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An Efficient Continuous Flow Approach to Furnish Furan-Based Biaryls

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Suzuki cross-couplings of 5-formyl-2-furanylboronic acid with activated or neutral aryl bromides were performed under continuous flow conditions in the presence of (Bu)4N+F- and the immobilised t-butyl based palladium catalyst CatCart™ FC1032™. Deactivated aryl bromides and activated aryl chlorides were cross-coupled with 5-formyl-2-furanylboronic in the presence of (Bu)4N+OAc- using the bis-triphenylphosphine CatCart™ PdCl2(PPh3)2-DVB. Initial evidence indicates the latter method may serve as a universal approach to conduct Suzuki cross-couplings with the protocol successfully employed in the synthesis of the current gold standard hedgehog pathway inhibitor LDE225.

INTRODUCTION

The furan-based biaryl motif is an intriguing molecular framework which serves as a pivotal core for a range of bioactive molecules. The furan biaryl motif is an integral feature of a number of kinase inhibitors including pan-Pim (1)1 and class I phosphoinositide 3-kinase2 inhibitors (2), a family of Bcl-xL inhibitors (3), HIV-1 fusion inhibitors (4), in addition to a class of antibacterial agents (5)5 (Figure 1). However, of particular interest to our research, the furan-based biaryl motif forms the core of a number of small molecules possessing inhibitory activity within the hedgehog signalling pathway such as 6.6-8

It is unknown if the diverse bioactivities of furan-biaryl based molecules are related to unique molecular recognitions or is simply a reflection of the scaffold being overrepresented in high-throughput-screening libraries. Nevertheless, a noteworthy feature of the furanyl-biaryl scaffold is that in contrast to the majority of biaryl molecular frameworks, modelling9 and crystallographic data10 demonstrate that this system preferentially adopts a planar conformation.

Figure 1: Illustrative examples of bioactive compounds constructed around the furanyl-biaryl core. Structure of the pan-Pim (1)1 and class I phosphoinositide 3-kinase (2)2 inhibitors, along with the Bcl-xL inhibitor (3),7 the HIV-1 fusion inhibitors (4),4 the gram-negative antibacterial agent (5), and the hedgehog signalling pathway inhibitor (6).6,7
Given the abundance of furanyl-biaryl analogues in the literature it is unsurprising that synthetic methodologies to access the scaffold have been extensively reported. Typical approaches involve the use of a furanylboronic acid or furanylbromide in Suzuki cross-coupling conditions with a range of Pd-based catalysts including Pd(OAc)$_2$, PdCl$_2$(PPh$_3$)$_2$, Pd(PPh$_3$)$_4$, Pd$_2$(dba)$_3$, and Pd(OH)$_2$. Whilst these methodologies typically afford the furanyl-biaryl scaffold in good to excellent yields a common problem faced, particularly by the pharmaceutical industry, in using homogeneous catalysts is the removal of residual Pd from catalyst leaching. This has in part been negated by the use of immobilised solid supported catalysts that can be simply partitioned from reaction mixtures. To this end, a suite of solid supported precursors to L$_2$Pd(0) catalysts, known as FibreCats®, are now commercially available. A number of these FibreCats® systems are available in pre-packed cartridges which are compatible with a number of flow reactors including the ThalesNano X-Cube™. Further various flow systems utilising a range of immobilised catalysts have previously been successfully utilised to conduct a number of cross-coupling reactions. Herein we report the development of a FibreCats® compatible flow chemistry methodology that provides a robust and expedient means of accessing furanyl-biaryl based analogues as building blocks for drug development programs.

**Results and Discussion**

Our primary interest in the furan-based biaryl motif relates to our current interest in developing a series of Hedgehog signalling pathway inhibitors. To this end our primary aim was to develop a series of furfural-based analogues, e.g. 7 (Scheme 1), as the aldehyde moiety readily permits further synthetic manipulations. To this end, our investigations commenced with flowing a methanolic solution of 5-formyl-2-furanylboronic acid (8), 3-bromobenzyl alcohol (9), and three equivalents of (Bu)$_4$N$^+$F$^-$ through an X-cube™ charged with an FC1001 FibreCat® at 0.5 mL.min$^{-1}$ at an temperature of 80 °C (Scheme 1). This equated to a 2.2 min catalyst residence time. The effect of recycling through the catalyst was evaluated by HPLC-MS analysis.

![Figure 2](https://example.com/figure2.png)

**Figure 2:** Co-crystallised structure of 3-[5-[5-(4-chloro-phenyl)-furan-2-yminylmethylene]-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid with the Bacillus anthracis lethal factor metalloproteinase. This structure indicates that in contrast to the majority of biaryl systems the furan-biaryl motif adopts a planar conformation. (PDB accession code 1ZXV.pdb).10

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### Table 1. Ratio of 7 and 9 peak areas obtained after subsequent cycles through various FibreCat® catalysts. Reagents and conditions are as per Scheme 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd-Ligand</th>
<th>FibreCat®</th>
<th>Number of catalyst cycles</th>
<th>Ratio of 7:9</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[8]</td>
<td>FC1001™</td>
<td>1:1.2</td>
<td>1:0.7</td>
<td>1:0.5</td>
<td>1:0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>[8]</td>
<td>FC1007™</td>
<td>1:1.3</td>
<td>1:0.7</td>
<td>1:0.4</td>
<td>1:0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>[8]</td>
<td>FC1032™</td>
<td>1:0.7</td>
<td>1:0.4</td>
<td>1:0.3</td>
<td>1:0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>[8]</td>
<td>Pd-Tetrakis</td>
<td>1:0.4</td>
<td>1:0.3</td>
<td>1:0.3</td>
<td>1:0.2</td>
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<td></td>
</tr>
</tbody>
</table>

*a* Ratio of peak areas determined by HPLC analysis at 220 nm.

The initial reaction conditions gave a 1:1.2 ratio of 7 to 9 obtained after a single cycle (Table 1), increasing to 2:1 after 4 cycles using FibreCat® 1001. However, given that the Suzuki reaction coupling efficiencies can be significantly affected by the ligand utilised, we investigated a number of alternative FibreCat® columns (Table 1, entries 2-4). Each FibreCat® catalyst furnished the desired Suzuki reaction with relatively high efficiencies with Pd-Tetrakis providing the most efficient coupling with a near 4:1 ratio of 7 to 9 afforded within two catalyst cycles (Table 1, entry 4).

Further improvements in the Pd-Tetrakis coupling efficiency were noted on increasing reaction temperature to 120 °C with a 1:0.08 ratio of 7:9 observed at a 0.5 mL.min$^{-1}$ flow rate (a 1.3 min catalyst residence time) (Figure 3b). However, at T > 100 °C increased aryl-bromide homocoupling with the excessive formation of 10 observed at 140 °C (Figure 3b). Increased reaction pressures at 80 °C afforded similar results, with pressures above 60 bar enhancing the formation of both 7 and 10 (Figure 3c). At elevated pressure the aryl-bromide homocoupled product 10 was the major product.
Given the undesired production of 10, we re-examined FibreCat® 1032 (Table 1, entry 3), while not as effective as Pd-Tetrakis, it did produce a higher level of coupling selectivity with only trace levels of homocoupled product after 4 catalyst cycles. Consequently FibreCat® 1032 was subjected to a temperature screen as with Pd-Terrakis (Scheme 1 & Table 2). Optimisation of the reaction temperature and flow rate revealed near quantitative conversion to 7 at 120 °C and 0.5 mL.min⁻¹. After two catalyst cycles (2.6 min retention time). Only trace levels of starting material (9) and homocoupled (10) were evident (Table 2). Workup furnished the desired product 7 in a 93% isolated yield, which compares favourably with the reported batch yield of 88%.48 Further, constant with the previous studies which examined palladium leaching,29, 30 ICP analysis demonstrated negligible levels of palladium leaching with a maximum total recoverable palladium content of 5.2 ppm observed for a crude sample of compound 7. As context the European Agency for the Evaluation of Medicines states that for oral administration the permitted daily exposure of class A1 metals such as palladium should not exceed 10 mg kg⁻¹ and thus the Pd content of 7 is within this guideline.39, 40

<table>
<thead>
<tr>
<th>Temperature °C</th>
<th>Ratio of Peak Area After Two Cycles⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>7 1 7.8 0</td>
</tr>
<tr>
<td>80</td>
<td>9 1 1.1 0</td>
</tr>
<tr>
<td>100</td>
<td>10 1 0.37 0</td>
</tr>
<tr>
<td>120</td>
<td>1 0.05 0</td>
</tr>
</tbody>
</table>

⁴Ratio of peak areas determined HPLC analysis at 220 nm. Maximum total recoverable Pd content by ICP analysis 5.2 ppm.

While the optimised protocol efficiently furnished 7, the practicality of this continuous flow approach could only be judged by amenability to aryl bromide variations. Thus, the coupling of a small library of aryl bromides, sulfonamide based aryl bromides, and an amide based aryl bromide was investigated. The data presented in Table 3 illustrates the utility of FibreCat® 1032, (Bu)₄N⁺F⁻, at a flow rate of 0.5 mL/min, over two catalyst cycles and temperature of 120 °C in furnishing a small library in excellent isolated yields (82-92%).

Given our success with FibreCat® 1032 we next turned our attention to the Suzuki cross-coupling of deactivated aryl bromides such as 4-bromophenol (13, Scheme 2). The synthesis of the desired analogue 14 had been previously reported via coupling of 4-iodophenol and 8 using Pd-Tetrakis to afford 14 in an 87 % yield,19 however, equivalent Pd-Tetrakis coupling with 4-bromophenol (13) gave 14 in only 10 %.2 Using our flow protocol resulted in an improvement on the batch synthesis with an approximate 30 % conversion (and 23%
isolated yield) of 14 after three catalyst cycles (Table 3, entry 1). This however, was not the near quantitative yields obtained with the more activated aryl bromides (9a-f). Given that our prior studies with Pd-Tetrakis highlighted increasing homocoupled product with increased temperature and pressures, our initial reaction optimisation examined the effect of varying the tetrabutylammonium salt which has previously been observed impart subtle variations on cross-coupling yields.41

Scheme 2: Reagents and Conditions: (i) 5-formyl-2-furanylboronic acid (8) (1 mmol), 4-bromophenol benzyl alcohol (13) (1 mmol), (Bu)4N+ F- 3H2O (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL-min-1, and 120 ºC.

Varying the halogen counterion from –F to –Cl, -Br and –I resulted in reduced coupling efficiencies (Table 4, entries 2-5), as with the BF4⁻ (Table 4, entry 5), and HSO4⁻ salts (Table 4, entry 7) resulted in improved coupling efficiency with a near 80 % conversion after a single catalyst cycle. Presumably the excess acetate ions activate the boronic acid (as is the case with K2CO3), and halogen abstraction from the first organopalladium intermediate in the Suzuki cycle.

Binary mixtures of (Bu)4N+F⁻ and Cs2CO3 improved the efficiency of the cross coupling from 0.46 : 1 with (Bu)4N+F⁻-alone (Table 4, entry 1) to 0.2 : 1 (Table 4, entry 8). The binary combination of (Bu)4N+OAc⁻ and Cs2CO3 gave a coupling efficiency ratio of 0.24 : 1, essentially identical to that of (Bu)4N+OAc⁻alone (Table 4, entry 9 and 7 respectively), supporting the hypothesized additional role of the OAc.

Performing the cross-coupling reaction with only Cs2CO3 the halocoupled product was obtained in a 52 % yield confirming the crucial nature of the tetrabutylammonium salt.

Using (Bu)4N+OAc⁻ in conjunction with FibreCat® 1032 gave 14 in a 72 % isolated yield of 14, from 13. However other deactivated aryl bromides such as the dimethylamino analogues 15a and 15b, the methoxy analogue 15c, and the indole 15d, aryl chlorides 15e and 15f gave unacceptably low levels of the desired cross coupled products (Table 5).

We consequently investigated the more activated CatCart™ PdCl2(PPh3)2-DVB catalysts which has been shown to be highly effective in Sonogashira couplings.42 The flow coupling steps were optimised as before with the CatCart™ PdCl2(PPh3)2-DVB catalyst and we noted that clean coupling, with near quantitative conversions was accomplished at 120 ºC, after three catalyst cycles at 0.3 mL/min-1 (Table 5).

Table 5: Suzuki couplings with deactivated aryl bromides and aryl chlorides.

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Product</th>
<th>Percent Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>15a</td>
<td>14a</td>
<td>28</td>
</tr>
<tr>
<td>15b</td>
<td>14b</td>
<td>12</td>
</tr>
<tr>
<td>15c</td>
<td>14c</td>
<td>16</td>
</tr>
<tr>
<td>15d</td>
<td>14d</td>
<td>16</td>
</tr>
<tr>
<td>15e</td>
<td>14e</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>15f</td>
<td>14f</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

a Reagents and Conditions: (i) 5-formyl-2-furylboronic acid (1 mmol), aryhalide (1 mmol), (Bu)4N+OAc⁻ (3 mmol), MeOH (30 mL), X-Cube™, 0.3 mL/min-1, and 120 ºC, three catalyst cycles. B Percentage conversion determined by HPLC analysis at 220 nm.

We subsequently used this protocol to effect the cross-coupling of 16 and 17 and gained expedient access to the potent smoothened inhibitor LDE225 (18) which is a crucial component of our Hedgehog pathway inhibitor development program.

Thus whilst increasing catalyst retention time and catalysts cycles significantly enhanced coupling efficiencies of...
deactivated aryl-bromides and aryl-chlorides, we were cognisant that these conditions may promote increased levels of palladium leaching. However as outlined in table 6, negligible levels of palladium leaching were observed with a maximum total recoverable Pd content by ICP analysis of 52 ppm for 15d, 5.2 ppm for 15e, whilst the remainder of samples analysed containing less than 1 ppm palladium content.

| Table 6: Total recoverable trace palladium by ICP of selected samples. |
|-----------------|-----------------|-----------------|
| Product a       | PdCl₂(PPh₃)₂-DVB | Palladium Content a |
| 15a             | 96              | 0.65 ppm        |
| 15c             | 92              | 0.48 ppm        |
| 15e             | 83              | 0.72 ppm        |
| 18              | 87              | 5.2 ppm         |

*ICP analysis was conducted by the Australian National Measurement Institute.

CONCLUSION

A combination of un-distilled methanol, (Bu)₄N+OAc-, 5-formyl-2-furanylboronic acid, an activated or neutral aryl bromide, along with the X-cube™ continuous flow reactor charged with the t-butyl based palladium catalyst FC1032™ efficiently afforded Suzuki cross-coupled products in excellent yield (>80%) with negligible homocoupling observed. In relation to deactivated aryl bromides or aryl chlorides the use of a more active Pd-based catalyst such as PdCl₂(PPh₃)₂-DVB, provided efficient coupling to the desired products. This optimised continuos flow Suzuki cross-coupling methodology appears amenable with a range of boronic acids. However, we note that when CatCart™ PdCl₂(PPh₃)₂-DVB was employed to perform the initial cross-coupling investigation (i.e. Scheme 1), as was the case with Pd-Tetrakis, a significant (~ 30 %) amount of aryl bromide homocoupling product was observed. Consequently we propose that FC1032™ serves as a more effective catalyst for the cross-coupling of activated or neutral aryl bromides. We have used this protocol to provide expedient access to the potent smoothened inhibitor LDE225 (18). Significantly, negligible palladium leaching was observed with the immobilised catalysts²⁹, ³¹ and thus this continuous flow Suzuki cross-coupling protocol is ideally suited to medicinal chemistry research programs. We are currently investigating the versatility of these conditions with other palladium catalysed cross-coupling reactions and the outcomes of these investigations will be reported in due course.

EXPERIMENTAL SECTION

All reagents were purchased from Sigma Aldrich and were used without purification, with the exception of furfural, which was distilled through glass prior to use. Solvents were bulk, and distilled through glass prior to use.

¹H and ¹³C NMR spectra were recorded on a Bruker Advance™ AMX 400 MHz spectrometer at 400.13 and 100.62 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) measured to relative the internal standards. Coupling constants (J) are expressed in Hertz (Hz). Mass spectra were recorded on a Shimadzu LCMS 2010 EV using a mobile phase of 1:1 acetonitrile:H2O with 0.1 % formic acid. Gas chromatography-mass spectrometry (GC-MS) was performed on a Shimadzu GC-MS QF2010 EI/NCl System equipped with a ZB-5MS capillary column of 5% phenyl-arylene stationary phase. High-resolution mass spectra (HRMS) were determined on a Micromass QToF2 spectrometer using polyethylene glycol or polypropylene glycol as lockmass. Monoisotopic molecular masses were calculated utilising ChemDraw Ultra 8.0.

Analytical HPLC traces were obtained using a Shimadzu system possessing a SIL-20A auto-sampler, dual LC-20AP pumps, CBM-20A bus module, CTO-20A column heater, and a SPD-20A UV/vis detector. This system was fitted with an Altima™ C18 5u 150 mm x 4.6 mm column with solvent A: 0.06% TFA in water and solvent B: 0.06% TFA in CH₃CN:H₂O (90:10). In each case HPLC traces were acquired at a flow rate of 2.0 mL/min, gradient 10-100 (%B), curve = 6, over 15.0 mins, with detection at 220 nm and 265 nm.

Where applicable, melting points were recorded on a BUCHI Melting Point M-565. IR spectra were recorded on a PerkinElmer Spectrum Two™ FTIR Spectrometer. Thin layer chromatography (TLC) was performed on Merck 60 F254 pre-coated aluminium plates with a thickness of 0.2 mm. Column chromatography was performed under ‘flash’ conditions on Merck silica gel 60 (300-400 mesh).

ICP analysis was conducted by the Australian National Measurement Institute 105 Delhi Road, North Ryde NSW 2113 (www.measurement.gov.au)

Biphenyl-3,3′-diylldimethanol (10) and 5-(3-(hydroxymethyl)phenyl)furan-2-carbaldehyde (7)

A solution of (3-bromophenyl)methanol (0.28 mL, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol) and TBAF (2.16 g, 6.86 mmol) was diluted with MeOH (30 mL) to afford a 0.05 M. This solution was flowed through an X-Cube™ fitted with a Fibrecat®1001 catalyst at flow rate of 0.5 mL/min, at a temperature of 80 °C, and 0 bar pressure for 2 h (i.e. total of two catalyst cycles). The eluent was concentrated in vacuo, diluted with DCM (30 mL), washed with 1 M HCl (2 x 30 mL), dried (MgSO₄), concentrated in vacuo, and the crude was subjected to flash silica gel chromatography (1:1 EtOAc:Hexanes) to afford biphenyl-3,3′-diylldimethanol (10) as a colourless oil (0.01 g, 3 %). LRMS (ESI+) m/z 215(M+1). ¹H NMR (400 MHZ, CDCl₃) δ 7.61 (s, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 4.76 (d, J = 7.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 141.4, 141.3,
5-(4-acetylphenyl)-2-furancarbaldehyde (12a)

General procedure 1: A solution of 4-bromoanisole (0.40 g, 2.1 mmol), 5-formyl-2-furanylarboxonic acid (0.30 g, 2.1 mmol) and TBAF (2.16 g, 6.86 mmol) was diluted with MeOH (30 mL) to afford a 0.05 M. This solution was flowed through an X-Cube™ fitted with a Fibrecat®1032 catalyst at flow rate of 0.5 mL/min, at a temperature of 120 °C and 0 bar pressure for 2 h (i.e. total of two catalyst cycles). The eluent was concentrated in vacuo, diluted with DCM (30 mL), washed with 1 M HCl (2 x 30 mL), dried (MgSO4), and concentrated to yield an oil which was further purified using flash chromatography (5:1 EtOAc:Hexanes) to afford 5-(4-acetylphenyl)-2-furancarboxaldehyde (12a) as a yellow oil (0.36 g, 87 %). LRMS (ESI+) m/z 421 (M+1); HRMS (ES+) for C23H21N2O4S; calculated 421.1144, found 421.1144; 1H NMR (400 MHz, CDCl3) δ 9.63 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.48 – 7.42 (m, 1H), 7.23 (d, J = 3.7 Hz, 1H), 7.16 (d, J = 3.7 Hz, 1H), 6.87 (d, J = 3.7 Hz, 1H), 3.81 (s, 2H); 13C NMR (CDCl3, 101 MHz): δ 177.0, 160.91, 159.8, 151.9, 151.6, 127.0, 121.8, 114.4, 106.3, 55.4; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, tR 14.26 min.

2-(4-(5-formylfuran-2-yl)phenyl)acetonitrile (12b)

Compound (12b) was synthesised as described in general procedure 1 from 4-bromoacetantrile (0.44 g, 2.2 mmol), 5-formyl-2-furanylarboxonic acid (0.31 g, 2.2 mmol) and TBAF (2.04 g, 6.7 mmol). The crude reaction mixture was subjected to flash silica gel chromatography (4:1 Hex:EtOAc) to afford 12b as an orange solid (0.38 g, 82 %). LRMS (ESI+) m/z 212 (M+1); HRMS (ES+) for C13H11O3; calculated 212.0678, found 212.0671; 1H NMR (CDCl3, 400 MHz): δ 9.60 (s, 1H), 7.77 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 3.7 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.72 (d, J = 3.7 Hz, 1H), 3.86 (s, 2H); 13C NMR (CDCl3, 101 MHz): δ 176.9, 160.91, 159.8, 151.9, 151.6, 129.0, 127.0, 121.8, 114.4, 106.3, 55.4; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, tR 14.27 min.

5-(dimethylamino)-N-(4-(5-formylfuran-2-yl)phenyl)naphthalene-1-sulfonamide (12d)

Compound 12d was prepared utilising general procedure 1, and N-(4-bromophenyl)-5-(dimethylamino)naphthalene-1-sulfonamide (0.92 g, 2.3 mmol), 5-formyl-2-furanylarboxonic acid (0.32 g, 2.3 mmol), TBAF (2.16 g, 6.86 mmol), and MeOH (30 mL). The eluent was concentrated in vacuo, the crude material was diluted with DCM (30 mL) and washed with 1 M HCl (2 x 30 mL). The organic layer was dried (MgSO4), and concentrated in vacuo to yield an oil which was further purified using flash chromatography (5:1 EtOAc:Hexanes) to afford 5-(4-Methylphenyl)-2-furancarboxaldehyde as an yellow oil/solid (0.82 g, 87 %). LRMS (ESI+) m/z 421 (M+1); HRMS (ES+) for C23H21N2O4S; calculated 421.1144, found 421.1144; 1H NMR (CDCl3, 400 MHz) δ 9.51 (s, 1H), 7.74 (s, 1H), 7.69 – 7.66 (m, 3H), 6.76 (d, J = 3.7 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 3.7 Hz, 1H), 3.81 (s, 2H); 13C NMR (CDCl3, 101 MHz): δ 177.1, 159.8, 151.8, 140.0, 129.7, 126.3, 125.3, 123.2, 117.8, 107.3, 45.4; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, tR 9.60 min.
126.6, 125.8, 121.1 (C=C), 107.6. RP-HPLC Alltima™ C18 5u 150mm × 4.6 mm, 10-100 % B in 15 min, tR 15.58 min.

N-(2,4-dimethoxyphenyl)-4-(5-formylfuran-2-yl)benzamide (12f)

Compound 12f was synthesised utilising general procedure 1, 4-bromo-N-(2,4-dimethoxyphenyl)benzamide (0.73 g, 2.2 mmol), 5-formyl-2-furanylboronic acid (0.31 g, 2.2 mmol) and TBAF (2.14 g, 6.6 mmol) to afford N-(2,4-dimethoxyphenyl)-4-(5-formylfuran-2-yl)benzamide as a light brown solid (0.71 g, 92 %). LRMS (ESI-) m/z 352 (M-1); HRMS (ES-) for C20H18NO5; calculated 352.1107, found 352.1113; 1H NMR (400 MHz, DMSO-d6): δ 9.66 (s, 1H), 9.54 (s, NH), 8.09 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 3.8 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 3.7 Hz, 1H), 6.67 (d, J = 2.6 Hz, 1H), 6.55 (dd, J = 8.7, 2.6 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H); 13C NMR (400MHz, DMSO-d6): δ 178.6, 164.8, 158.5, 157.6, 154.1, 152.6, 135.55, 131.6, 128.9, 127.1, 125.3, 120.0, 110.7, 104.7, 99.4, 56.2, 55.8; RP-HPLC Alltima™ C18 5u 150mm × 4.6 mm, 10-100 % B in 15 min, tR 18.12 min.

5-(4-hydroxyphenyl)-2-furancarboxaldehyde (14)

Compound 14 was synthesised utilising general procedure 1, 4-bromophenol (0.38 g, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol) and TBAF (2.10 g, 6.9 mmol). The crude was subjected to silica gel chromatography (4:1 EtOAc:Hx) to afford 5-(4-hydroxyphenyl)-2-furancarboxaldehyde as an orange oil (0.90 g, 30 %). LRMS (ESI+) m/z 187 (M+1); HRMS (ES+) for C7H7O3; calculated 187.0473, found 187.0468; 1H NMR (CDCl3, 400 MHz): δ 9.60 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 3.7 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 3.7 Hz, 1H); 13C NMR (CDCl3, 101 MHz): δ 176.9, 157.1, 128.0, 127.3, 122.0, 116.0, 115.6, 106.3. RP-HPLC Alltima™ C18 5u 150mm × 4.6 mm, 10-100 % B in 15 min, tR 16.68 min.

5-(3-(dimethylamino)phenyl)-2-furancarboxaldehyde (15a)

General Procedure 2: A solution of 3-bromo-N,N-dimethylaniline (0.28 mL, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol) and TBAF (2.08 g, 6.86 mmol) was diluted with MeOH (30 mL) to afford a 0.05 M. This solution was flowed through a X-Cube™ fitted with a CatCart® PdCl2(PPh3)2-DVB catalyst at flow rate of 0.3 mL/min, in a temperature of 120 °C, and 0 bar pressure for 3 h (i.e. total of three catalyst cycles). The eluent was concentrated in vacuo, diluted with DCM (30 mL) and washed with 1 M HCl (2 x 30 mL), dried (MgSO4), concentrated in vacuo, and the crude was subjected to flash silica gel chromatography (7:1 EtOAc:Hexanes) to afford 5-(3-(dimethylamino)phenyl)-2-furancarboxaldehyde as a colourless oil (0.43 g, 87 %). LRMS (ESI+) m/z 216 (M+1); HRMS (ES+) for C13H14NO2; calculated 216.0946, found 216.0942; 1H NMR (DMSO-d6, 400 MHz): δ 9.59 (s, 1H), 7.64 (d, J = 3.7 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 3.7 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H); 13C NMR (CDCl3, 101 MHz): δ 176.8, 161.3, 151.8, 125.9, 120.3, 119.2, 112.6, 106.8, 103.1; RP-HPLC Alltima™ C18 5u 150mm × 4.6 mm, 10-100 % B in 15 min, tR 18.92 min.

5-(1H-indol-6-yl)-2-furancarboxaldehyde (15d)

Compound 15d was synthesised utilising general procedure 2, 6-bromo-1H-indole (0.41 g, 2.1 mmol), 5-formyl-2-furanylboronic acid (0.29 g, 2.1 mmol) and TBAF (1.90 g, 6.3 mmol). The crude was subjected to flash silica gel chromatography (3:1 EtOAc:Hx) to afford 5-(1H-indol-6-yl)-2-furancarboxaldehyde as an off-white solid (0.48 g, 83 %). LRMS (ESI+) m/z 212 (M+1); HRMS (ES+) for C14H13NO2; calculated 212.0633, found 212.0635; 1H NMR (CDCl3, 400 MHz): δ 9.61 (s, 1H), 8.43 (s, NH), 7.95 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.54 (dd, J = 8.3, 1.4 Hz, 1H), 7.34 (d, J = 3.7 Hz, 1H), 7.33 – 7.31 (m, 1H), 6.83 (d, J = 3.7 Hz, 1H), 6.60 – 6.56 (m, 1H); 13C NMR (CDCl3, 101 MHz): δ 176.8, 161.3, 151.6, 135.9, 129.2, 126.5, 122.9, 121.2, 117.7, 108.4, 106.8, 103.1; RP-HPLC Alltima™ C18 5u 150mm × 4.6 mm, 10-100 % B in 15 min, tR 15.58 min.

5-(4-benzoylphenyl)-2-furancarboxaldehyde (15e)
Compound 15e was synthesised using general procedure 2, (4-chlorophenyl)(phenyl)methanone,(0.41 g, 2.2 mmol), 5-formyl-2-furanylboronic acid (0.31 g, 2.2 mmol) and TBAFB (1.99 g, 6.60 mmol). The crude was subjected to flash silica gel chromatography (4:1 Hex:EtOAc) to afford 5-(4-benzoylphenyl)-2-furancarboxaldehyde as a white solid (0.38 g, 87 %). LRMS (ESI+) m/z 277 (M+1); HRMS (ESI-) for C25H13O3; calculated 384.0892, found 384.0888; 1H NMR (101 MHz, DMSO) δ 10.11 (s, 1H), 9.66 (s, 1H), 8.38 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.98 (d, J = 5.3 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.70 (d, J = 3.7 Hz, 1H), 7.46 (d, J = 3.7 Hz, 1H); 13C NMR (101 MHz) δ 193.33, 178.61, 157.24, 152.51, 137.38, 131.03, 130.63, 129.99, 126.09, 125.91, 125.91, 110.34; RP-HPLC Alltima™ C18 5u 150 mm x 4.6 mm, 10-100 % B in 15 min, tR 17.41 min.

5-(3-formylphenyl)furan-2-carbaldehyde (15f)

Compound 15f was synthesised using general procedure, 3-chlorobenzaldehyde (0.28 g, 2.0 mmol), 5-formyl-2-furanylboronic acid (0.28 g, 2.0 mmol) and TBAF (1.05 g, 5.0 mmol). The crude was subjected to flash silica gel chromatography (9:1 Hex:EtOAc) to afford 5-(4-benzoylphenyl)-2-furancarboxaldehyde as a white solid (0.34 g, 85 %). LRMS (ESI+) m/z 199 (M+1); HRMS (ESI+) for C12H10O2; calculated 199.0517, found 199.0512; 1H NMR (400 MHz, DMSO-d6) δ 9.67 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.78 – 7.75 (m, 2H), 7.73 – 7.69 (m, 2H), 7.59 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 3.8 Hz, 1H); 13C NMR (CDCl3, 100 MHz) δ 195.5, 178.7, 157.3, 152.8, 137.7, 132.5, 129.99, 126.09, 125.91, 110.34; RP-HPLC Alltima™ C18 5u 150 mm x 4.6 mm, 10-100 % B in 15 min, tR 10.68 min.

N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4’-(trifluoromethoxy)biphenyl-3-carboxamide (LDE225) (18)

Compound 18 was synthesised using general procedure 2, 3-bromo-N-6-(2,6-Diisopropylphenyl)pyridin-3-yl)-2-methylbenzamide (0.48 g, 1.2 mmol), 4-(trifluoromethoxy)phenylboronic acid (0.25 g, 1.2 mmol), and TBAFB (1.08 g, 3.6 mmol). The crude was subjected to flash silica gel chromatography (9:1 DCM:MeOH) to afford LDE225 as a white solid (0.55 g, 94 %). LRMS (ESI+) m/z 486 (M+1); 1H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 9.1, 2.5 Hz, 1H), 7.47 (s, 4H), 7.42 – 7.25 (m, 2H), 6.86 (d, J = 9.1 Hz, 1H), 4.06 (d, J = 12.0 Hz, 2H), 3.67 – 3.54 (m, 2H), 2.41 – 2.27 (m, 2H), 2.22 (s, 3H), 1.16 (d, J = 6.2 Hz, 6H); 13C NMR (101 MHz, DMSO-d6) δ 19.19, 156.18, 148.00, 141.40, 140.63, 139.87, 139.05, 132.53, 131.52, 131.14, 130.66, 127.49, 127.05, 126.26, 121.85, 121.38, 119.31, 107.32, 71.32, 51.25, 19.30, 17.71;193.33, 178.61, 157.24, 152.51, 137.38, 131.03, 130.65, 130.63, 129.99, 126.09, 125.91, 125.67, 110.34; RP-HPLC Alltima™ C18 5u 150 mm x 4.6 mm, 10-100 % B in 15 min, tR 17.64 min.

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Supporting Information Available: Supplementary data (GS chromatographic traces, 1H and 13C NMR spectra) associated with this article can be found in the online version at: doi:xxxxxxx.

NOTES AND REFERENCES


