

## Polyhalogenoheterocyclic compounds. Part 53.<sup>1</sup> Sonogashira reactions of 2,4,6-tribromo-3,5-difluoropyridine

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### Abstract

Palladium catalysed Sonogashira reactions between 2,4,6-tribromo-3,5-difluoropyridine and a variety of phenylacetylene derivatives gave a series of 4-bromo-2,6-bis(2-phenylethynyl)-3,5-difluoropyridine derivatives arising from displacement of bromine atoms attached to positions *ortho* to ring nitrogen.

**Keywords:** Heterocycle, pyridine, fluoropyridine, Sonogashira, palladium catalysis

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### Introduction

It is now well established that the incorporation of fluorine atoms into heterocyclic molecules can have a significant effect upon the chemical and biological properties of these systems.<sup>2,3</sup> This has been used to great effect in the development of various commercially important life-science products, such as 5-fluorouracil, 5-fluoroprimaquine and Ciprofloxacin, that owe their useful biological activity to the presence of a fluorine substituent located on the heterocyclic ring.<sup>3</sup> However, efficient synthesis of functional fluorinated heterocyclic derivatives is not trivial and presents a considerable challenge to the synthetic chemist.<sup>4</sup>

In the life science/drug discovery arena, strategies for the synthesis of novel families of polysubstituted heterocyclic systems of readily variable molecular architecture are of increasing importance, due to the surprisingly high proportion of commercially important pharmaceutical and plant protection products that are based upon a small heterocyclic ring core scaffold.<sup>5-8</sup> Consequently, effective methodology for the synthesis of selectively fluorinated polyfunctional heterocyclic systems is an important research goal.

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<sup>†</sup> Dick Chambers was Chairman of the RSC Heterocyclic Group during the period 1987-1989.

In this series, we are developing the chemistry of perhalogenated heteroaromatic systems and we have demonstrated that perfluorinated heterocyclic derivatives, such as pentafluoropyridine, are very useful polyfunctional heterocyclic scaffolds<sup>4,9</sup> because, in principle, all of the fluorine atoms are activated towards nucleophilic attack and may be replaced by appropriate nucleophilic species.<sup>10</sup> Related polybromofluoropyridine derivatives are, potentially, very valuable scaffolds for the synthesis of pyridine derivatives because not only are nucleophilic substitution reactions possible, involving either replacement of fluorine or bromine depending upon the nature of the nucleophile,<sup>11</sup> but also palladium catalysed processes involving activation of a carbon-bromine bond. We have developed efficient methodology for the synthesis of various polybromofluoroheteroaromatic systems<sup>11</sup> and are exploring the use of these novel scaffolds for a variety of synthetic applications.

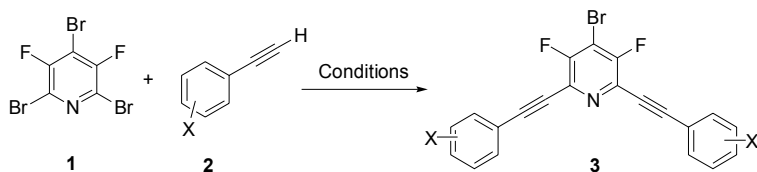
In this paper we describe palladium catalysed Sonogashira reactions<sup>12</sup> of the readily prepared 2,4,6-tribromo-3,5-difluoropyridine<sup>11</sup> and demonstrate the use of this readily accessible system as an excellent building block for the synthesis of polyfunctional fluoropyridine derivatives.

## Results and Discussion

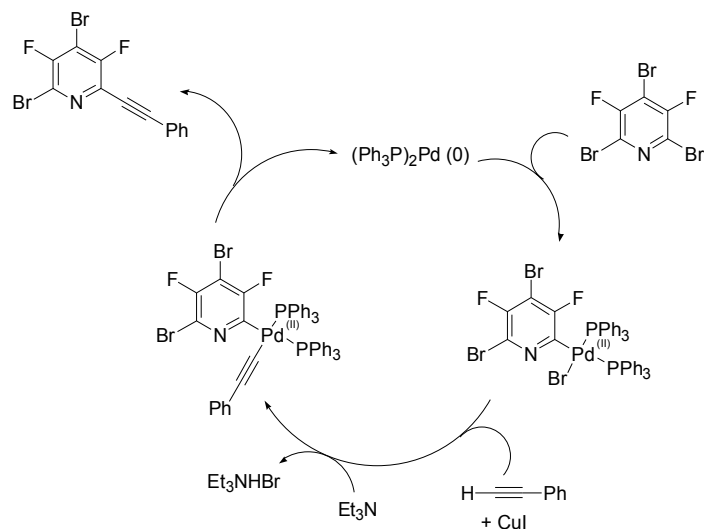
Sonogashira reaction of 2,4,6-tribromo-3,5-difluoropyridine **1** with various phenylacetylene substrates **2a-f**, in the presence of a palladium catalyst ( $\text{PdCl}_2(\text{PPh}_3)_2$ ), copper (I) iodide and either triethylamine or cesium carbonate, gave the corresponding diacetylenic pyridine systems **3a-f** and these results are collated in Table 1. In all cases the isolated yields are fair and reflect the sometimes difficult purification steps required for palladium catalysed processes. We found that the reactions were not especially sensitive to the presence of either an electron releasing or withdrawing group on the aromatic ring because, in these cases, the substituents in the aryl group are relatively remote from the reaction centre.

A consideration of the generally accepted mechanism for Sonogashira reactions<sup>12</sup> (Scheme 1) allows us to assess the effect of using perhalogenated heterocyclic substrates as starting materials.

In the first stage, the palladium species acts as a nucleophile and reaction with an electron deficient halogenated heterocycle is, therefore, a favoured process. Insertion of the palladium nucleophile occurs at the weaker and softer carbon-bromine bond rather than at the stronger carbon-fluorine bond, at positions that are *ortho* to ring nitrogen. Although most other nucleophiles attack preferentially at the 4- rather than the 2-position in perhalogenated pyridines,<sup>2,4</sup> these insertion reactions present a further example where transition metal induced reactions give a different outcome for displacement of either fluorine or bromine in heteroaromatic systems, suggesting some involvement of charge on nitrogen in the transition state.<sup>13,14</sup>

**Table 1.** Sonogashira reactions of 2,4,6-tribromo-3,5-difluoropyridine

Phenylacetylene	Conditions	Product	Yield (%)
<b>2a</b>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> CuI, Et <sub>3</sub> N rt, 22 h	<b>3a</b>	75
<b>2b</b>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> CuI, Et <sub>3</sub> N rt, 48 h	<b>3b</b>	42
<b>2c</b>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> CuI, Cs <sub>2</sub> CO <sub>3</sub> Toluene, 60°C, 19 h	<b>3c</b>	58
<b>2d</b>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> CuI, Et <sub>3</sub> N rt, 72 h	<b>3d</b>	37
<b>2e</b>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> CuI, Et <sub>3</sub> N rt, 22 h	<b>3e</b>	38
<b>2f</b>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> CuI, Et <sub>3</sub> N 100°C, 48 h	<b>3f</b>	42



**Scheme 1.** Mechanism of Pd catalysed Sonogashira coupling process

## X-ray Crystallography

Single crystals of **3b**, **3c** and of two polymorphs of **3d** (**3dA** and **3dB**) were grown and their structures determined by X-ray analysis (Figs. 1-3). In the structures of **3b** and **3c** the molecules are packed in layers in which the bromine atoms are sandwiched between two heterocycles of adjacent molecules. In the case of polymorphs **3dA** and **3dB**, the molecules form stacks and are linked together by  $\pi$ - $\pi$  interactions between both the terminal phenyl and heterocyclic rings. The heterocycles in the stacks are parallel to each other in the structure of **3dA** and anti-parallel in the polymorph **3dB**.

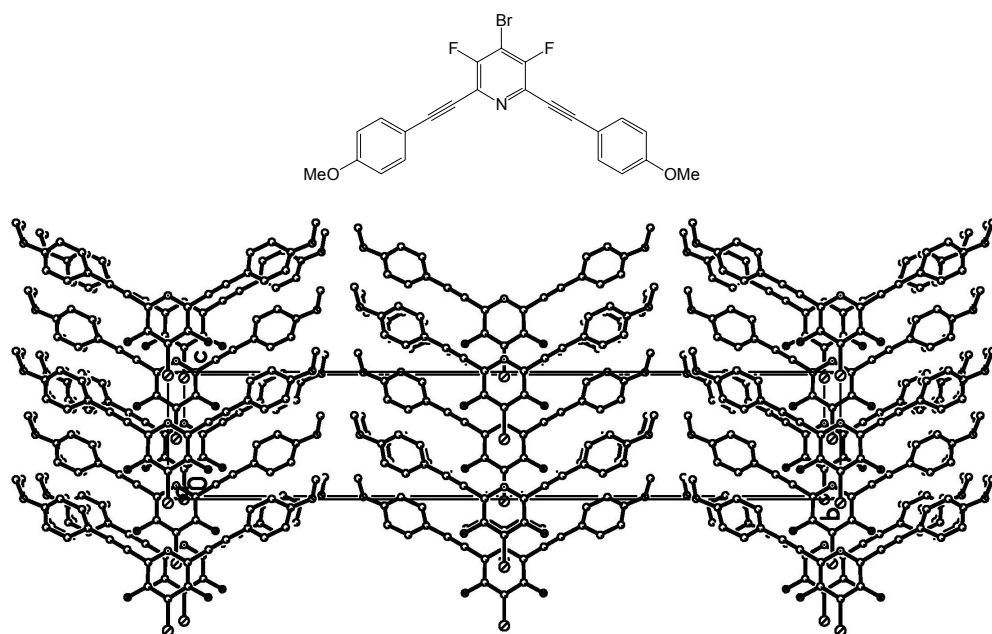


Figure 1. X ray structure of 3b.

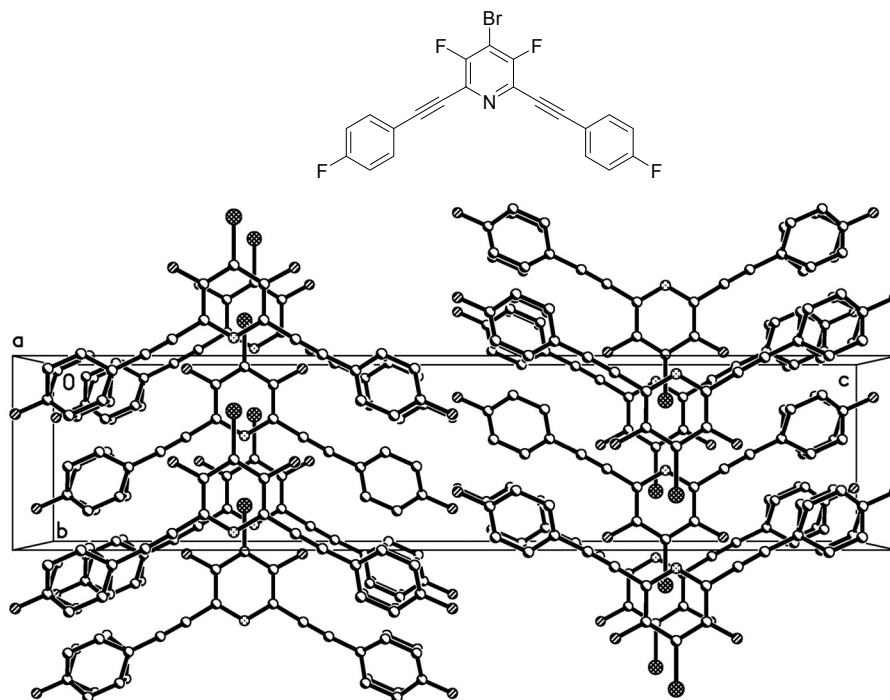
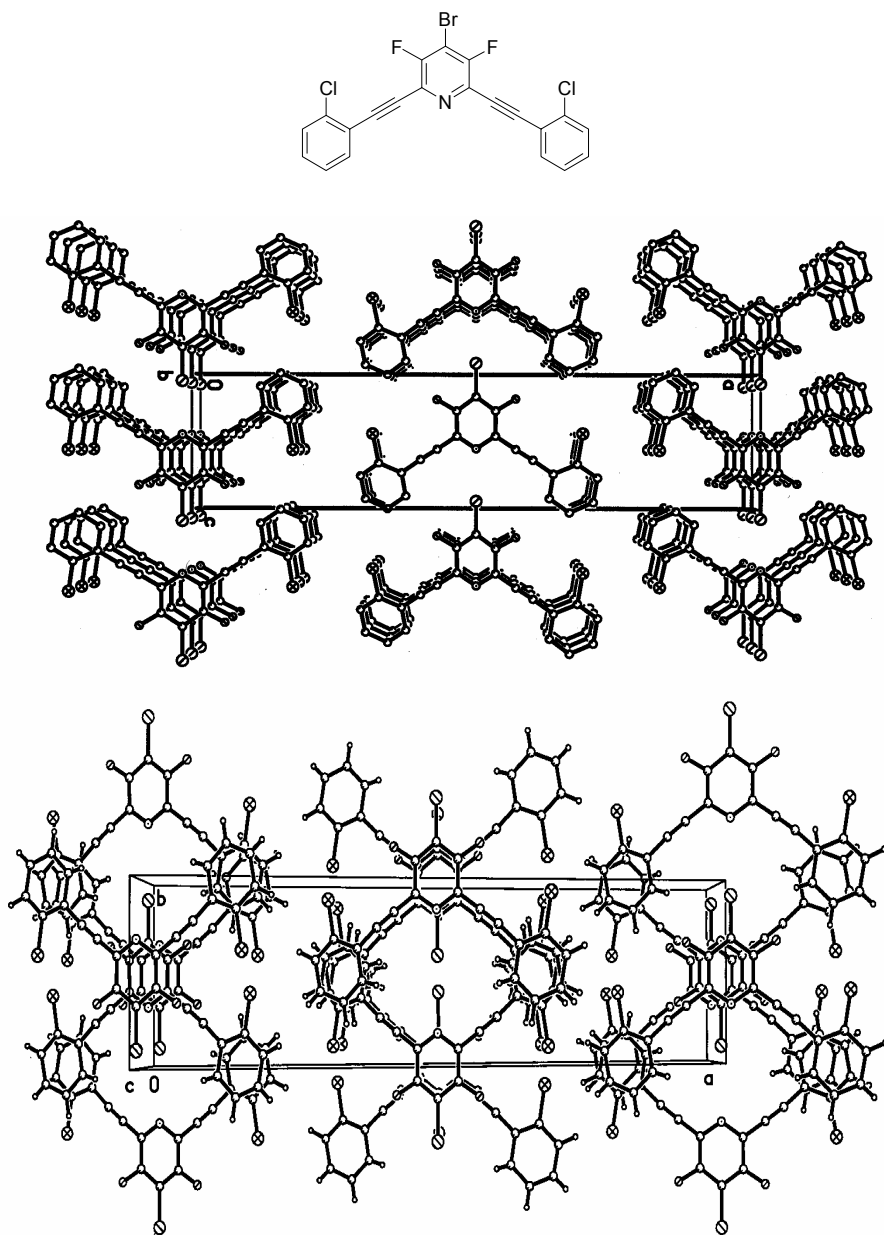


Figure 2. X-ray structure of 3c



**Figure 3.** Packing arrangement in two polymorphs of 3d

In conclusion, palladium catalysed Sonogashira reactions involving 2,4,6-tribromo-3,5-difluoropyridine give products arising from the displacement of bromine atoms located at the 2- and 6-positions, *ortho* to ring nitrogen, further demonstrating the use of perhalogenated scaffolds for synthetic applications.

## Experimental Section

**General Procedures.** All starting materials were obtained commercially. All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a spectrometer operating at 500 MHz ( $^1\text{H}$  n.m.r.), 376 MHz ( $^{19}\text{F}$  n.m.r.) and 100 MHz ( $^{13}\text{C}$  n.m.r.) with tetramethylsilane and trichlorofluoromethane as internal standards. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions was monitored by  $^{19}\text{F}$  n.m.r. Column chromatography was carried out on silica gel. 2,4,6-Tribromo-3,5-difluoropyridine was prepared following the literature procedure.<sup>11</sup>

All crystallographic data<sup>ψ</sup> were collected on a Bruker SMART-CCD 1K diffractometer ( $\lambda\text{MoK}\alpha$ ,  $\omega$ -scan,  $0.3^\circ/\text{frame}$ ) at  $T = 110(1)$  (**3b**, **3c**, **3dA**) and  $100(1)$  K (**3dB**). The structures were solved by direct method and refined by full-matrix least squares on  $F^2$  for all data using SHELXTL software. All non-hydrogen atoms, except the disordered carbon atoms of terminal aromatic rings in the structures of **3b** and **3c**, were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications<sup>†</sup> CCDC 618929 - 618932.

### Synthesis of 4-bromo-2,6-bis(2-phenylethynyl)-3,5-difluoropyridine derivatives

**General procedure.** 2,4,6-Tribromo-3,5-difluoropyridine **1** was added under nitrogen to a solution of triethylamine and stirred until dissolution. The palladium catalyst, copper (I) iodide and the phenylacetylene **2** were then added. After stirring at the desired temperatures, the reaction mixture was filtered and water was added to the filtrate, which was extracted into dichloromethane (3 x 30 mL). The organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated to give a crude product **3** which was purified by column chromatography on silica gel or recrystallization.

**4-Bromo-3,5-difluoro-2,6-bis-phenylethynyl-pyridine (3a).** **1** (1 g, 2.84 mmol), phenylacetylene **2a** (2.0 g, 20.0 mmol),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (2%, 40 mg) and  $\text{CuI}$  (1%, 5.4 mg) in triethylamine (20 ml), after stirring at room temperature for 12 hours and column

<sup>ψ</sup>

*Selected crystallographic data:* **3b**:  $\text{C}_{23}\text{H}_{14}\text{BrF}_2\text{NO}_2$ , orthorhombic, space group F mm2,  $a = 6.7680(2)$ ,  $b = 39.553(1)$ ,  $c = 7.4739(2)$  Å,  $U = 2000.7(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $R_1(\text{F}) = 0.0233$ ,  $wR_2(\text{F}^2) = 0.0569$ , GOF = 1.168;

**3c**:  $\text{C}_{21}\text{H}_8\text{BrF}_4\text{N}$ , orthorhombic, space group C mcm,  $a = 6.7571(5)$ ,  $b = 7.5303(6)$ ,  $c = 34.319(2)$  Å,  $U = 1746.3(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $R_1(\text{F}) = 0.0296$ ,  $wR_2(\text{F}^2) = 0.0684$ , GOF = 1.284;

**3dA**:  $\text{C}_{21}\text{H}_8\text{BrCl}_2\text{F}_2\text{N}$ , monoclinic, space group C 2/c,  $a = 30.759(3)$ ,  $b = 8.0868(8)$ ,  $c = 7.3531(8)$  Å,  $\beta = 101.63(3)^\circ$ ,  $U = 1791.5(6)$  Å<sup>3</sup>,  $Z = 4$ ,  $R_1(\text{F}) = 0.0565$ ,  $wR_2(\text{F}^2) = 0.1322$ , GOF = 1.120;

**3dB**:  $\text{C}_{21}\text{H}_8\text{BrCl}_2\text{F}_2\text{N}$ , orthorhombic, space group P 2<sub>1</sub>2<sub>1</sub>2,  $a = 31.194(1)$ ,  $b = 3.8128(2)$ ,  $c = 7.6002(4)$  Å,  $U = 903.94(8)$  Å<sup>3</sup>,  $Z = 4$ ,  $R_1(\text{F}) = 0.0369$ ,  $wR_2(\text{F}^2) = 0.0698$ , GOF = 1.105.

<sup>†</sup> CCDC 618929 - 618932 contain the supplementary crystallographic data for this paper. These data can be viewed free of charge via <http://www.ccdc.cam.ac.uk/cont/retrieving.html> or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ; fax: +44-1223-336033. E-mail: deposit@ccdc.cam.ac.uk

chromatography on silica gel with hexane-dichloromethane (1:1) as the eluant, gave *4-bromo-3,5-difluoro 2,6-bis-phenylethynyl-pyridine 3a* (82%, 0.87g) as a white solid; m.p. 186 °C (Found C, 64.1; H, 2.6; N, 3.6. C<sub>21</sub>H<sub>10</sub>BrF<sub>2</sub>N requires C, 64.0; H, 2.5; N, 3.4%); δ<sub>H</sub> 7.33 (3H, m, ArH), 7.56 (2H, m, ArH); δ<sub>F</sub> -108.1 (s); δ<sub>C</sub> 81.0 (m, Ar-C≡), 96.3 (m, ArC≡C), 108.4 (t, <sup>2</sup>J<sub>CF</sub> 22.7, C-Br), 121.0 (s, ArC<sub>ipso</sub>), 128.5 (s, ArC<sub>meta</sub>), 128.9 (m, C-2), 129.7 (s, ArC<sub>para</sub>), 132.2 (s, ArC<sub>ortho</sub>), 156.8 (d, <sup>1</sup>J<sub>CF</sub> 269, C-3); *m/z* (EI<sup>+</sup>) 395 ([M]<sup>+</sup>, 100%), 393 ([M]<sup>+</sup>, 100%), 373 (15), 293 (12), 187 (20).

**4-Bromo-3,5-difluoro-2,6-bis-(4-methoxy-phenylethynyl)-pyridine (3b).** **1** (0.83g, 2.36 mmol), 1-ethynyl-4-methoxybenzene **2b** (0.39g, 2.95 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2%, 32.8 mg) and CuI (1%, 4.5 mg) in triethylamine (20 ml) after stirring at room temperature for 48 hours and column chromatography on silica gel with dichloromethane-hexane (1:3) as eluent, gave *4-bromo-3,5-difluoro-2,6-bis-(4-chloro-phenylethynyl)-pyridine 3b* (42%, 0.44 g) as a white solid; m.p. 198-200 °C (Found: C, 60.5; H, 2.8; N, 3.1. C<sub>23</sub>H<sub>14</sub>BrF<sub>2</sub>NO<sub>2</sub> requires C, 60.8; H, 3.10; N, 3.08%); δ<sub>H</sub> 3.86 (3H, s, OMe), 7.21 - 7.54 (4H, m, ArH); δ<sub>F</sub> -109.3 (s); δ<sub>C</sub> 55.2 (s, CH<sub>3</sub>), 80.3 (m, Ar-C≡), 96.6 (m, ArC≡C), 108.5 (t, <sup>2</sup>J<sub>CF</sub> 23.1, C-Br), 113.5 (s, ArC<sub>ipso</sub>), 114.1 (s, ArC<sub>ortho</sub>), 129.4 (m, C-2), 134.0 (s, ArC<sub>meta</sub>), 156.5 (d, <sup>1</sup>J<sub>CF</sub> 268, C-3), 160.6 (s, C-OCH<sub>3</sub>); *m/z* (EI<sup>+</sup>) 455 ([M]<sup>+</sup>, 44%), 453 ([M]<sup>+</sup>, 44%), 193 (37), 191 (37), 111 (34).

**4-Bromo-3,5-difluoro-2,6-bis-(4-fluoro-phenylethynyl)-pyridine (3c).** **1** (0.18 g, 0.52 mmol), 1-ethynyl-4-fluorobenzene **2c** (0.25 g, 2.08 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2%, 7.3 mg) and CuI (1%, 1 mg) in triethylamine (20 ml), after heating at 60 °C for 24 hours and column chromatography on silica gel with dichloromethane-hexane(1:2) as the eluant, gave *4-bromo-3,5-difluoro 2,6-bis-(4-fluoro-phenylethynyl)-pyridine 3c* (58%, 0.63 g) as a white solid; m.p. 225-227 °C (Found: C, 58.4; H, 1.8 ; N, 3.2. C<sub>21</sub>H<sub>8</sub>BrF<sub>4</sub>N requires C, 58.6; H, 1.8; N, 3.25); δ<sub>H</sub> 7.36 (2H, m, ArH), 7.50 (2H, m, ArH); δ<sub>F</sub> -108.1 (1F, s, F-3), -108.4 (1F, s, ArF); δ<sub>C</sub> 80.7 (m, Ar-C≡), 95.2 (m, ArC≡C), 108.7 (t, <sup>2</sup>J<sub>CF</sub> 22.9, C-Br), 116.1 (s, ArC<sub>meta</sub>), 117.4 (s, ArC<sub>ipso</sub>), 128.8 (m, C-2), 134.3 (s, ArC<sub>ortho</sub>), 156.5 (d, <sup>1</sup>J<sub>CF</sub> 268.9, ArCF), 163.3 (d, <sup>1</sup>J<sub>CF</sub> 269, C-3); *m/z* (EI<sup>+</sup>) 431 ([M]<sup>+</sup>, 100%), 429 ([M]<sup>+</sup>, 100%), 329 (15), 204 (90), 155 (16), 145 (36).

**4-Bromo-3,5-difluoro-2,6-bis-(2-chloro-phenylethynyl)-pyridine (3d).** **1** (0.32 g, 0.915 mmol), 1-ethynyl-2-chlorobenzene **2d** (0.5g, 3.66 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2%, 12.7 mg) and CuI (1%, 1.74 mg) in triethylamine after stirring at room temperature for 3 days and recrystallisation, gave *4-bromo-3,5-difluoro-2,6-bis-(4-chloro-phenylethynyl)-pyridine 3d* (37%, 0.15 g) as a white solid, m.p. 196.4-197.6 (dichloromethane), (Found: M<sup>+</sup> 462.918. C<sub>21</sub>H<sub>8</sub>BrCl<sub>2</sub>F<sub>2</sub>N requires M<sup>+</sup> 462.916); δ<sub>H</sub> 7.28 - 7.6 (m, ArH); δ<sub>F</sub> -106.7 (s); δ<sub>C</sub> 85.7 (m, Ar-C≡), 93.0 (m, ArC≡C), 108.8 (t, <sup>2</sup>J<sub>CF</sub> 22.7, C-Br), 121.7 (s, ArC<sub>ipso</sub>), 126.6 (s, C-5'), 126.8 (s, C-4'), 129.0 (s, C-2), 129.7 (s, C-3'), 131.1 (s, C-6'), 134.2 (s, C-Cl), 157.7 (d, <sup>1</sup>J<sub>CF</sub> 270, C-3); *m/z* (EI<sup>+</sup>) 465 ([M]<sup>+</sup>, 8%), 463 ([M]<sup>+</sup>, 16%), 461 ([M]<sup>+</sup>, 10%), 409 (30), 407 (45), 351 (100).

**4-Bromo-3,5-difluoro-2,6-bis-(4-chloro-phenylethynyl)-pyridine (3e).** **1** (0.31 g, 0.88 mmol), 1-ethynyl-4-chlorobenzene **2e** (0.15 g, 1.10 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2%, 12 mg) and CuI (1%, 1.67 mg) in triethylamine (20 ml), after stirring at 80 °C for 10 hours and recrystallisation in DCM and sublimation, gave *4-bromo-3,5-difluoro-2,6-bis-(4-chloro-phenylethynyl)-pyridine 3e* (42%,



0.17 g) as a white solid; m.p. > 250°C (Found C, 54.5; H, 1.6; N, 3.00. C<sub>21</sub>H<sub>8</sub>BrF<sub>2</sub>Cl<sub>2</sub>N requires C, 54.4; H, 1.7; N, 3.0%);  $\delta_{\text{H}}$  7.37 (2H, m, ArH), 7.54 (2H, m, ArH);  $\delta_{\text{F}}$  -107.6 (s);  $\delta_{\text{C}}$  81.7 (m, Ar-C $\equiv$ ), 95.1 (m, ArC $\equiv$ C), 108.5 (t,  $^2\text{J}_{\text{CF}}$  22.5, C-Br), 119.7 (s, ArC<sub>ipso</sub>), 128.6 (m, C-2), 128.9 (m, ArC<sub>meta</sub>), 133.4 (s, ArC<sub>ortho</sub>), 136.0 (s, ArC<sub>para</sub>), 157.0 (d,  $^1\text{J}_{\text{CF}}$  269, C-3); *m/z* (EI<sup>+</sup>) 465 ([M]<sup>+</sup>, 26%), 463 ([M]<sup>+</sup>, 54%), 461 ([M]<sup>+</sup>, 34%), 409 (69), 407 (100), 247 (23).

**4-Bromo-3,5-difluoro-2,6-bis-(4-bromo-phenylethynyl)-pyridine (3f).** **1** (1 g, 2.84 mmol), 1-ethynyl-4-bromobenzene **2f** (0.5 g, 2.84 mmol), triethylamine (20ml), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2%, 40 mg) and CuI (1%, 5.4 mg), after stirring at 100 °C for 48 hours and column chromatography on silica gel with DCM-hexane (1:3) as eluant, gave *4-bromo-3,5-difluoro-2,6-bis-(4-bromo-phenylethynyl)-pyridine 3f* (56%, 0.72 g) as a white solid; m.p. 270-272 °C (Found: C, 45.7; H, 1.4; N, 2.5. C<sub>13</sub>H<sub>4</sub>Br<sub>3</sub>F<sub>2</sub>N requires C, 45.5; H, 1.4; N, 2.5%);  $\delta_{\text{H}}$  7.18 - 7.23 (m, ArH);  $\delta_{\text{F}}$  -107.5 (s);  $\delta_{\text{C}}$  80.9 (m, Ar-C $\equiv$ ), 94.1 (m, ArC $\equiv$ C), 108.8 (t,  $^2\text{J}_{\text{CF}}$  22.7, C-Br), 119.1 (s, ArC<sub>ipso</sub>), 123.5 (s, ArCBr), 128.9 (m, C-2), 132.1 (s, ArC<sub>ortho</sub>), 133.8 (s, ArC<sub>meta</sub>), 155.9 (d,  $^1\text{J}_{\text{CF}}$  269, C-3); *m/z* (EI<sup>+</sup>) 549 ([M]<sup>+</sup>, 7%), 551 ([M]<sup>+</sup>, 24%), 553 ([M]<sup>+</sup>, 24%), 555 ([M]<sup>+</sup>, 7%).

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