 (100, M + 1), 361 (43).

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