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Facile Syntheses of Aryldifluorophosphonate Building Blocks

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Abstract:

The copper-catalysed zinc phosphonate chemistry described by Yokomatsu and Shibuya can be used directly in the synthesis of phosphotyrosine analogue F_2Pmp, and in entering the classical organometallic coupling repertoire *via* Stille and Suzuki-Miyaura couplings. Herein, we report a streamlined synthesis of F_2Pmp, and of a pivotal triflate, which undergoes a range of palladium-catalysed couplings with aryl and heteroaryl components.

The non-hydrolysable phosphotyrosine mimic (difluorophosphonomethyl)phenyl alanine **1** has aroused the interest 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 [1-4].

Early published routes to aryl difluorophosphonates (including **1**) involved DAST fluorinations which required large excesses of this rather toxic and expensive reagent deployed in reactions which were prone to detonation upon scale up [5,6], lending some impetus to the search for non-DAST using routes to these interesting compounds. While recent developments using electrophilic fluorinating agents have emerged from the Toronto group, we had explored a non-DAST route progressing to an advanced intermediate using a cerium-mediated addition of a difluorophoshonate building block to a commercially-available benzoquinone monoketal [7]. However, our chemistry was superceded by developments from laboratories in Iowa and Tokyo. Burton and co-workers described an approach which allowed direct linkage between an organocadmium reagent derived from diethyl bromodifluoromethyl phosphonate and iodoarenes [8], then, in a still more significant development, the Shibuya group described similar couplings with the same building blocks *via* a copper-catalysed reaction of an organozinc reagent [9]. Qabar and co-workers used the Burton chemistry in solid and solution phase syntheses of the discrete and supported protected target [10], but to our astonishment, there is but one report of a useful application of the Shibuya chemistry which describes a rather indirect synthesis of the phosphotyrosine analogue, and of related β-aminoacid analogues [11]. The Qabar synthesis uses the rather expensive 4-iodophenyl alanine as a coupling substrate but we have found that 1,4-diiodobenzene can be used as a starting material for the phosphoamino acid analogue.

As described by Shibuya, 1,4-diiodobenzene underwent smooth coupling (**Scheme 1**) to afford the iodophenyl phosphonate **2** and bis-coupled **3** which could be separated from each other, and from homo-coupled **4**, by simple column chromatography. Exposure of **2** to the organozinc reagent prepared from commercially-available **5** under the conditions described by Jackson afforded the fully-protected phosphoamino acid analogue in 15% overall yield in the most direct synthesis to date of this valuable compound [12]. The conditions described by Burke, which differ in the method of preparation of the organozinc reagent, and the nature of the palladium catalyst, failed to afford any coupled product in our hands [5]. This route represents the most direct approach to fully protected F_2Pmp available so far, though there is room for improvement in the selectivity of the coupling to form **2**, and in the yield of the final coupling to form **1**. Intermediates such as **2** also present an opportunity for

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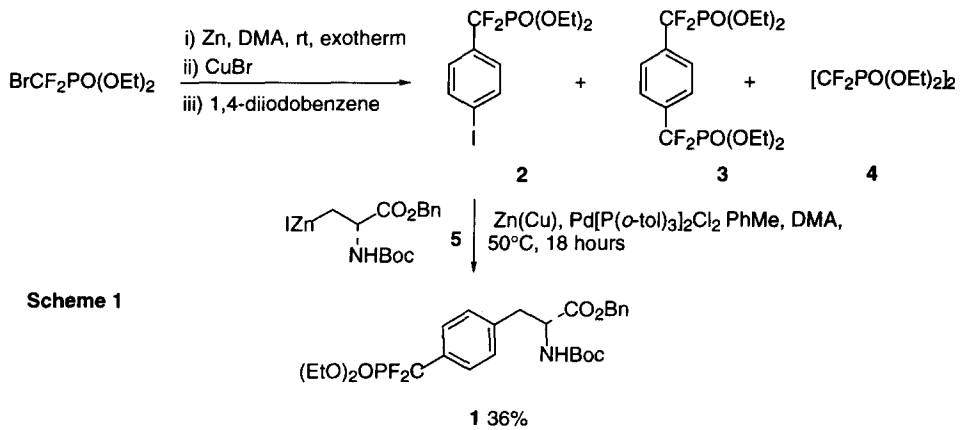
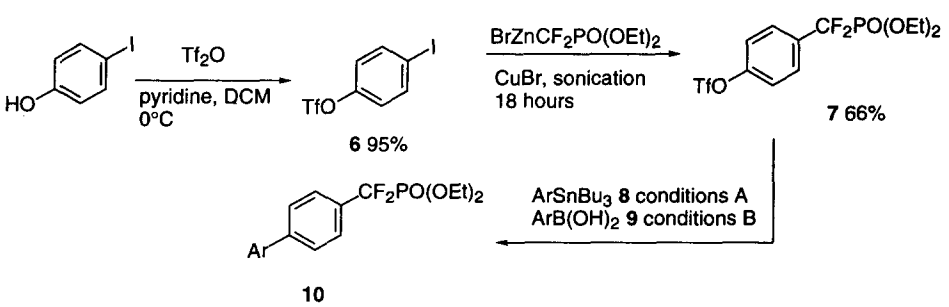
the generation of molecular diversity through exploitation of the second carbon-iodine bond in a palladium-catalysed coupling reaction. Of course, aryl triflates are also accepted in this repertoire of reactions, whereas the Shibuya coupling does not run for aryl triflate substrates, so we decided to explore the behaviour of **6** under the Shibuya conditions.



Scheme 1

1 36%

Consistent with the reactivity described by Shibuya, iodotriflate **6**, prepared from 4-iodophenol on a 50 g scale under standard conditions (triflic anhydride, pyridine, 0°C, 95%) [13] underwent efficient coupling under sonication conditions to afford **7** in a pleasing 66% isolated, purified yield (**Scheme 2**). This intermediate could be stored for extended periods in the freezer without decomposition.

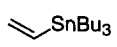
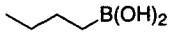
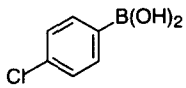
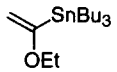
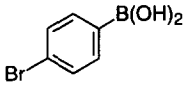
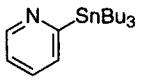
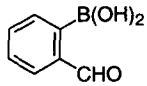
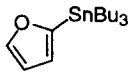
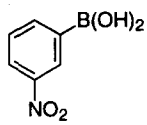
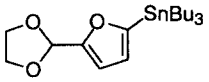
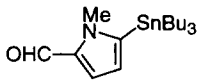
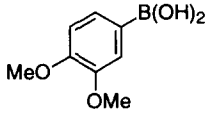
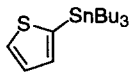
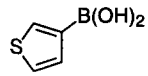
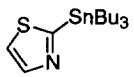
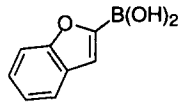


Scheme 2
Conditions A ; 1.0 $ArSnBu_3$, 5% $Pd(PPh_3)_2Cl_2$, DMF (*ca*1.0 M), 60°C, 1 - 6 hours.
Conditions B; 2.0 $ArB(OH)_2$, 5% $Pd(PPh_3)_2Cl_2$, 4.0 TEA, DMF (*ca*1.0 M), 90°C, 1 - 2 hours.

Stille [14] and Suzuki coupling reactions of **7** with a range of aliphatic, aryl and heteroaryl tributylstannanes **8** and boronic acids **9** afforded coupling products **10** in moderate to high yields, thus presenting the phosphate mimicking group on a wide range of biaryl scaffolds (**Table 1**).

Coupling conditions were not optimised exhaustively but *tetrakis*(triphenylphosphino)palladium(0) and (dppb)$PdCl_2$ were ineffective catalysts for the reaction. The addition of lithium chloride to the Stille reactions either inhibited the coupling, or resulted in decomposition of **6**. Lower yields were obtained when couplings were attempted in 1,4-dioxan 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.

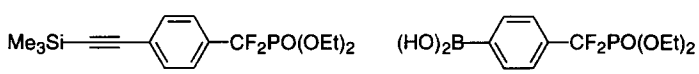
Table 1.
Stille and Suzuki Couplings of **7**.

Stannane **8**	Time (hrs)	Yield of **10** (%)	Boronic acid **9**	Time (hrs)	Yield of **10** (%)
	5	51[a]		1.3	63
	1	84[b]		1.3	72
	6	51		2	47
	6	52		1	63
	6	79		1	86
	6	60			
	1	53		2	45
	6	64		1.3	75
	6	52		1	66

[a]Yield from **7**. [b]Yield from **3** under these conditions.

Direct coupling with (trimethylsilyl)ethyne also proceeded well to afford **11** (80% yield) under the palladium catalysed conditions.

Less efficient, but ultimately of considerable importance, was the preparation of boronic acid **12** from **2**, by halogen-metal exchange. Treatment of the iodide with *tert*-butyllithium at -100°C followed by trapping with tri-*iso*propylborate and hydrolysis afforded **12** after a simple work-up. The behaviour of this compound and our efforts to improve the synthesis will be reported elsewhere. We are also exploring the utility of the Shibuya chemistry for preparing polyfunctionalised aryl and heteroaryl nucleii bearing the difluorophosphonate.



11 **12**

These results show tolerance by the difluorophosphonato group of non-nucleophilic coupling conditions, and the availability of arylphosphonate building blocks of different levels (**2** and **7**) and types (**12**) 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.

Acknowledgement

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[14] **General Procedure for Stille Couplings of Triflate 7.**
$PdCl_2(PPh_3)_2$ (5 mol %) was added to a stirred solution of triflate (1 mmol, 0.41 g) and 2-(tributylstannyl)thiazole (1mmol, 0.36 g) in DMF (1 mL) and the mixture was heated to 60 °C for the time indicated. After cooling, the black suspension was diluted with water and ether, and filtered through a pad of Harbolite®. The mixture was extracted with ether, and the combined organic extracts were washed with brine. After drying ($MgSO_4$), the solvent was removed *in vacuo* to afford the crude coupling product which was purified by flash chromatography (silica gel; 30 % ethyl acetate:light petroleum) to afford the bisaryl adduct (R_F = 0.36, 40 % ethyl acetate:light petroleum) as a colourless oil (0.18 g, 52 %); Found:C, 48.50 %; H, 4.83 %; N, 3.97 %. Calcd for $C_{14}H_{16}F_2NO_3PS$: C, 48.41 %; H, 4.64 %; N, 4.03 %; δ_H (300 MHz, $CDCl_3$) 8.02 (2H, d, $^3J_{Ha\text{-}Hb}$ 8.1 Hz, *Ha*), 7.86 (1H, d, $^3J_{H\text{-}H}$ 3.3 Hz), 7.67 (2H, d, $^3J_{H\text{-}H}$ 8.1 Hz), 7.36 (1H, d, $^3J_{H\text{-}H}$ 3.3 Hz), 4.28-4.05 (4H, m), 1.29 (6H, t, $^3J_{H\text{-}H}$ 7.0 Hz); δ_C (75 MHz, $CDCl_3$) 167.8, 144.1, 135.7, 134.1 (dt, $^2J_{C\text{-}F}$ 22.1 Hz, $^2J_{C\text{-}P}$ 13.6 Hz), 127.0 (t, $^3J_{C\text{-}F}$ 5.1 Hz), 126.5, 119.8, 117.8 (dt, $^1J_{C\text{-}F}$ 263.9 Hz, $^1J_{C\text{-}P}$ 218.1 Hz), 64.9 (d, $^2J_{C\text{-}P}$ 6.8 Hz), 16.4 (d, $^3J_{C\text{-}P}$ 5.7 Hz); δ_F (282 MHz, $CDCl_3$) -108.4 (d, $^2J_{F\text{-}P}$ 115.7 Hz); δ_P (121 MHz, $CDCl_3$) 6.36 (t, $^2J_{P\text{-}F}$ 115.7 Hz); *m/z* (CI) 348 (100 %, M+1), 320 (6 %), 188 (11 %).