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# Accepted Article

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FULL PAPER

# Access to some C5-cyclised 2-pyrones and 2-pyridones via direct arylation; retention of chloride as a synthetic handle

Aisling M. Prendergast,[a] Leticia M. Pardo,[a] Ian J. S. Fairlamb[b] and Gerard P. McGlacken*[a]

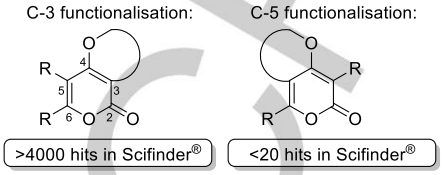
**Abstract:** The synthetic effort towards the functionalisation of C–H bonds on 2-pyrones and 2-pyridones has been funnelled by the preferential reactivity of the C-3 position. Herein, we report a direct arylation protocol for the intramolecular coupling of 2-pyrones and 2-pyridones, allowing access to a previously unavailable class of C-5 cyclised products with an unstudied biological profile. A C–Cl bond was retained at C-3 during the direct arylation process allowing further derivatisation at C-3, which we have demonstrated with a Suzuki-Miyaura cross-coupling reaction.

## Introduction

Effective routes to aryl-heteroaryl (Ar-HetAr) bonds are among the most important in organic synthesis[1] due to the abundance of the Ar-HetAr moiety in natural products and pharmaceuticals.[2] The development of direct arylation protocols involving at least one C–H activation event is highly sought after by academic[3] and industrial groups.[4]

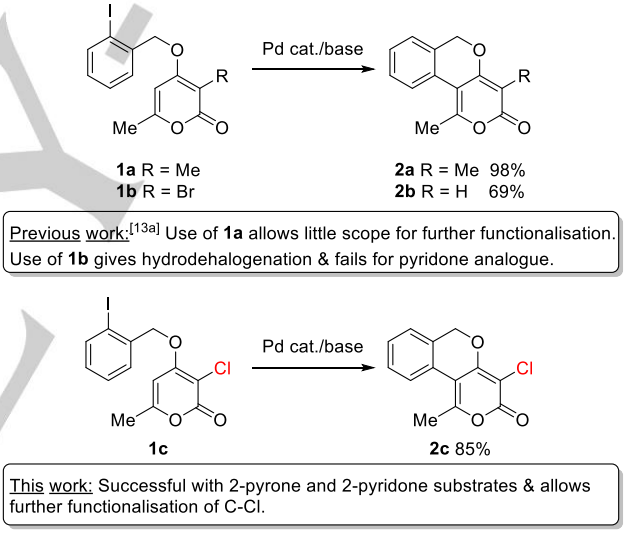
We chose to focus on the 2-pyrone substrate, specifically 4-hydroxy-2-pyrone[5] derivatives due to their status as a privileged scaffold with broad spectrum biological activity,[6] spanning cytotoxic,[5] antibiotic,[6] and antifungal activity.[7] 2-Pyridones (isosteres of 2-pyrones) possess numerous biological effects including antifungal, antibacterial, insecticidal and cytotoxic activity.[8] The 2-pyrone moiety also displays chemical reactivity reminiscent of aromatics,[9] dienes[10] and enones,[11] and thus represents a highly challenging, yet rewarding, synthon. Moreover, it has been demonstrated to ring-open under certain cross-coupling conditions.[12]

In terms of functionalisation at the free C-3 and C-5 positions, the inherent reactivity of the C-3 position on the 2-pyrone scaffold has completely funnelled the synthetic effort (Scheme 1). More specifically, direct arylation at the C-3 position has been well-studied by us[13] and others.[14] What has been almost completely untapped, is the biological profile of similar compounds, functionalised at C-5 position (Scheme 1), presumably because of the lack of selective synthetic methods.




**Scheme 1.** Untapped 2-pyrone framework cyclised at C-5.

Previously, we reported that the use of a methyl group (**1a**) or a bromo group (**1b**) at the C-3 position could facilitate access to the C-5 coupled products (Scheme 2).[13a]




**Scheme 2.** Comparison to previous work, which was limited to a non-functional C-3 blocking group.

While the transformation of **1a** to **2a** proceeded in good yield, the methyl group cannot be easily manipulated. We reasoned that by using bromide (**1b**), the direct arylation at C-5–H could be achieved, provided oxidative addition was preferred at the aryl iodide and that no complications were encountered due to the Br at C-3. While direct arylation was accomplished, prohibitive hydrodebromination dominated (giving **2b**).

Using the direct arylation/hydrodebromination protocol, we set about elaboration of the substrate scope. Unfortunately, all attempts were met with failure. For example, an analogue bearing a phenyl ring at C-6 failed to give any product. Neither did the 2-pyridone isostere, under otherwise identical reaction conditions. Even if this strategy had proved successful, gaining access to 5-cyclised compounds bearing a halogen at C-3 for further elaboration, would have to occur via a

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hydrodehalogenation/rehalogenation protocol, which is clearly neither atom- nor step-economic.

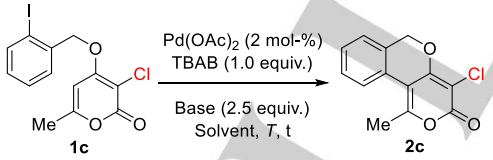
Instead, we sought to develop a Pd-catalysed direct arylation protocol which would (1) give direct arylation at C-5, (2) be generally applicable and (3) allow further decoration of the 2-pyrone motif at C-3. As Lautens observed,[15] there is a notable absence of polyhalogenated substrates in Pd-catalysed cross-couplings, which is probably due to selectivity issues. This potential pitfall was offset by the potential for follow-on coupling using an (hetero)aryl chloride, the benefits of which have been well documented by Buchwald,[16] Hartwig[17] and Fu.[18]

## Results and Discussion

In our study, using a chloride as the blocking group in pyrone **1c** proved successful (Scheme 2). As expected, complications arose when employing other combinations of halides (X = Br and I, possessing weaker C–X bonds) on the aryl ring and on the C-3 position (see SI).

An optimisation screen was performed using **1c** as starting material. Employing $Cs_2CO_3$ as the base in THF under Jeffery-type conditions[19] gave the desired product **2c** in 55% yield (Table 1, entry 1). Changing to $K_2CO_3$ gave a slight improvement in yield to 60% (Table 1, entry 2). This is in line with our previous observation that $Cs_2CO_3$ can degrade the 2-pyrone motif.[13b] Employing KOAc as the base in toluene gave a 68% yield (Table 1, entry 3) and it was determined to be the optimal base. Switching to a protic polar solvent system inhibited the reaction (Table 1, entry 4), but using an aprotic polar solvent gave a 95% yield in just 4 hours (Table 1, entry 5). In THF the reactions worked very well (85%, isolated yield) and it was chosen over DMF[20] as our reaction solvent (Table 1, entry 6). With our optimised conditions in hand, we next investigated the substrate scope. To this end, a variety of 2-pyrone and 2-pyridone precursors were prepared.

**Table 1.** Optimisation of direct arylation conditions (**1c**→**2c**).



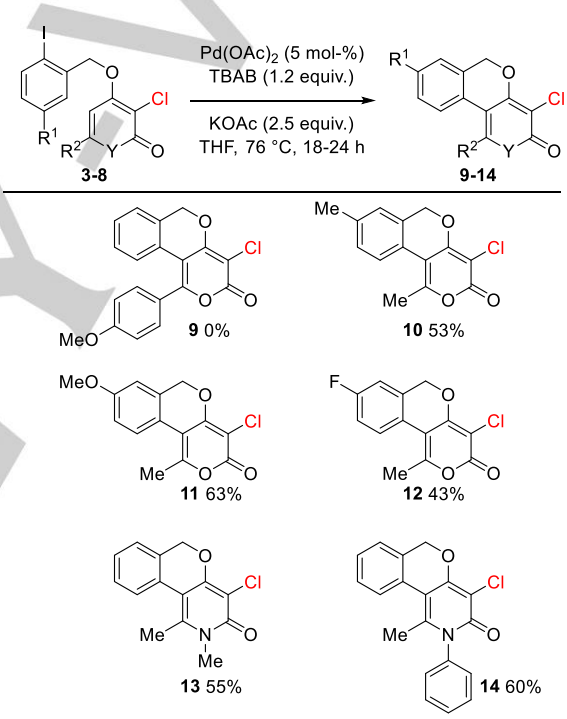

| | Solvent | Base | *T* (°C) | Time (h) | Product (%)[a] |
|---|---|---|---|---|---|
| 1 | THF | $Cs_2CO_3$ | 76 | 8 | 55 |
| 2 | THF | $K_2CO_3$ | 76 | 8 | 60 |
| 3 | Toluene | KOAc | 110 | 6 | 68 |
| 4 | EtOH/$H_2O$ | KOAc | 100 | 16 | 0 |
| 5 | DMF | KOAc | 100 | 4 | 95 |
| **6** | **THF** | **KOAc** | **76** | **18** | **85** |

[a] Isolated yields, following chromatography on silica gel.

Pleasingly, a number of substrates were well tolerated under the reaction conditions (Scheme 3). Substituents *para* to the oxidative addition site worked well, with a *p*-methyl substituted aryl halide giving product **10** in 53% yield, a *p*-methoxy substituted aryl halide giving **11** in 63% yield and a *p*-fluoro substituted aryl halide giving **12** in 43% yield.

Importantly, and in contrast to our previous studies,[13a] the 2-pyridone substrates also coupled well, giving the desired products **13** and **14** in moderate yields.

Unfortunately, employing a larger substituent at the 6-position failed to give any product **9**, presumably due to unfavourable steric interactions at Pd. In any case, the 6-Me 2-pyrone is the more common and useful synthon due to its biosynthetic pathway (from acetyl-CoA via two sequential condensations with malonyl-CoA and subsequent ring closure to produce triacetic acid lactone also called 4-hydroxy-6-methyl-2-pyrone).[21]



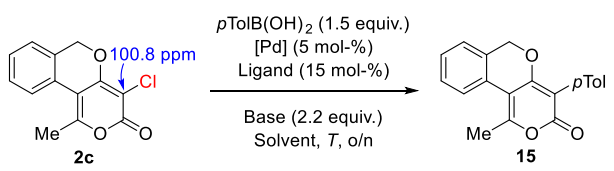

**Scheme 3.** Substrate scope, showcasing the viability of the C-5 direct arylation protocol.

Having demonstrated the scope of the direct arylation reaction we turned our attention towards further functionalisation of the 2-pyrone product via Suzuki-Miyaura cross-coupling at the C-3–Cl position of **2c**. To this end, we expected to be able to harness the plethora of conditions reported for the Suzuki-Miyaura cross-coupling of aryl chlorides. Disappointingly, conditions such as those reported by Fu (Table 2, entry 1)[18c] and Buchwald (Table 2, entry 2)[16a] for the cross-coupling of aryl chlorides failed to give the desired product **15**.

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**Table 2.** Optimisation of Suzuki-Miyaura cross-coupling.

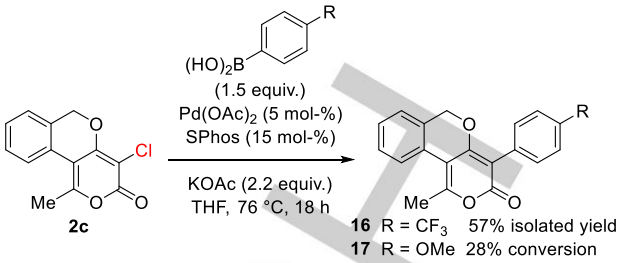



| | [Pd] | Ligand | Base | Solvent | *T* (°C) | Conv. (%)[a] |
|---|---|---|---|---|---|---|
| 1[b] | $Pd_2(dba)_3$ | $P(tBu)_3.HBF_4$ | KF | THF | 60 | 0 |
| 2[c] | $Pd(OAc)_2$ | DavePhos | CsF | Dioxane | 110 | 0 |
| 3 | $Pd(OAc)_2$ | SPhos[d] | $K_2CO_3$ | Toluene | 110 | 60 |
| 4 | $Pd(OAc)_2$ | SPhos[d] | KOAc | Toluene | 110 | 70 |
| 5 | $Pd(OAc)_2$ | SPhos | KOAc | 2-MeTHF | 90 | 69 |
| 6 | $Pd(OAc)_2$ | SPhos | KOAc | Dioxane | 110 | 44 |
| 7 | $Pd_2(dba)_3$ | SPhos | KOAc | THF | 76 | 6 |
| 8 | $Pd(OAc)_2$ | XPhos | KOAc | THF | 76 | 29 |
| 9 | $Pd(OAc)_2$ | RuPhos | KOAc | THF | 76 | 64 |
| **10** | **$Pd(OAc)_2$** | **SPhos** | **KOAc** | **THF** | **76** | **93 (92)** |

[a] Conversion calculated from $^1$H NMR spectrum of crude reaction mixture. Isolated yields in parenthesis. [b] $Pd_2(dba)_3$ (1.5 mol-%), $P(tBu)_3.HBF_4$ (3.6 mol-%) and KF (3.3 equiv.). [c] $Pd(OAc)_2$ (2 mol-%), DavePhos (3 mol-%) and CsF (3.0 equiv.). [d] 10 mol-%.

However, upon consideration of the $^{13}$C NMR spectrum of **2c**, it became apparent that the C-3–Cl bond ($^{13}$C at 100.8 ppm) did not necessarily possess the characteristics of an aryl chloride bond. We therefore tested the conditions reported by Hultin for the Suzuki-Miyaura cross-coupling of an α-chloro-α,β-unsaturated ester (Table 2, entry 3).[22] To our delight, similar conditions gave 60% conversion to the desired product **15**.[23] Using KOAc as base (Table 2, entry 4), gave a slightly increased conversion (to 70%). Using 2-MeTHF (Table 2, entry 5) and 1,4-dioxane (Table 2, entry 6) as solvents, did not promote the reaction. Changing to a Pd(0) source in THF surprisingly led to poor catalytic turnover (6% conversion, Table 2, entry 7), and using bulkier phosphine ligands (Table 2, entries 8-9) was also relatively unsuccessful. Finally, using KOAc in refluxing THF (Table 2, entry 10) gave 93% conversion and an excellent isolated yield of 92%.[24]

Use of an electron-poor *p*-($CF_3$)phenylboronic acid gave the appropriate product **16** in 57% (isolated yield) however, electron-rich *p*-(OMe)phenylboronic acid gave only 28% conversion to **17** (Scheme 4).




**Scheme 4.** Substrate scope for the Suzuki-Miyaura cross-coupling reaction.

## Conclusions

We have developed a valuable synthetic methodology allowing access to previously inaccessible, C-5-cyclised, 2-pyrones and 2-pyridones. This protocol proceeds via direct arylation with the retention of a C–Cl bond; the latter can be utilised in a Suzuki-Miyaura cross-coupling, enabling further elaboration at C-3.

## Experimental Section

**1. General Information:** THF was distilled from sodium in the presence of benzophenone. $Pd(OAc)_2$ was recrystallised from toluene. All other reagents and solvents were used as purchased unless otherwise stated. Melting points were measured in a Thomas Hoover Capillary Melting Point apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrophotometer. Liquid samples were examined as thin films interspersed between sodium chloride plates. Solid samples were dissolved in dichloromethane (DCM), applied as a thin film to sodium chloride plates and the DCM allowed to evaporate prior to the recording of spectra. Mass spectra were recorded on a Waters LCT Premier Tof LC-MS instrument in electrospray ionisation mode using 50% acetonitrile-water, containing 0.1% formic acid, as eluent; samples were made up in acetonitrile or methanol. All spectra were recorded at University College Cork. NMR spectra were run in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as the internal standard, unless otherwise specified. NMR spectra were recorded on a Bruker AVANCE 300 instrument at University College Cork. Thin layer chromatography was performed on precoated silica gel (Merck $HF_{254}$) plates and compounds were visualised under U.V. light. Column chromatography was carried out using Fluka silica gel 60.

**2. Experimental Procedures**

**2.1 General Procedure for Preparation of 4-benzyloxy-2-pyrones:** Pyrone (1.0 equiv.), 2-iodobenzylbromide (1.2 equiv.), $K_2CO_3$ (3.0 equiv.) and acetone (4 mL/mmol pyrone) were added to a round-bottomed flask. The flask was placed in an oil bath preheated to 79 °C and the reaction was stirred at this temperature for 4 h, then cooled to ambient temperature. The reaction mixture was diluted with 15 mL water and extracted with 3 × 15 mL EtOAc. The combined organic layers were washed with 20 mL water, dried over $MgSO_4$ and concentrated under reduced pressure. The residues were purified by column chromatography using the indicated eluent to afford the products.

**4-((2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one**[13a] 0.5:99.5 MeOH:DCM; White solid (1.022 g, 33%); m.p. (DCM) 105–106 °C (lit.[13a] 101–103 °C); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8, 1H), 7.39 (d,

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*J* = 4.2, 2H), 7.15 – 6.99 (m, 1H), 5.87 (dd, *J* = 2.0, 0.9, 1H), 5.51 (d, *J* = 2.2, 1H), 5.01 (s, 2H), 2.23 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.9 (qC), 164.8 (qC), 162.4 (qC), 139.7 (CH), 136.8 (qC), 130.3 (CH), 129.0 (CH), 128.6 (CH), 100.3 (CH), 97.8 (qC), 88.8 (CH), 74.4 ($CH_2$), 19.9 ($CH_3$); m/z (ES+) 343 ($(M+H)^+$ 100%).

**4-((2-Iodo-5-methylbenzyl)oxy)-6-methyl-2*H*-pyran-2-one** DCM; White solid (0.236 g, 38%); m.p. (MeOH) 125–127 °C; IR $\nu_{max}$ 1719, 1649, 1566, 1245, 1013, 806; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0, 1H), 7.20 (d, *J* = 1.6, 1H), 6.89 (dd, *J* = 8.0, 1.7, 1H), 5.88 (dd, *J* = 2.1, 0.9, 1H), 5.50 (d, *J* = 2.1, 1H), 4.96 (s, 2H), 2.32 (s, 3H), 2.22 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.0 (qC), 164.8 (qC), 162.4 (qC), 139.4 (CH), 138.7 (qC), 136.4 (qC), 131.3 (CH), 130.0 (CH), 100.4 (CH), 93.7 (qC), 88.7 (CH), 74.4 ($CH_2$), 21.0 ($CH_3$), 19.9 ($CH_3$); m/z (ES+) 357 ($(M+H)^+$ 40%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{14}IO_3$ 356.9988; Found 356.9987.

**4-((2-Iodo-5-fluorobenzyl)oxy)-6-methyl-2*H*-pyran-2-one** DCM; Pale yellow solid (0.143 g, 40%); m.p. (MeOH) 123–126 °C; IR $\nu_{max}$ 1714, 1650, 1569, 1239, 1020, 666; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.7, 5.5, 1H), 7.15 (dd, *J* = 9.3, 3.0, 1H), 6.84 (td, *J* = 8.4, 3.0, 1H), 5.90 (dd, *J* = 2.1, 0.9, 1H), 5.48 (d, *J* = 2.2, 1H), 4.96 (s, 2H), 2.24 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.6 (qC), 164.6 (qC), 163.2 (d, *J* = 249, qC), 162.7 (qC), 140.7 (d, *J* = 8, CH), 139.0 (d, *J* = 7, qC), 117.5 (d, *J* = 22, CH), 115.9 (d, *J* = 24, CH), 100.2 (CH), 89.4 (d, *J* = 3, qC), 88.9 (CH), 73.7 (d, *J* = 1, $CH_2$), 19.9 ($CH_3$); $^{19}$F NMR (282 MHz, $CDCl_3$) δ -113; m/z (ES+) 361 ($(M+H)^+$ 6%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{11}IFO_3$ 360.9737; Found 360.9741.

**4-((2-Iodo-5-methoxybenzyl)oxy)-6-methyl-2*H*-pyran-2-one** 0.5:99.5 MeOH:DCM; Yellow solid (0.015 g, 4%, with the remainder (0.197 g) isolated as an inseparable mixture which was carried forward into the chlorination step); m.p. (MeOH) 100–104 °C; IR $\nu_{max}$ 1727, 1651, 1566, 1244, 1000, 811; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7, 1H), 6.96 (d, *J* = 3.0, 1H), 6.66 (dd, *J* = 8.7, 3.0, 1H), 5.88 (dd, *J* = 2.1, 0.9, 1H), 5.49 (d, *J* = 2.1, 1H), 4.96 (s, 2H), 3.80 (s, 3H), 2.23 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.9 (qC), 164.7 (qC), 162.4 (qC), 160.2 (qC), 140.1 (CH), 137.7 (qC), 115.8 (CH), 115.3 (CH), 100.3 (CH), 88.9 (CH), 85.6 (qC), 74.2 ($CH_2$), 55.5 ($CH_3$), 19.9 ($CH_3$); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{14}IO_4$ 372.9937; Found 372.9949.

**4-((2-Iodobenzyl)oxy)-6-(4-methoxyphenyl)-2*H*-pyran-2-one** DCM; Yellow solid (0.160 g, 67%); m.p. (MeOH) 107–109 °C; IR $\nu_{max}$ 1720, 1634, 1510, 1178, 752; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 1H), 7.74 – 7.62 (m, 2H), 7.41 – 7.26 (m, 2H), 7.00 (ddd, *J* = 7.9, 6.9, 2.3, 1H), 6.93 – 6.83 (m, 2H), 6.34 (d, *J* = 2.1, 1H), 5.51 (d, *J* = 2.1, 1H), 4.98 (s, 2H), 3.78 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.3 (qC), 164.2 (qC), 162.0 (qC), 160.6 (qC), 139.7 (CH), 136.9 (qC), 130.4 (CH), 129.1 (CH), 128.6 (CH), 127.4 (2 x CH), 123.6 (qC), 114.3 (2 x CH), 97.8 (qC), 96.3 (CH), 89.0 (CH), 74.5 ($CH_2$), 55.5 ($CH_3$); m/z (ES–) 433 ($(M–H)^-$ 14%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{16}IO_4$ 435.0093; Found 435.0095.

**2.2 General Procedure for Preparation of 4-benzyloxy-2-pyridones** A Schlenk tube was heated under vacuum and refilled with $N_2$ three times. Pyridone (1.0 equiv.), 2-iodobenzylbromide (1.12 equiv.) and $K_2CO_3$ (3.0 equiv.) were added under a flow of $N_2$. Anhydrous DMF (4 mL/mmol pyridone) was added via syringe. The flask was placed in an oil bath preheated to 25 °C and the reaction was stirred at this temperature for 18 h. The reaction mixture was diluted with 20 mL water and extracted with 3 × 15 mL EtOAc. The combined organic layers were washed with 20 mL brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residues were purified by column chromatography to afford the pure products.

**4-((2-Iodobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one[13b]** 50:50 EtOAc:hexanes; White solid (0.112 g, 29%); m.p. (hexanes) 134–136 °C (lit.[13b] 134–136 °C); IR $\nu_{max}$ 2906, 1644, 1591, 1566, 1435, 1356, 1236, 1200; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.72 (m, 1H), 7.54 – 7.22 (m, 2H), 6.02 – 5.73 (m, 2H), 5.06 – 4.77 (m, 2H), 3.65 – 3.34 (m, 3H), 2.41 – 2.22 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 165.9 (qC), 165.3 (qC), 146.4 (qC), 139.5 (CH), 137.8 (qC), 129.8 (CH), 128.7 (CH), 128.4 (CH), 100.8 (CH), 97.5 (qC), 95.9 (CH), 73.7 ($CH_2$), 30.6 ($CH_3$), 20.9 ($CH_3$); m/z (ES+) 356 ($(M+H)^+$ 16%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}INO_2$ 356.0148; Found 356.0144.

**4-((2-Iodobenzyl)oxy)-6-methyl-1-phenylpyridin-2(1*H*)-one** 70:30 EtOAc:hexanes; Yellow solid (0.805 g, 78%); m.p. (MeOH) 120–124 °C; IR $\nu_{max}$ 1662, 1590, 1558, 1354, 1241, 118, 1044, 755; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 0.8, 1H), 7.59 – 7.32 (m, 5H), 7.24 – 7.15 (m, 2H), 7.05 (td, *J* = 7.7, 1.7, 1H), 5.98 (dd, *J* = 11.8, 2.2, 2H), 5.01 (s, 2H), 1.92 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.6 (qC), 165.4 (qC), 146.4 (qC), 139.5 (CH), 138.6 (qC), 137.8 (qC), 129.9 (CH), 129.7 (2 x CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.3 (2 x CH), 100.8 (CH), 97.6 (qC), 96.4 (CH), 73.9 ($CH_2$), 21.5 ($CH_3$); m/z (ES+) 418 ($(M+H)^+$ 100%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{17}INO_2$ 418.0304; Found 418.0307.

**2.3 General Procedure for chlorination of 4-benzyloxy-2-pyrones and 2-pyridones** Pyrone or pyridone (1.0 equiv.) and *N*-chlorosuccinimide (1.2 equiv.) were added to a round-bottomed flask. $CHCl_3$ (5 mL/mmol pyrone or pyridone) was added, followed by trifluoroacetic acid (1.2 equiv.). The flask was covered in aluminium foil to exclude light and placed in an oil bath, which was heated to 55 °C. The reaction was stirred at this temperature until TLC analysis showed that all starting material had been consumed (18–24 h). The reaction mixture was cooled to ambient temperature, diluted with 10 mL $CHCl_3$ and washed with 15 mL saturated aqueous $NaHCO_3$ and 2 × 15 mL water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residues were purified by column chromatography using the indicated eluent to afford the pure products.

**3-Chloro-4-((2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one, 1c** 0.5:99.5 MeOH:DCM; White solid (0.742 g, 67%); m.p. (MeOH) 183–185 °C; IR $\nu_{max}$ 1725, 1640, 1543, 1322, 758; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.0, 1H), 7.45 (dtd, *J* = 8.8, 7.8, 1.4, 2H), 7.09 (td, *J* = 7.8, 1.9, 1H), 6.06 (d, *J* = 0.7, 1H), 5.21 (s, 2H), 2.29 (d, *J* = 0.8, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.0 (qC), 161.8 (qC), 160.8 (qC), 139.5 (CH), 136.7 (qC), 130.3 (CH), 128.9 (CH), 128.4 (CH), 100.5 (qC), 96.4 (qC), 96.1 (CH), 75.3 ($CH_2$) 20.3 ($CH_3$); m/z (ES+) 377 ($^{35}$Cl $(M+H)^+$ 20%), 379 ($^{37}$Cl $(M+H)^+$ 8%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{11}IClO_3$ 376.9441; Found 376.9446.

**3-Chloro-4-((2-iodobenzyl)oxy)-6-(4-methoxyphenyl)-2*H*-pyran-2-one, 3** 0.5:99.5 MeOH:DCM; Yellow solid (0.080 g, 49%); m.p. (MeOH) 183–185 °C; IR $\nu_{max}$ 1713, 1625, 1507, 1265, 1180, 1107, 738; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.9, 1H), 7.81 – 7.71 (m, 2H), 7.54 (d, *J* = 7.7, 1H), 7.44 (t, *J* = 7.5, 1H), 7.09 (t, *J* = 7.6, 1H), 6.96 (d, *J* = 8.9, 2H), 6.53 (s, 1H), 5.33 (s, 2H), 3.87 (d, *J* = 1.2, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.3 (qC), 162.4 (qC), 160.3 (qC), 159.8 (qC), 139.5 (CH), 136.9 (qC), 130.4 (CH), 129.0 (CH), 128.6 (CH), 127.7 (2 x CH), 123.0 (qC), 114.5 (2 x CH), 100.7 (qC), 96.6 (qC), 91.8 (CH), 75.3 ($CH_2$), 55.5 ($CH_3$); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}IClO_3$ 468.9704; Found 468.9715.

**3-Chloro-4-((2-iodo-5-methylbenzyl)oxy)-6-methyl-2*H*-pyran-2-one, 4** 0.5:99.5 MeOH:DCM; White solid (0.164 g, 75%); m.p. (MeOH) 204–206 °C; IR $\nu_{max}$ 1722, 1638, 1544, 1319, 1239, 1075, 742; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0, 1H), 7.28 (d, *J* = 1.2, 1H), 6.91 (dd, *J* = 8.0, 1.7, 1H), 6.06 (s, 1H), 5.17 (s, 2H), 2.34 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.0 (qC), 161.8 (qC), 160.8 (qC), 139.2 (CH), 139.1 (qC), 136.4 (qC), 131.3 (CH), 129.3 (CH), 100.5 (qC), 96.2 (CH), 92.4 (qC), 75.3 ($CH_2$), 21.1 ($CH_3$), 20.3 ($CH_3$); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}IClO_3$ 390.9598; Found 390.9601.

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**3-Chloro-4-((2-iodo-5-methoxybenzyl)oxy)-6-methyl-2*H*-pyran-2-one, 5** DCM; White solid (0.052 g, 24%); m.p. (DCM) 180–184 °C; IR $\nu_{max}$ 1718, 1637, 1545, 1318, 1232, 1053, 873; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.7, 1H), 7.08 (d, *J* = 3.0, 1H), 6.67 (dd, *J* = 8.7, 3.0, 1H), 6.07 (d, *J* = 0.6, 1H), 5.16 (s, 2H), 3.80 (s, 3H), 2.29 (d, *J* = 0.6, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.9 (qC), 161.9 (qC), 160.8 (qC), 160.4 (qC), 139.9 (CH), 137.7 (qC), 116.4 (CH), 114.2 (CH), 100.6 (qC), 96.1 (CH), 84.1 (qC), 75.1 ($CH_2$), 55.5 ($CH_3$), 20.3 ($CH_3$); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}IClO_4$ 406.9547; Found 406.9550.

**3-Chloro-4-((2-iodo-5-fluorobenzyl)oxy)-6-methyl-2*H*-pyran-2-one, 6** 0.5:99.5 MeOH:DCM; White solid (0.036 g, 29%); m.p. (DCM) 221–223 °C; IR $\nu_{max}$ 1719, 1639, 1544, 1321, 1235, 1074, 868; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.7, 5.4, 1H), 7.37 – 7.15 (m, 2H), 6.86 (td, *J* = 8.4, 3.0, 1H), 6.05 (d, *J* = 0.6, 1H), 5.14 (s, 2H), 2.31 (d, *J* = 0.7, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.5 (qC), 163.4 (d, *J* = 249, qC), 161.7 (qC), 160.6 (qC), 140.6 (d, *J* = 8, CH), 139.0 (d, *J* = 8, qC), 117.6 (d, *J* = 22, CH), 115.8 (d, *J* = 24, CH), 100.8 (qC), 95.9 (CH), 88.3 (d, *J* = 3, qC), 74.6 (d, *J* = 1, $CH_2$), 20.3 ($CH_3$); $^{19}$F NMR (282 MHz, $CDCl_3$) δ -112; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{10}ClFIO_3$ 394.9347; Found 394.9360.

**3-Chloro-4-((2-iodobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one, 7** Recrystallised from EtOH; White solid (0.109 g, 50%); m.p. (EtOH) 170–171 °C; IR $\nu_{max}$ 1659, 1635, 1600, 1019, 735; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.1, 1H), 7.67 – 7.49 (m, 1H), 7.40 (td, *J* = 7.6, 1.2, 1H), 7.05 (ddd, *J* = 7.9, 7.4, 1.7, 1H), 5.96 (s, 1H), 5.14 (s, 2H), 3.56 (s, 3H), 2.37 (d, *J* = 0.6, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 160.9 (qC), 160.6 (qC), 145.2 (qC), 139.2 (CH), 137.7 (qC), 129.9 (CH), 128.7 (CH), 128.3 (CH), 106.4 (qC), 96.2 (qC), 95.9 (CH), 74.4 ($CH_2$), 32.1 ($CH_3$), 21.4 ($CH_3$); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{14}IClNO_2$ 389.9758; Found 389.9761.

**3-Chloro-4-((2-iodobenzyl)oxy)-6-methyl-1-phenylpyridin-2(1*H*)-one, 8** 90:10 EtOAc:hexanes; Yellow solid (0.115 g, 15%); m.p. (MeOH) 239–243 °C; IR $\nu_{max}$ 1654, 1531, 1350, 1222, 1052, 751; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 0.9, 1H), 7.60 (d, *J* = 7.7, 1H), 7.46 (m, 4H), 7.22 – 7.13 (m, 2H), 7.07 (td, *J* = 7.8, 1.6, 1H), 6.05 (s, 1H), 5.20 (s, 2H), 1.98 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.2 (qC), 161.0 (qC), 145.3 (qC), 139.3 (CH), 138.5 (qC), 137.7 (qC), 129.9 (CH), 129.8 (2 x CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 127.9 (2 x CH), 106.8 (qC), 96.2 (qC), 95.9 (CH), 74.6 ($CH_2$), 22.0 ($CH_3$); m/z (ES+) 452 ($^{35}$Cl (M+H)$^+$ 100%), 454 ($^{37}$Cl (M+H)$^+$ 38%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{16}IClNO_2$ 451.9914; Found 451.9918.

**2.4 General Procedure for Direct Arylation** A Schlenk tube was heated under vacuum and refilled with $N_2$ three times. Pyrone or pyridone (1.0 equiv.), $Pd(OAc)_2$ (5 mol-%), tetrabutylammonium bromide (TBAB) (1.2 equiv.) and KOAc (2.5 equiv.) were added to the Schlenk tube under flow of $N_2$. Freshly distilled THF (0.03 M) was added via syringe. The Schlenk was placed in an oil bath preheated to 76 °C and the reaction was stirred at this temperature for 18 h (pyrones) or 24 h (pyridones), then cooled to ambient temperature. The reaction mixture was diluted with 10 mL water and extracted with 3 × 10 mL DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residues were purified by column chromatography using the indicated eluent to afford the pure products.

**4-Chloro-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 2c** DCM; White solid (0.028 g, 85%); m.p. (MeOH) 155–158 °C; IR $\nu_{max}$ 1726, 1638, 1544, 1185, 770; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 2H), 7.38 (td, *J* = 7.3, 1.7, 1H), 7.27 (d, *J* = 7.4, 1H), 5.19 (s, 2H), 2.65 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.1 (qC), 159.9 (qC), 156.9 (qC), 131.0 (qC), 129.1 (CH), 128.2 (CH), 125.7 (CH), 125.6 (qC), 125.4 (CH), 107.8 (qC), 100.8 (qC), 70.2 ($CH_2$), 20.3 ($CH_3$); m/z (ES+) 249 ($^{35}$Cl (M+H)$^+$ 16%), 251 ($^{37}$Cl (M+H)$^+$ 6%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{10}ClO_3$ 249.0318; Found 249.0318. Reaction performed with $Pd(OAc)_2$ (2 mol-%) and TBAB (1.0 equiv).

**4-Chloro-1,8-dimethyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 10** DCM; White solid (0.016 g, 53%); m.p. (DCM) 158–163 °C; IR $\nu_{max}$ 1726, 1634, 1548, 1301, 1190, 1033, 824; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1, 1H), 7.25 (d, *J* = 8.4, 1H), 7.08 (s, 1H), 5.16 (s, 2H), 2.63 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.1 (qC), 160.0 (qC), 156.2 (qC), 138.4 (qC), 130.9 (qC), 129.8 (CH), 126.0 (CH), 125.6 (CH), 122.7 (qC), 107.8 (qC), 100.8 (qC), 70.2 ($CH_2$), 21.2 ($CH_3$), 20.2 ($CH_3$); m/z (ES+) 263 ($^{35}$Cl (M+H)$^+$ 18%), 265 ($^{37}$Cl (M+H)$^+$ 6%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}ClO_3$ 263.0475; Found 263.0471.

**4-Chloro-8-methoxy-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 11** 0.5:99.5 MeOH:DCM; White solid (0.013 g, 63%); m.p. (DCM) 193–197 °C; IR $\nu_{max}$ 1728, 1635, 1544, 1502, 1140, 1052, 934; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7, 1H), 6.98 (dd, *J* = 8.7, 2.7, 1H), 6.79 (d, *J* = 2.6, 1H), 5.16 (s, 2H), 3.86 (s, 3H), 2.61 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.9 (qC), 160.0 (qC), 159.4 (qC), 155.3 (qC), 132.6 (qC), 127.2 (CH), 117.8 (qC), 114.7 (CH), 110.7 (CH), 107.6 (qC), 100.9 (qC), 70.2 ($CH_2$), 55.5 ($CH_3$), 20.2 ($CH_3$); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}ClO_4$ 279.0424; Found 279.0428.

**4-Chloro-8-fluoro-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 12** DCM; White solid (0.012 g, 43%); m.p. (DCM) 147–151 °C; IR $\nu_{max}$ 1733, 1635, 1549, 1495, 1185, 1027, 834; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.8, 5.0, 1H), 7.17 (td, *J* = 8.6, 2.7, 1H), 7.01 (dd, *J* = 8.0, 2.6, 1H), 5.17 (s, 2H), 2.63 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.6 (qC), 162.0 (d, *J* = 251, qC), 159.7 (qC), 156.5 (d, *J* = 2, qC), 133.3 (d, *J* = 8, qC), 127.8 (d, *J* = 8, CH), 121.8 (d, *J* = 3, qC), 116.2 (d, *J* = 22, CH), 112.7 (d, *J* = 23, CH), 107.2 (qC), 101.2 (qC), 69.6 (d, *J* = 2, $CH_2$), 20.2 ($CH_3$); $^{19}$F NMR (282 MHz, $CDCl_3$) δ -111.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_9ClFO_3$ 267.0224; Found 267.0229.

**4-Chloro-1,2-dimethyl-2,6-dihydro-3*H*-isochromeno[4,3-*c*]pyridin-3-one, 13** 0.3:99.7 MeOH:DCM; White solid (0.011 g, 55%); m.p. (DCM) 218–220 °C; IR $\nu_{max}$ 1730, 1651, 1533, 1266, 738; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.14 (m, 4H), 5.06 (s, 2H), 3.70 (s, 3H), 2.73 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 160.2 (qC), 159.6 (qC), 141.9 (qC), 132.1 (qC), 128.5 (CH), 128.5 (qC), 127.0 (CH), 126.3 (CH), 125.4 (CH), 107.9 (qC), 106.1 (qC), 70.0 ($CH_2$), 32.6 ($CH_3$), 19.8 ($CH_3$); m/z (ES+) 262 ($^{35}$Cl (M+H)$^+$ 100%), 264 ($^{37}$Cl (M+H)$^+$ 38%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}NO_2Cl$ 262.0635; Found 262.0639.

**4-Chloro-1-methyl-2-phenyl-2,6-dihydro-3*H*-isochromeno[4,3-*c*]pyridin-3-one, 14** 70:30 EtOAc:hexanes; Brown solid (0.018 g, 60%); m.p. (DCM) >250 °C; IR $\nu_{max}$ 1655, 1528, 1349, 1206, 1041, 700; $^1$H NMR (300 MHz, DMSO) δ 7.65 – 7.50 (m, 4H), 7.48 – 7.31 (m, 5H), 5.23 (s, 2H), 2.27 (s, 3H); $^{13}$C NMR (75 MHz, DMSO) δ 160.7 (qC), 159.6 (qC), 143.6 (qC), 139.3 (qC), 132.5 (qC), 130.1 (CH), 129.3 (2 x CH), 128.9 (CH), 128.9 (2 x CH), 128.3 (qC), 127.4 (CH), 126.8 (CH), 125.9 (CH), 107.1 (qC), 104.9 (qC), 69.9 ($CH_2$), 21.4 ($CH_3$); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}NO_2Cl$ 324.0791; Found 324.0787.

**2.5 General Procedure for Suzuki-Miyaura Cross-Coupling** A Schlenk tube was heated under vacuum and refilled with $N_2$ three times. KOAc (2.2 equiv.) was added. The Schlenk tube was heated under vacuum and refilled with $N_2$ twice. Pyrone or pyridone (1.0 equiv.), boronic acid (1.5 equiv.), $Pd(OAc)_2$ (5 mol-%) and SPhos (15 mol-%) were added. The Schlenk tube was evacuated and refilled with $N_2$ three times. Freshly distilled THF (0.03 M) was added via syringe. The Schlenk tube was placed in an oil bath preheated to 76 °C. The reaction was stirred at this temperature for 18 h, then cooled to ambient temperature. The reaction mixture was diluted with 15 mL water and extracted with 3 × 15 mL EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated

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under reduced pressure. The residues were purified by column chromatography using the indicated eluent to afford the pure products.

**1-Methyl-4-(*p*-tolyl)-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 15** DCM; White solid (0.034 g, 92%); m.p. (hexanes) 159–164 °C; IR $\nu_{max}$ 1711, 1555, 1161, 1013; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7, 1H), 7.49 – 7.29 (m, 4H), 7.22 (d, *J* = 8.3, 3H), 5.00 (s, 2H), 2.68 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.5 (qC), 163.4 (qC), 157.7 (qC), 137.6 (qC), 131.7 (qC), 130.3 (2 x CH), 128.8 (CH), 128.7 (2 x CH), 128.0 (qC), 127.6 (CH), 126.8 (qC), 125.9 (CH), 125.2 (CH), 107.9 (qC), 107.1 (qC), 69.6 ($CH_2$), 21.3 ($CH_3$), 20.3 ($CH_3$); m/z (ES+) 305 ($(M+H)^+$ 100%); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{17}O_3$ 305.1178; Found 305.1174.

**1-Methyl-4-(4-(trifluoromethyl)phenyl)-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 16** DCM; White solid (0.033 g, 57%); m.p. (DCM) 188–191 °C; IR $\nu_{max}$ 1713, 1325, 1110, 845; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 4H), 7.54 (d, *J* = 7.6, 1H), 7.47 (td, *J* = 7.7, 1.2, 1H), 7.37 (td, *J* = 7.4, 1.2, 1H), 7.25 (d, *J* = 6.9, 1H), 5.03 (s, 2H), 2.70 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.3 (qC), 162.8 (qC), 158.7 (qC), 134.9 (d, *J* = 1, qC), 131.4 (qC), 130.9 (2 x CH), 129.5 (q, *J* = 32, qC), 129.0 (CH), 127.9 (CH), 126.4 (qC), 125.9 (CH), 125.3 (CH), 124.8 (q, *J* = 4, 2 x CH), 124.2 (q, *J* = 272, qC), 107.9 (qC), 105.7 (qC), 69.8 ($CH_2$), 20.4 ($CH_3$); $^{19}$F NMR (282 MHz, $CDCl_3$) δ -63; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{14}F_3O_3$ 359.0895; Found 359.0885.

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[24] We thank a reviewer for the suggestion to carry out the direct arylation and Suzuki-Miyaura reactions in one pot. However, attempts to do so have so far been unsuccessful, demonstrating the difficulty in using one

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precatalyst for two mechanistically distinct transformations, and the exquisitely precise conditions which are required for each transformation. Further details are provided in the SI.

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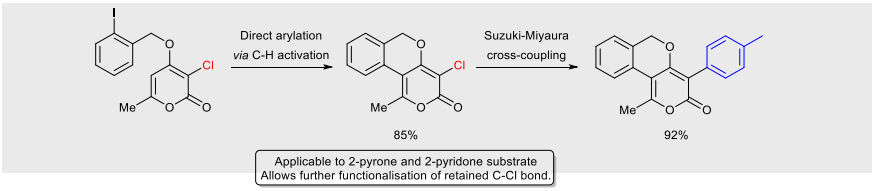
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## Entry for the Table of Contents

Layout 2:

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A direct arylation protocol was developed for the intramolecular coupling of 2-pyrones and 2-pyridones, allowing access to a previously unavailable class of products. A C–Cl bond was retained at C-3 during the direct arylation process allowing further derivatisation (demonstrated by Suzuki-Miyaura coupling) at C-3.

**C-H activation**

*Aisling M. Prendergast, Leticia M. Pardo, Ian J. S. Fairlamb and Gerard P. McGlacken**

***Page No. – Page No.***

**Access to some C5-cyclised 2 pyrones and 2-pyridones via direct arylation; retention of chloride as a synthetic handle**

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