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Pd/Pivalic Acid Mediated Direct Arylation of 2-Pyrones and Related Heterocycles

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Direct arylation represents a favourable alternative to traditional cross-coupling reactions and has found widespread use with simple aryls and robust heterocycles. Herein a direct arylation protocol has been optimised and applied to more delicate, privileged biological motifs. The intramolecular direct arylation of 2-pyrones, 2-coumarins, 2-pyridones and 2-quinolones occurs in very good to excellent yields using a Pd^0 source and pivalic acid as a crucial additive. Preliminary mechanistic investigations were also carried out.

Introduction

The formation of aryl–heteroaryl (Ar–HetAr) bonds is a very important transformation in organic synthesis[1] due to the abundance of the Ar–HetAr moiety in natural products and pharmaceuticals.[2] The most widely used methods for its formation involve Suzuki–Miyaura,[3–5] Stille,[6–8] Negishi,[9,10] and similar reactions.[11] More recently the development of Direct Arylation protocols which involve at least one C–H activation event has emerged, and offers a number of advantages over traditional cross-coupling.[12–14] For example, the need for installation of activating groups is not required and the production of waste (e.g. B, Sn or Zn based) is eliminated. One impediment to the widespread application of direct arylation methodology is the development of regioselective methods. In many cases a number of C–H bonds are available as coupling sites. Thus it can be troublesome to control and predict regioselectivity, and directing groups are needed to guide the transition metal into position and facilitate smooth reactivity.[15]

Direct arylation protocols have been applied to a number of Ar–HetAr bond forming reactions.[16] In most of these cases, harsh conditions are utilised including very high temperatures, strong bases and long reaction times. This is not necessarily a problem in many cases due to the stability of many simple aryls and prominent heterocyclic systems. For example, indoles,[17] purines[18] and (benz)imidazoles[19] tolerate strong bases such as Cs_2CO_3, CsOAc and KO*t*Bu in direct arylation reactions at temperatures exceeding 100 °C.

It seems to us that development of direct arylation methodology [Pd, base and pivalic acid (PivOH)] would be well served by the optimisation of reaction conditions for less robust heterocyclic systems,[20] more specifically those prominent in natural products and mimetics.

We chose the 2-pyrone substrate, specifically 4-hydroxy-2-pyrones[21] due to their status as a privileged biological scaffold with broad spectrum biological activity,[22] spanning cytotoxic,[21] antibiotic,[23] and antifungal activity.[24] For example, the bufadienolide class of compounds has been shown to have diverse biological effects, including causing cardiac poisoning in animals and inhibitory activity towards leukaemia cell lines.[21] Radicinin (Figure 1) dem-

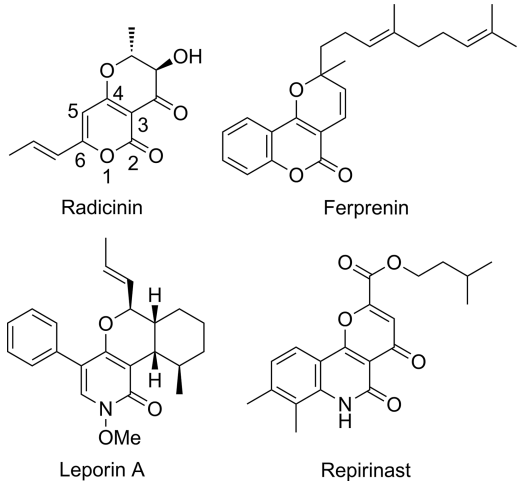

Figure 1. Biologically active examples of a 4-alkoxy-2-pyrone, 2-coumarin, 2-pyridone and 2-quinolone.

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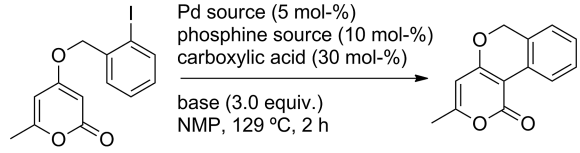
onstrates inhibitory activity towards the growth of some Gram-positive bacteria, such as *Staphylococcus aureus* and *Clostridium* species.[23] The 2-pyrone would also prove suitable to probe the regioselectivity of an optimised direct arylation methodology as it bears two potential sites for C-H activation. Finally the 2-pyrone moiety displays reactivity reminiscent of aromatic compounds,[25] dienes,[26,27] and enones[28] and thus represents both a challenging and rewarding synthon.

The related 2-coumarins also display a wide and varied biological profile.[29] 4-Hydroxycoumarins represent an important and common subgroup, as well as intermediates in the production of dye stuffs, herbicides and anticancer agents.[30] Ferprenin (Figure 1), from *Ferula communis*, shows antithrombotic activity.[31] While 2-coumarins have only one obvious site for C-H activation under the conditions described here, the added aromaticity, presumably bestowed on the entire system by an additional ring, could hinder cleavage of the key C–H bond. 2-Pyridones (isosteres of 2-pyrones) possess numerous biological effects, including antifungal, antibacterial, insecticidal and cytotoxic activity.[32] Leporin A (Figure 1) shows activity against the corn earworm *Helicoverpa zea* and antibacterial activity against *Bacillus subtilis*.[32] 2-Quinolones also have a prominent biological profile,[33] such as the antihistamine Repirinast (Figure 1).[34,35] 2-Pyridones and 2-quinolones bear a nitrogen and thus a potentially problematic Pd-ligation site. Development to include to these substrates would greatly improve the widespread usability of any protocol. The Pd-cyclisation of pyrones to form a five-membered ring has been reported by Taylor and Fairlamb.[36] Importantly, no conditions were reported to form the *6-membered* analogues and the conditions reported,[36] failed to form six-membered rings in our hands. Previous cyclisations by Majumbar[37,38] and us,[39] using so-called Jeffrey's conditions, require the use of stoichiometric or superstoichiometric amounts of TBAB and thus suffer from poor atom and cost economy, falter from an environmental viewpoint (halide waste) and would be avoided by the pharmaceutical industry. Finally, a direct mechanistic probe was unavailable to us under Jeffrey's conditions due the requirement of P-ligands for the isolation of oxidative addition products.

Results and Discussion

Thus we turned our attention to concerted metalation-deprotonation (CMD) conditions which would facilitate the turnover under a different mechanism. Fagnou[40] and Echavarren[41,42] demonstrated that pivalic acid (PivOH) is a key additive in direct arylation reactions and facilitates high yields when used with a Pd source [usually $Pd(OAc)_2$], added phosphine and an inorganic base. Our initial test involved an intramolecular direct arylation reaction, and we chose a catalytic system of $Pd_2(dba)_3$, PPh_3, Na_2CO_3 and PivOH using pyrone **1** (Scheme 1). A promising yield (77%) was obtained (Table 1, entry 1) after 2 h. A number of other acid co-catalysts were investigated (not included here), with 1-adamantanecarboxylic acid (AdmOH) being the most useful, affording **2** in 62% yield (Table 1, entry 2). In the absence of PivOH or AdmOH under otherwise identical conditions, only 11% of pyrone **2** was detected (Table 1, entry 3). The use of Cs_2CO_3 and KO*t*Bu, which had previously proved successful in the direct arylation of purines[18] and (benz)imidazoles[19] respectively, caused degradation of the 2-pyrone motif, verifying our hypothesis that conditions must be sought which better tolerate sensitive functional groups and the privileged motifs found in natural products. The use of K_2CO_3 gave a reduced yield of 38% (Table 1, entry 4) as did NaOAc (70%) (Table 1, entry 5). Of the palladium sources screened, $Pd(OAc)_2$ (Table 1, entry 6) and $Pd_2(dba)_3$ (Table 1, entry 1) facilitated complete consumption of starting material, whereas $Pd(dba)_2$ (Table 1, entry 7) and $Pd(PPh_3)_4$ (Table 1, entry 8) did not. None of the other phosphine ligands performed as well as PPh_3 (Table 1, entries 9–11). Polar aprotic solvents are generally the solvents of choice for direct arylation reactions involving palladium catalysts, so it is unsurprising that toluene gave a very poor yield of 7% (Table 1, entry 12). DMA (Table 1, entry 13) as solvent allowed complete consumption of starting material, however, the reduced isolated yield led us to favour NMP for future reactions. Finally, the Pd loading could be reduced to 2 mol-% with a concomitant reduction of PPh_3 to 4 mol-% with no erosion of the product yield (Table 1, entry 14). In all cases,



1 2

Scheme 1. General procedure for direct arylation reaction of pyrone **1** to **2**.

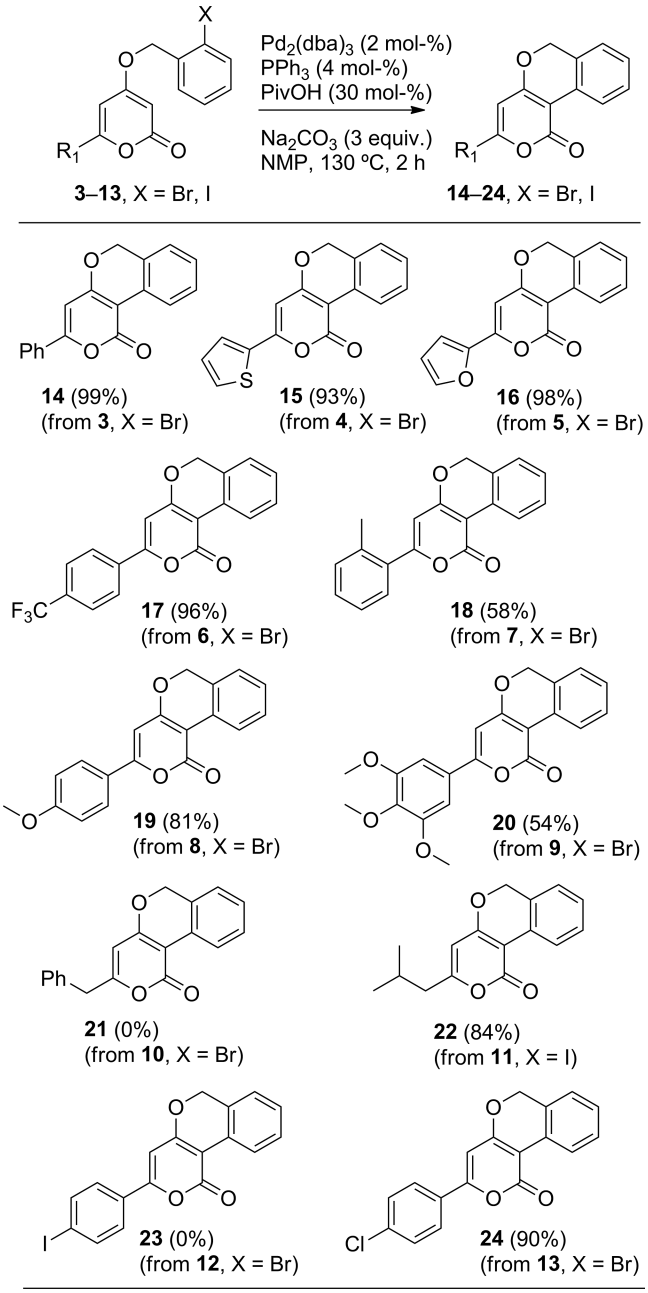
Table 1. Optimisation of direct arylation reaction of pyrone **1** to **2**.

Entry	Pd source, phosphine, carboxylic acid, base, solvent	% Yield of **2**[a]
1	$Pd_2(dba)_3$, PPh_3, PivOH, Na_2CO_3, NMP	77
2	$Pd_2(dba)_3$, PPh_3, **AdmOH**, Na_2CO_3, NMP	62
3	$Pd_2(dba)_3$, PPh_3, –, Na_2CO_3, NMP	(11)
4	$Pd_2(dba)_3$, PPh_3, PivOH, **K_2CO_3**, NMP	38
5	$Pd_2(dba)_3$, PPh_3, PivOH, **NaOAc** NMP	(70)
6	**$Pd(OAc)_2$**, PPh_3, PivOH, Na_2CO_3, NMP	54
7	**$Pd(dba)_2$**, PPh_3 PivOH, Na_2CO_3, NMP	(51)
8	**$Pd(PPh_3)_4$**, PPh_3, PivOH, Na_2CO_3, NMP	(66)
9	$Pd_2(dba)_3$, **DavePhos**, PivOH, Na_2CO_3, NMP	(48)
10	$Pd_2(dba)_3$, **cataCXium®A**, PivOH, Na_2CO_3, NMP	(52)
11	$Pd_2(dba)_3$, **$P(Cy)_3{\cdot}HBF_4$**, PivOH, Na_2CO_3, NMP	(60)
12	$Pd_2(dba)_3$, PPh_3, PivOH, Na_2CO_3, **toluene**	(7)
13	$Pd_2(dba)_3$, PPh_3, PivOH, Na_2CO_3, **DMA**	30
14	$Pd_2(dba)_3$ (**2 mol-%**), PPh_3 (**4 mol-%**), PivOH, Na_2CO_3, NMP	78
15	$Pd_2(dba)_3$ (2 mol-%), PPh_3 (4 mol-%), PivOH, Na_2CO_3, NMP, **100 °C for 5 h**	46

[a] Isolated yields. NMR yields are given in parentheses using 1,3,5-trimethoxybenzene as the internal standard and were consistent with isolated yields in test cases.

very good regioselectivity was observed favouring the 3-position.[43]

The reaction also occurs at 100 °C (Table 1, entry 15). While complete conversion was achieved at the lower temperature, an erosion of yield and regioselectivity was observed. With our optimised conditions in hand, we sought to test the broader applicability of our system to a range of novel 2-pyrones in terms of yield and regioselectivity. As can be seen from Scheme 2, the procedure proved to be general for most substrates tested, giving moderate to excellent yields under the optimised reaction conditions. Despite the relative difficulty in accessing 6-aryl- and 6-alkyl-4-hydroxy-2-pyrones, we were keen to ensure that our optimised conditions tolerated a wide range of C-6 substitutions



Scheme 2. Substrate scope of optimised direct arylation reaction.

which are found in natural products.[23] In the case of 6-(hetero)aryl substrates, the presence of either electron-donating or withdrawing groups resulted in excellent yields (Scheme 2, compounds **14**–**17**). However, the *o*-tolyl- and trimethoxy-substituted 2-pyrones gave reduced yields (Scheme 2, compounds **18** and **20**), presumably due to a steric and reduced acidity[44] effect respectively. Pyrone **10** with a benzyl group at the 6-position failed to cyclise perhaps due to the acidic benzylic hydrogens. A methylene group was tolerated at C-6 however, and isobutyl-substituted pyrone **11**[45] gave the corresponding cyclised pyrone **22** in a very good yield of 84%. A favourable alternative site for oxidative addition inhibited turnover of the cyclisation, and no cyclised pyrone was observed using **12**. However, chloro analogue **13** was cyclised successfully in 90% yield, leaving the chloride bond unaffected and available for further cross-coupling. It is noteworthy that in all these cases complete regioselectivity was observed and none of the 5-cyclised product could be isolated. Furthermore, no significant amounts of hydrodehalogenation products were detected.

We next probed the electronics of the benzyl group (Figure 2, pyrones **25** and **26**). The positioning of an electron-donating substituent on the benzyl group *para* to the oxidative addition site, proved a significant hindrance to coupling (Figure 2, pyrone **42**). Conversely, introduction of an electron-withdrawing group *para* to the oxidative addition site gave an excellent yield of pyrones **43** and **44**.[46] Remarkably, the regioselectivity previously observed, declined significantly and substantial amounts of the C-5 cyclised analogue was isolated.[47]

The wide range of tolerated substituents on our 2-pyrones encouraged us to test our procedure on related heterocycles. Thus a range of substituted 2-coumarins, 2-pyridinones and a 2-quinolone was synthesised and subjected to the optimised protocol (Figure 2). (Bromobenzyloxy)coumarin **27** gave moderate yields, but returning to the iodo analogue **28** facilitated smooth coupling and furnished **45** in excellent yield. A short substrate scope was investigated and good yields were maintained affording **46**–**49**. It is pleasing that our protocol is widely applicable across a range of substituted 2-pyridone heterocycles **33**–**40** (Figure 2).

A range of N-substituents are tolerated by this protocol and the successful coupling of pyridone **33** containing a free NH is particularly gratifying, as *N*-functionalization protocols can be subsequently applied. 2-Quinolone **41** was also cyclised to **56** in a 60% yield. The broad applicability of the catalytic system prompted us to carry out some preliminary mechanistic investigations. Firstly, we used coumarin substrate **28** as a model to isolate and test the potential oxidative addition (OA) product formed. $Pd_2(dba)_3$ and 8 equiv. of PPh_3 were mixed to give precatalyst $Pd^0(\eta^2\text{-dba})(PPh_3)_2$ in THF, which is the optimal solvent for the isolation of oxidative addition products. Addition of coumarin **28** and heating allowed formation of oxidation product [I-Pd-R(L)$_2$] **57** in 90% yield. The nature of **57** as a catalytically relevant intermediate was then established. Thus coumarin

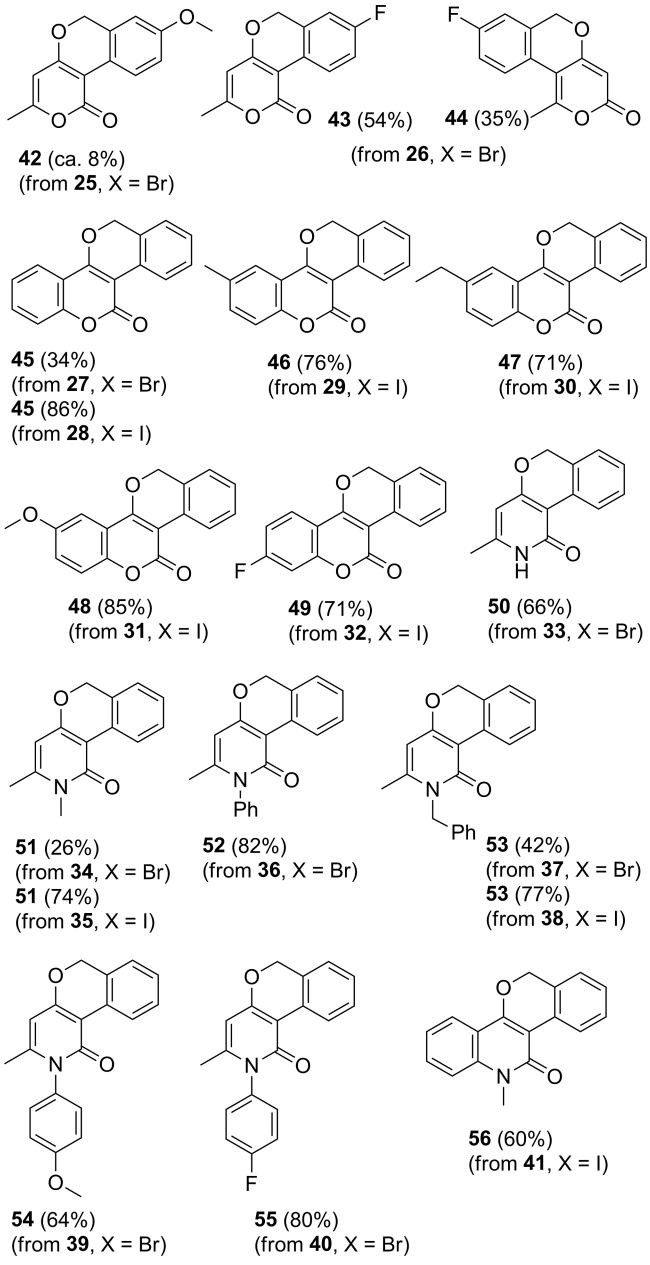
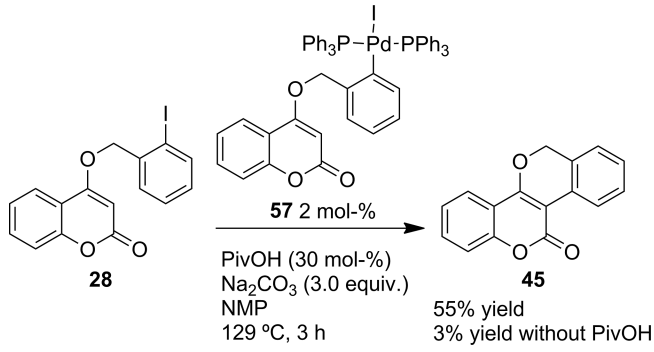


Figure 2. Extension of methodology to further 2-pyrones, 2-coumarins, 2-pyridones and 2-quinolones.

28 was subjected to the optimised reaction conditions, replacing $Pd_2(dba)_3$ (2 mol-%) and PPh_3 (4 mol-%) with **57** (2 mol-%). The cyclisation product **45**, was obtained in 55% yield, comparable to results under the standard reaction conditions (Scheme 3).

This reaction was also performed in the absence of PivOH, resulting in only 3% yield of product **45** by NMR spectroscopy. Isolated oxidative addition product **57** (in the absence of substrate **28**) also gave cyclised product **45** in 36% yield in the presence of PivOH and Na_2CO_3 in NMP. In the absence of PivOH under otherwise identical conditions, only 5% of **45** was identified. Finally, stoichiometric amounts of oxidative addition product **57** were also clearly identified in NMP (our optimised reaction solvent) after



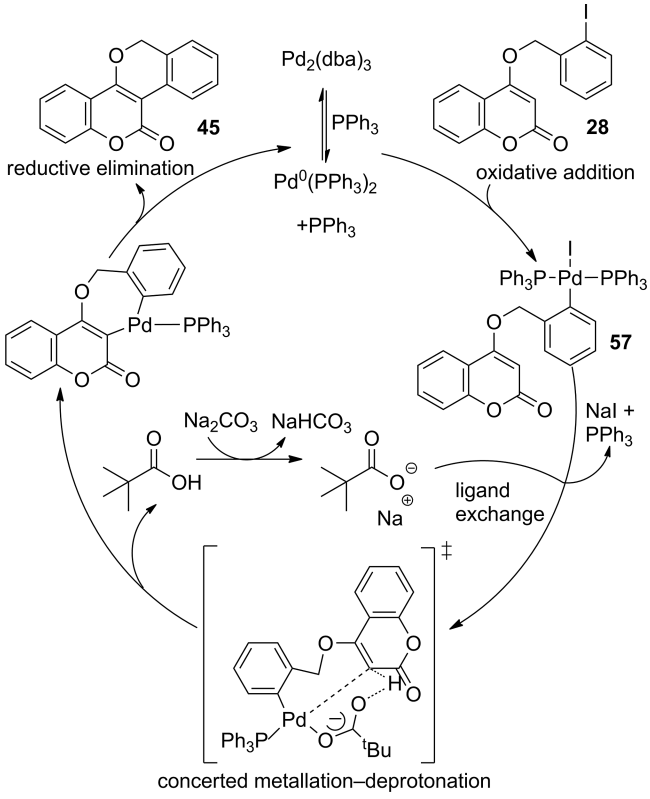
Scheme 3. Isolated oxidative addition product as a catalytically relevant intermediate.

stirring at 70 °C for 1 h. Subsequent addition of Na_2CO_3 (10 equiv.) and PivOH (3 equiv.) and stirring at 129 °C for a further 3 h, resulted in cyclised product **45** in 47% yield.[48]

Given the proficiency of oxidative addition compound **57** to facilitate coupling, we postulate oxidative addition as the first critical mechanistic step.[49] However, an alternative initial step could involve a C-H activation. Given the apparent acidity of the C3–H bond,[50] the potential for an initial reversible C–H bond activation was considered. This was assessed using three tests with PivOD. The experiments consisted of (1) Exposing **28** to the optimised reaction conditions in the presence of PivOD and halting the reaction before completion. (2) Using an *unhalogenated* variant of **28** under the standard conditions with PivOD. (3) Using an *unhalogenated* variant of **28** with PivOD but with a stoichiometric amount of the Pd and phosphine sources. All three failed to give any deuterium incorporation. This rules out an initial step involving a pivalate assisted reversible C–H activation.[51]

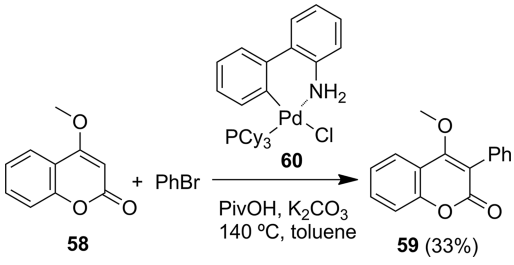
Based on our preliminary mechanistic studies, we envisage an initial oxidative addition (OA) step resulting in Pd^{II} complex **57**. It is tempting to consider OA as the rate-limiting step given the improvement in yields on changing from an aryl bromide to aryl iodide in a number of cases (to form **45**, **51** and **53**), and the favourable result when electron-poor aryl halide **26** (87% yield of **2** regioisomers) is used vs. electron-rich **25** (8%). However the OA step should be facile, occurring at room temperature, and we consider it unlikely to be the rate-limiting step. In any case, we postulate a mechanism involving an initial OA, followed by a ligand exchange and a concerted metallation-deprotonation promoted by PivOH.[52] Finally, ligand dissociation and reductive elimination restores the catalyst and expels arylated product **45** (Scheme 4). The importance of PivOH to the success of our system could be interpreted as evidence that these arylation reactions proceed via CMD, based on work by the Fagnou and Echavarren groups which demonstrates the importance of PivOH as a promoter of phosphine dissociation from the Pd^{II} intermediate, enabling the CMD transition state,[52] and as a catalytic proton shuttle[40] in the CMD mechanism.[53] It should be noted that an S_EAr mechanism[54] would also account for the deleterious effect on yield when an electron-donating group is present on aryl

halide **25** and the corresponding excellent yield using an electron poor aryl halide **26**. A Heck-type mechanism would require an *anti*-hydride elimination (or an isomerisation) and is thus deemed unlikely. Further studies are ongoing to delineate the likely modes of action.



Scheme 4. Suggested mechanism.

Initial application of our optimised conditions to the more challenging intermolecular variant (**58** to **59**) did not allow coupling.[55] However, when precatalyst **60**[56] (designed to produce active Pd^0 quickly) was used, an encouraging yield was obtained. Further optimisation is ongoing and will be reported in due course (Scheme 5).



Scheme 5. Preliminary intermolecular variant.

Conclusions

In conclusion, we report the intramolecular cyclisation of the privileged 2-pyrone, 2-coumarin, 2-pyridone and 2-quinolone motifs under direact arylation conditions conditions using pivalic acid as a necessary additive. Excellent regioselectivity is observed and conditions and mechanistic studies suggest an initial oxidative addition followed by a pivalate assisted CMD-type mechanism, although a S_EAr route cannot be ruled out at this time.

Experimental Section

General: Melting point determinations were performed by the open capillary method and are reported uncorrected. ^1H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ at 300 and 75 MHz spectrometer unless otherwise specified, with TMS as the internal standard. Chemical shifts (δ_H, δ_C and δ_P) were expressed as parts per million (ppm) positive shift being downfield from TMS; coupling constants (*J*) are expressed in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a TOF MS instrument with ESI source. High-resolution mass spectra were recorded only for new compounds. Literature citations are provided for known compounds and representative characterisation data. IR spectra were recorded on an FT-IR spectrometer as a thin film (liquid samples) or applied as a solution in chloroform, and the chloroform was allowed to evaporate (solid samples). Column chromatography was carried out using 60 Å (35–70 μm) silica.

General Procedure for Starting Materials 1, 3–13 and 25–41: Starting materials **1**, **3**–**13** and **25**–**41** were prepared as follows: a solution of pyrone,[57] coumarin,[30,58] pyridone[59] or quinolone[60] (1.0 equiv.), 2-bromobenzyl bromide or 2-iodobenzyl bromide (1.2 equiv.) and K_2CO_3 (3.0 equiv.) in acetone (4.0 mL/mmol starting material) was refluxed (79 °C) for 4 h. The mixture was quenched with water (20 mL), extracted with EtOAc (3× 10 mL), dried and the solvents evaporated. The crude obtained was purified by column chromatography (SiO_2, DCM/MeOH, 99.5:0.5).

4-[(2-Iodobenzyl)oxy]-6-methyl-2*H*-pyran-2-one (1): See ref.[39]

4-[(2-Bromobenzyl)oxy]-6-phenyl-2*H*-pyran-2-one (3): See ref.[39]

4-[(2-Bromobenzyl)oxy]-6-(thiophen-2-yl)-2*H*-pyran-2-one (4): Yellow solid (0.1458 g, 42%), m.p. 124–125 °C (hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.58 (m, 2 H), 7.47–7.43 (m, 2 H), 7.39–7.34 (m, 1 H), 7.27–7.21 (m, 1 H), 7.11–7.08 (m, 1 H), 6.35 (d, *J* = 2.3 Hz, 1 H), 5.57 (d, *J* = 2.3 Hz, 1 H), 5.13 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8 (C), 163.3 (C), 156.0 (C), 134.7 (C), 133.7 (C), 133.0 (CH), 130.3 (CH), 129.4 (CH), 129.1 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 123.0 (C), 96.7 (CH), 89.3 (CH), 70.3 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1724 cm^{-1}. HRMS (ESI, $[M + H]^+$) *m*/*z* calcd. for $C_{16}H_{12}O_3SBr$ 362.9691, found 362.9675.

4-Hydroxy-6-(thiophen-2-yl)-2*H*-pyran-2-one: See ref.[57]

4-[(2-Bromobenzyl)oxy]-6-(furan-2-yl)-2*H*-pyran-2-one (5): Yellowish solid (0.0630 g, 36%), m.p. 132–133 °C (hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 1 H), 7.51–7.44 (m, 2 H), 7.39–7.34 (m, 1 H), 7.28–7.24 (m, 1 H) 7.01 (d, *J* = 3.2 Hz, 1 H), 6.54–6.52 (m, 1 H), 6.55 (d, *J* = 2.4 Hz, 1 H), 5.57 (d, *J* = 2.4 Hz, 1 H), 5.15 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9 (C), 163.2 (C), 152.4 (C), 146.2 (C), 144.9 (CH), 133.7 (C), 133.0 (CH), 130.2 (CH), 129.2 (CH), 127.7 (CH), 122.9 (C), 112.4 (CH), 112.3 (CH), 96.1 (CH), 89.5 (CH), 70.2 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1732 cm^{-1}. MS (M^+, ES^+) *m*/*z* (%) 347 (44), 291 (60), 42 (100). HRMS (ESI, $[M + H]^+$) *m*/*z* calcd. for $C_{16}H_{12}O_4Br$ 346.9919, found 346.9910.

6-(Furan-2-yl)-4-hydroxy-2*H*-pyran-2-one: See ref.[57]

4-[(2-Bromobenzyl)oxy]-6-[4-(trifluoromethyl)phenyl]-2*H*-pyran-2-one (6): See ref.[39]

4-[(2-Bromobenzyl)oxy]-6-(*o*-tolyl)-2*H*-pyran-2-one (7): White solid (0.2210 g, 60%), m.p. 133–135 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (dd, J = 9.9, 0.9 Hz, 1 H), 7.54–7.44 (m, 2 H), 7.37–7.31 (m, 2 H), 7.27–7.23 (m, 3 H), 6.20 (d, J = 2.2 Hz, 1 H), 5.64 (d, J = 2.2 Hz, 1 H), 5.15 (s, 2 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8 (C), 164.2 (C), 162.6 (C), 136.7 (C), 133.8 (C), 133.1 (CH), 131.9 (C), 131.3 (CH), 130.4 (CH), 130.3 (CH), 129.4 (CH), 128.9 (CH), 127.8 (CH), 126.1 (CH), 123.0 (C), 102.0 (CH), 89.5 (CH), 70.2 (CH_2), 20.8 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1715 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 371 (10), 323 (100), 150 (700). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{19}H_{16}O_3Br$ 371.0283, found 371.0284.

4-Hydroxy-6-(*o*-tolyl)-2*H*-pyran-2-one: White solid, m.p. 191–192 °C (MeOH). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.88 (br. s, 1 H), 7.48–7.29 (m, 4 H), 6.28 (d, J = 2.0 Hz, 1 H), 5.40 (d, J = 2.0 Hz, 1 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 170.7 (C), 163.9 (C), 162.7 (C), 136.5 (C), 132.5 (C), 131.6 (CH), 130.7 (CH), 129.2 (CH), 126.7 (CH), 102.7 (CH), 89.7 (CH), 20.6 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1636 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 202 (100), 64 (30), 42 (30). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{12}H_{11}O_3$ 203.0708, found 203.0700.

4-[(2-Bromobenzyl)oxy]-6-(4-methoxyphenyl)-2*H*-pyran-2-one (8): White solid (0.0389 g, 15%), m.p. 82–86 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 9.0 Hz, 2 H), 7.62 (dd, J = 7.9, 1.1 Hz, 1 H), 7.47 (dd, J = 7.9, 1.6 Hz, 1 H), 7.40 (dtd, J = 8.8, 7.6, 1.4 Hz, 1 H), 7.24 (dt, J = 7.7, 2.0 Hz, 1 H), 6.95 (d, J = 9.0 Hz, 2 H), 6.41 (d, J = 2.1 Hz, 1 H), 5.58 (d, J = 2.1 Hz, 1 H), 5.14 (s, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (C), 164.2 (C), 160.6 (C), 160.6 (C), 133.9 (C), 133.0 (CH), 130.2 (CH), 129.3 (CH), 127.8 (CH), 127.4 (CH), 123.5 (C), 123.0 (C), 114.3 (CH), 96.3 (CH), 88.9 (CH), 70.1 (CH_2), 55.4 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1715 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 387 (74), 46 (35). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{19}H_{16}O_4Br$ 387.0232, found 387.0232.

4-Hydroxy-6-(4-methoxyphenyl)-2*H*-pyran-2-one: Yellow solid, m.p. 193–195 °C (hexanes). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.75 (br. s, 1 H), 7.80 (d, J = 9.0 Hz, 2 H), 7.07 (d, J = 9.0 Hz, 2 H), 6.63 (d, J = 1.9 Hz, 1 H), 5.33 (d, J = 1.9 Hz, 1 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 171.3 (C), 163.6 (C), 161.9 (C), 160.7 (C), 127.7 (CH), 123.9 (C), 114.9 (CH), 97.1 (CH), 89.1 (CH), 55.9 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1634 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 218 (100), 64 (42). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{12}H_{11}O_4$ 219.0657, found 219.0650.

4-[(2-Bromobenzyl)oxy]-6-(3,4,5-trimethoxyphenyl)-2*H*-pyran-2-one (9): See ref.[39]

6-Benzyl-4-[(2-bromobenzyl)oxy]-2*H*-pyran-2-one (10): Yellow oil (0.1008 g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.1 Hz, 1 H), 7.57–7.19 (m, 8 H), 5.72 (d, J = 2.2 Hz, 1 H), 5.50 (d, J = 2.2 Hz, 1 H), 5.05 (s, 2 H), 3.77 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9 (C), 164.9 (C), 164.5 (C), 134.6 (C), 133.7 (C), 133.0 (C), 133.0 (CH), 130.2 (CH), 129.4 (CH), 129.3 (CH), 128.9 (CH), 127.7 (CH), 127.4 (CH), 100.5 (CH), 88.9 (CH), 70.1 (CH_2), 39.9 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1720 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 371 (68), 323 (32), 42 (100). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{19}H_{16}O_3Br$ 371.0283, found 371.0265.

6-Benzyl-4-hydroxy-2*H*-pyran-2-one: Cream solid, m.p. 134–135 °C (MeOH). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.70 (br. s, 1 H), 7.35–7.28 (m, 5 H), 5.94 (s, 1 H), 5.23 (s, 1 H), 3.80 (s, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 170.8 (C), 165.6 (C), 164.2 (C), 136.4 (C), 129.6 (CH), 129.1 (CH), 127.4 (CH), 100.9 (CH), 88.9 (CH), 39.3 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1663 cm^{-1}. MS (M^-, ES-) m/z (%) 202 (12), 201 (100), 157 (33). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{12}H_{11}O_3$ 203.0708, found 203.0708.

4-[(2-Iodobenzyl)oxy]-6-isobutyl-2*H*-pyran-2-one (11): Yellow oil (0.0733 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, J = 7.6 Hz, 1 H), 7.33–7.30 (m, 2 H), 7.02–6.96 (m, 1 H), 5.77 (d, J = 2.2 Hz, 1 H), 5.43 (d, J = 2.2 Hz, 1 H), 4.93 (s, 2 H), 2.24 (d, J = 7.2 Hz, 2 H), 2.06–1.97 (m, 1 H), 0.88 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8 (C), 165.2 (C), 164.9 (C), 139.6 (CH), 136.8 (C), 130.3 (CH), 129.0 (CH), 128.5 (CH), 100.6 (CH), 97.7 (C), 88.9 (CH), 74.3 (CH_2), 42.9 (CH_2), 26.7 (CH), 22.2 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1720 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 384 (100). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{16}H_{18}O_3I$ 385.0302, found 385.0301.

4-Hydroxy-6-isobutyl-2*H*-pyran-2-one: White solid, m.p. 106–108 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.82 (br. s, 1 H), 5.97 (d, J = 1.1 Hz, 1 H), 5.59 (d, J = 1.4 Hz, 1 H), 2.34 (d, J = 7.2 Hz, 2 H), 2.11–2.04 (m, 1 H), 0.95 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (C), 168.3 (C), 166.5 (C), 102.3 (CH), 89.9 (CH), 42.8 (CH_2), 26.1 (CH), 22.2 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1678 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 168 (100), 102 (10), 42 (10). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_9H_{13}O_3$ 169.0865, found 169.0857.

4-[(2-Bromobenzyl)oxy]-6-(4-iodophenyl)-2*H*-pyran-2-one (12): Yellow solid (0.1076 g, 37%), m.p. 188–192 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.6 Hz, 2 H), 7.67–7.58 (m, 1 H), 7.53 (d, J = 8.6 Hz, 2 H), 7.46 (dd, J = 7.6, 1.5 Hz, 1 H), 7.41–7.33 (m, 1 H), 7.30–7.17 (m, 1 H), 6.51 (d, J = 2.0 Hz, 1 H), 5.65 (d, J = 2.0 Hz, 1 H), 5.15 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8 (C), 163.6 (C), 159.5 (C), 138.2 (CH), 133.7 (C), 133.1 (CH), 130.5 (C), 130.3 (CH), 129.4 (CH), 127.8 (CH), 127.1 (CH), 123.1 (C), 98.2 (CH), 97.7 (C), 90.1 (CH), 70.4 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1720 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 483 (30), 389 (100). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{18}H_{13}O_3BrI$ 482.9093, found 482.9096.

4-Hydroxy-6-(4-iodophenyl)-2*H*-pyran-2-one: Orange solid, m.p. >230 °C (hexanes). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.89 (br. s, 1 H), 7.89 (d, J = 8.3 Hz, 2 H), 7.63 (d, J = 8.3 Hz, 2 H), 6.79 (d, J = 1.3 Hz, 1 H), 5.42 (d, J = 1.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 170.9 (C), 163.3 (C), 159.6 (C), 138.4 (CH), 131.0 (C), 127.7 (CH), 99.2 (CH), 98.7 (C), 90.4 (CH) ppm. IR (film): $\tilde{\nu}$ = 1601 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 314 (52), 242 (100), 64 (49). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{11}H_8O_3I$ 314.9518, found 314.9519.

4-[(2-Bromobenzyl)oxy]-6-(4-chlorophenyl)-2*H*-pyran-2-one (13): Yellow solid (0.1020 g, 30%), m.p. 146–148 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.67 (m, 2 H), 7.63 (dd, J = 7.0, 1.0 Hz, 1 H), 7.59–7.12 (m, 5 H), 6.49 (d, J = 2.1 Hz, 1 H), 5.65 (d, J = 2.1 Hz, 1 H), 5.15 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8 (C), 163.6 (C), 159.3 (C), 137.2 (C), 133.7 (C), 133.1 (CH), 130.3 (CH), 129.5 (C), 129.4 (CH), 129.2 (CH), 127.8 (CH), 127.0 (CH), 123.1 (C), 98.2 (CH), 90.0 (CH), 70.4 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1729 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 391 (90), 373 (60), 235 (57), 102 (50), 64 (79). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{18}H_{13}O_3ClBr$ 390.9737, found 390.9744.

6-(4-Chlorophenyl)-4-hydroxy-2*H*-pyran-2-one: Yellow solid, m.p. 215–216 °C (MeOH). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.91 (br. s, 1 H), 7.87 (d, J = 8.6 Hz, 2 H), 7.58 (d, J = 8.6 Hz, 2 H), 6.80 (d, J = 1.9 Hz, 1 H), 5.41 (d, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 170.9 (C), 163.2 (C), 159.3 (C), 136.1 (C), 130.4 (C), 129.6 (CH), 127.7 (CH), 99.3 (CH), 90.3 (CH) ppm. IR (film): $\tilde{\nu}$ = 1657 cm^{-1}. MS (M^+, ES$^+$) m/z (%) 222 (100), 83 (30),

42 (52). HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{11}H_8O_3Cl$ 223.0162, found 223.0167.

4-[(2-Bromo-5-methoxybenzyl)oxy]-6-methyl-2*H*-pyran-2-one (25): See ref.[37]

4-[(2-Bromo-5-fluorobenzyl)oxy]-6-methyl-2*H*-pyran-2-one (26): White solid (0.1370 g, 57%), m.p. 111–113 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (dd, J = 8.8, 5.2 Hz, 1 H), 7.17 (dd, J = 9.1, 3.0 Hz, 1 H), 7.03–6.89 (m, 1 H), 5.90 (d, J = 2.2 Hz, 1 H), 5.48 (d, J = 2.2 Hz, 1 H), 5.05 (s, 2 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6 (C), 164.5 (C), 162.6 (C), 162.3 (d, J = 124.0 Hz, F-C), 136.0 (d, J = 7.6 Hz, F-C), 134.2 (d, J = 8.0 Hz, F-CH), 117.1 (d, J = 22.5 Hz, F-CH), 116.1 (d, J = 3.4 Hz, F-C), 115.9 (d, J = 24.4 Hz, F-CH), 100.2 (CH), 88.8 (CH), 69.3 (CH_2), 19.8 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1729 cm^{-1}. MS (M^-, ES$^+$) *m/z* (%) 311(33), 81 (100), 79 (79). HRMS (ESI, [M + H]$^-$) *m/z* calcd. for $C_{13}H_{11}O_3FBr$ 312.9876, found 312.9872.

4-[(2-Bromobenzyl)oxy]-2*H*-chromen-2-one (27): See ref.[39]

4-[(2-Iodobenzyl)oxy]-2*H*-chromen-2-one (28): White solid (0.3390 g, 73%), m.p. 158–159 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.78 (m, 2 H), 7.66–7.23 (m, 5 H), 7.18–7.05 (m, 1 H), 5.80 (s, 1 H), 5.21 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0 (C), 162.7 (C), 153.4 (C), 139.8 (CH), 136.7 (C), 132.5 (CH), 130.5 (CH), 129.1 (CH), 128.6 (CH), 124.0 (CH), 123.2 (CH), 116.8 (CH), 115.6 (C), 97.9 (C), 91.5 (CH), 74.8 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1717 cm^{-1}. MS (M^+, ES$^+$) *m/z* (%) 378 (82), 235 (52), 64 (58). HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{16}H_{12}O_3I$ 378.9831, found 378.9827.

4-[(2-Iodobenzyl)oxy]-6-methyl-2*H*-chromen-2-one (29): White solid (0.0880 g, 20%), m.p. 168–169 °C (DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.2 Hz, 1 H), 7.65 (s, 1 H), 7.56–7.31 (m, 3 H), 7.24 (t, J = 8.2 Hz, 1 H), 7.11 (t, J = 7.6 Hz, 1 H), 5.77 (s, 1 H), 5.18 (s, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0 (C), 162.9 (C), 151.6 (C), 139.8 (CH), 136.8 (C), 136.8 (C), 133.5 (CH), 130.5 (CH), 129.1 (CH), 128.6 (CH), 122.8 (CH), 116.6 (CH), 115.2 (C), 97.9 (C), 91.5 (CH), 74.8 (CH_2), 20.9 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1715 cm^{-1}. MS (M^+, ES$^+$) *m/z* (%) 392 (100), 64 (24). HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{17}H_{14}O_3I$ 392.9988, found 392.9983.

4-Hydroxy-6-methyl-2*H*-chromen-2-one: See ref.[30]

6-Ethyl-4-[(2-iodobenzyl)oxy]-2*H*-chromen-2-one (30): White solid (0.4500 g, 42%), m.p. 156–161 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.3 Hz, 1 H), 7.67 (d, J = 2.0 Hz, 1 H), 7.54–7.35 (m, 3 H), 7.30–7.21 (m, 1 H), 7.11 (td, J = 1.7, 7.6 Hz, 1 H), 5.77 (s, 1 H), 5.19 (s, 2 H), 2.71 (q, J = 7.5 Hz, 2 H), 1.26 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1 (C), 162.9 (C), 151.7 (C), 140.2 (C), 139.8 (CH), 136.8 (C), 132.4 (CH), 130.5 (CH), 129.1 (CH), 128.6 (CH), 121.7 (CH), 116.7 (CH), 115.3 (C), 97.9 (C), 91.5 (CH), 74.8 (CH_2), 28.4 (CH_2), 15.8 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1716 cm^{-1}. MS (M^+, ES$^+$) *m/z* (%) 407 (18). HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{18}H_{16}O_3I$ 407.0144, found 407.0146.

6-Ethyl-4-hydroxy-2*H*-chromen-2-one: Brown solid (1.16 g, 76%).[61]

4-[(2-Iodobenzyl)oxy]-6-methoxy-2*H*-chromen-2-one (31): Yellow solid (0.2340 g, 55%), m.p. 132–133 °C (DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.9 Hz, 1 H), 7.52–7.38 (m, 2 H), 7.33–7.20 (m, 2 H), 7.19–7.04 (m, 2 H), 5.78 (s, 1 H), 5.19 (s, 2 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7 (C), 162.9 (C), 155.9 (C), 147.8 (C), 139.8 (CH), 136.7 (C), 130.5 (CH), 129.2 (CH), 128.6 (CH), 120.2 (CH), 117.9 (CH), 115.9 (C), 105.5 (CH), 97.9 (C), 91.8 (CH), 74.8 (CH_2), 55.9 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1715 cm^{-1}. MS (M^+, ES$^+$) *m/z* (%) 408 (100), 102 (7), 64 (15). HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{17}H_{14}O_4I$ 408.9937, found 408.9929.

4-Hydroxy-6-methoxy-2*H*-chromen-2-one: See ref.[30]

7-Fluoro-4-[(2-iodobenzyl)oxy]-2*H*-chromen-2-one (32): White solid (0.0760 g, 35%), m.p. 166–167 °C (DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.85 (m, 2 H), 7.50–7.39 (m, 2 H), 7.15–6.93 (m, 3 H), 5.76 (s, 1 H), 5.20 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C), 164.1 (d, J = 209.3 Hz, C-F), 162.4 (C), 154.6 (d, J = 13.2 Hz, C-F), 139.8 (CH), 136.5 (C), 130.6 (CH), 129.3 (CH), 128.6 (CH), 125.1 (d, J = 10.3 Hz, F-CH), 112.2 (C), 112.1 (d, J = 22.7 Hz, F-CH), 104.2 (d, J = 25.6 Hz, F-CH), 98.1 (C), 90.5 (CH), 74.9 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1703 cm^{-1}. MS (M^+, ES$^+$) *m/z* (%) 396 (20), 393 (100), 64 (24), 42 (16). HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{16}H_{11}O_3FI$ 396.9737, found 396.9733.

7-Fluoro-4-hydroxy-2*H*-chromen-2-one: White solid (0.1220 g, 15%).[58]

4-[(2-Bromobenzyl)oxy]-6-methylpyridin-2(1*H*)-one (33): White solid (0.1480 g, 23%), m.p. 191 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.89 (br. s, 1 H), 7.58 (d, J = 7.9 Hz, 1 H), 7.45 (d, J = 7.4 Hz, 1 H), 7.33 (t, J = 7.4 Hz, 1 H), 7.20 (t, J = 7.7 Hz, 1 H), 5.85 (d, J = 4.0 Hz, 2 H), 5.08 (s, 2 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (C), 167.6 (C), 146.0 (C), 134.8 (C), 132.8 (CH), 129.6 (CH), 128.8 (CH), 127.6 (CH), 122.5 (C), 99.9 (CH), 95.3 (CH), 69.4 (CH_2), 18.9 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1646 cm^{-1}. MS (M^+, ES$^+$) *m/z* (%) 294 (10). HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{13}H_{13}NO_2Br$ 294.0130, found 294.0121.

4-Hydroxy-6-methylpyridin-2(1*H*)-one: White solid (0.4920 g, 50%).[62]

4-[(2-Bromobenzyl)oxy]-1,6-dimethylpyridin-2(1*H*)-one (34): See ref.[39]

4-Hydroxy-1,6-dimethylpyridin-2(1*H*)-one: See ref.[39]

4-[(2-Iodobenzyl)oxy]-1,6-dimethylpyridin-2(1*H*)-one (35): White solid (0.4210 g, 29%), m.p. 134–136 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.9 Hz, 1 H), 7.44–7.31 (m, 2 H), 7.03 (td, J = 7.5, 1.8 Hz, 1 H), 5.93 (d, J = 2.6 Hz, 1 H), 5.88 (d, J = 2.4 Hz, 1 H), 4.96 (s, 2 H), 3.47 (s, 3 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9 (C), 165.3 (C), 146.4 (C), 139.5 (CH), 137.8 (C), 129.8 (CH), 128.7 (CH), 128.4 (CH), 100.8 (CH), 97.5 (C), 95.9 (CH), 73.7 (CH_2), 30.6 (CH_3), 20.9 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1644 cm^{-1}. MS (M^+, ES$^+$) *m/z* (%) 356 (18). HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{14}H_{15}NO_2I$ 356.0147, found 356.0144.

4-Hydroxy-1,6-dimethylpyridin-2(1*H*)-one: See ref.[39]

4-[(2-Bromobenzyl)oxy]-6-methyl-1-phenylpyridin-2(1*H*)-one (36): White solid (0.1101 g, 20%), m.p. 143 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (dd, J = 8.0, 1.2 Hz, 1 H), 7.53–7.40 (m, 4 H), 7.38–7.33 (td, J = 7.5, 1.2 Hz, 1 H); 7.24–7.18 (m, 3 H) 5.99 (d, J = 2.6 Hz, 1 H), 5.96 (dd, J = 2.6, 0.8 Hz, 1 H), 5.09 (s, 2 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C), 165.4 (C), 146.4 (C), 138.6 (C), 134.9 (C), 132.9 (CH), 129.7 (CH), 129.6 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 122.7 (CH), 100.8 (CH), 96.3 (CH), 69.5 (CH_2), 21.5 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1661 cm^{-1}. HRMS (ESI, [M + H]$^+$) *m/z* calcd. for $C_{19}H_{17}NO_2Br$ 370.0443, found 370.0427.

4-Hydroxy-6-methyl-1-phenylpyridin-2(1*H*)-one: White solid (0.3400 g, 21%).[63]

1-Benzyl-4-[(2-bromobenzyl)oxy]-6-methylpyridin-2(1*H*)-one (37): See ref.[39]

1-Benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one: See ref.[39]

1-Benzyl-4-[(2-iodobenzyl)oxy]-6-methylpyridin-2(1*H*)-one (38): White solid (0.2200 g, 55%), m.p. 129–134 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (dd, J = 7.9, 0.7 Hz, 1 H), 7.47–7.10 (m, 7 H), 7.04 (td, J = 7.6, 1.8 Hz, 1 H), 6.01 (d, J = 2.7 Hz, 1 H), 5.88 (d, J = 2.3 Hz, 1 H), 5.29 (s, 2 H), 5.00 (s, 2 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2 (C), 165.3 (C), 146.7 (C), 139.5 (CH), 137.8 (C), 136.8 (C), 129.9 (CH), 128.8 (CH), 128.4 (CH), 127.3 (CH), 126.4 (CH), 101.4 (CH), 97.5 (C), 96.1 (CH), 73.8 (CH_2), 46.6 (CH_2), 20.6 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1653 cm^{-1}. MS (M^+, ES^+) m/z (%) 432(28). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{20}H_{19}INO_2$ 432.0460, found 432.0444.

1-Benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one: See ref.[39]

4-[(2-Bromobenzyl)oxy]-1-(4-methoxyphenyl)-6-methylpyridin-2-(1*H*)-one (39): White solid (0.1250 g, 24%), m.p. 189–190 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (dd, J = 7.9, 1.0 Hz, 1 H), 7.48 (dd, J = 7.6, 1.4 Hz, 1 H), 7.35 (td, J = 7.5, 1.0 Hz, 1 H), 7.21 (td, J = 7.7, 1.6 Hz, 1 H), 7.08 (m, 2 H), 7.02–6.97 (m, 2 H), 5.99 (d, J = 2.6 Hz, 1 H), 5.94 (d, J = 2.4 Hz, 1 H), 5.09 (s, 2 H), 3.84 (s, 3 H), 1.94 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (C), 165.7 (C), 159.5 (C), 146.8 (C), 134.9 (C), 132.9 (CH), 131.2 (C), 129.7 (CH), 129.2 (CH), 129.0 (CH), 127.6 (CH), 122.7 (C), 115.0 (CH), 100.1 (CH), 96.3 (CH), 69.5 (CH_2), 55.5 (CH_3), 21.6 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1660 cm^{-1}. MS (M^+, ES^+) m/z (%) 432 (28). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{20}H_{19}NO_3Br$ 400.0563, found 400.0548.

4-Hydroxy-1-(4-methoxyphenyl)-6-methylpyridin-2(1*H*)-one: White solid (0.534 g, 29%).[64]

4-[(2-Bromobenzyl)oxy]-1-(4-fluorophenyl)-6-methylpyridin-2(1*H*)-one (40): White solid (0.1280 g, 23%), m.p. 172 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (dd, J = 7.6, 1.6 Hz, 1 H), 7.60 (dd, J = 7.9, 1.2 Hz, 1 H), 7.35 (td, J = 7.5, 1.2 Hz, 1 H), 7.23 (dd, J = 7.7, 1.8 Hz, 1 H), 7.19 (d, J = 0.4 Hz, 2 H), 7.17 (s, 2 H), 5.98–5.95 (m, 2 H), 5.09 (s, 2 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C), 165.4 (C), 162.4 (d, J = 249 Hz, F-C), 146.3 (C), 134.8 (C), 134.4 (d, J = 3.5 Hz, F-C), 132.9 (CH), 130.1 (d, J = 8.76 Hz, F-CH), 129.8 (CH), 129.1 (CH), 127.6 (CH), 122.8 (C), 116.8 (d, J = 23 Hz, F-CH), 101.1 (CH), 96.3 (CH), 69.5 (CH_2), 21.5 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1663 cm^{-1}. MS (M^+, ES^+) m/z (%) 388 (22). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{19}H_{16}NO_2FBr$ 388.0348, found 388.0347.

1-(4-Fluorophenyl)-4-hydroxy-6-methylpyridin-2(1*H*)-one: White solid (0.4190 g, 24%), m.p. 258–260 °C (hexanes). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.61 (br. s, 1 H), 7.35–7.20 (m, 4 H), 5.89 (dd, J = 2.5, 0.8 Hz, 1 H), 5.55 (d, J = 2.5 Hz, 1 H), 3.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.9 (C), 164.6 (C), 163.5 (d, J = 245.1 Hz, F-C), 147.5 (C), 135.5 (d, J = 3.19 Hz, F-C), 131.3 (d, J = 8.8 Hz, F-CH), 116.4 (d, J = 22.8 Hz, F-CH), 100.6 (CH), 96.5 (CH), 21.5 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1649 cm^{-1}. MS (M^+, ES^+) m/z (%) 220(30). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{12}H_{11}NO_2F$ 220.0774, found 220.0764.

4-[(2-Iodobenzyl)oxy]-1-methylquinolin-2(1*H*)-one (41): White solid (0.1660 g, 42%), m.p. 162–163 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.1 Hz, 1 H), 7.91 (d, J = 8.1 Hz, 1 H), 7.61 (t, J = 8.0 Hz, 1 H), 7.53 (dd, J = 7.6, 1.5 Hz, 1 H), 7.45–7.32 (m, 2 H), 7.25 (t, J = 7.6 Hz, 1 H), 7.08 (t, J = 7.6 Hz, 1 H), 6.15 (s, 1 H), 5.16 (s, 2 H), 3.69 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1 (C), 161.3 (C), 139.9 (C), 139.6 (CH), 137.7 (C), 131.3 (CH), 130.0 (CH), 128.8 (CH), 128.5 (CH), 123.6 (CH), 121.7 (CH), 116.4 (C), 114.1 (CH), 98.0 (CH), 74.2 (CH_2), 29.1 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1630 cm^{-1}. MS (M^+, ES^+) m/z (%) 391 (10). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{17}H_{15}INO_2$ 392.0141, found 392.0148.

4-Hydroxy-1-methylquinolin-2(1*H*)-one: See ref.[60]

General Procedure for the Coupling Reaction. Compounds 2, 14–24 and 42–56: A solution of pyrone, coumarin, pyridone or quinolone (1.0 equiv.), $Pd_2(dba)_3$ (2 mol-%), pivalic acid (30 mol-%), triphenylphosphine (4 mol-%) and Na_2CO_3 (3.0 equiv.) in *N*-methyl-2-pyrrolidone (3.0 mL/mmol starting material) was stirred in a Schlenk tube under N_2 at 129 °C. After 3 h, water (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with 1 M HCl (1 × 20 mL), water (3 × 10 mL), brine (1 × 20 mL), dried and the solvents evaporated. The crude obtained was purified by column chromatography (SiO_2, DCM).

3-Methylpyrano[4,3-*c*]isochromen-1(6*H*)-one (2): White solid (0.0480 g, 78%).[39]

3-Phenylpyrano[4,3-*c*]isochromen-1(6*H*)-one (14): Yellow solid (0.0368 g, 99%).[39]

3-(Thiophen-2-yl)pyrano[4,3-*c*]isochromen-1(6*H*)-one (15): Orange solid (0.0711 g, 93%), m.p. 165–167 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (d, J = 7.9 Hz, 1 H), 7.64 (d, J = 3.1 Hz, 1 H), 7.48 (d, J = 4.7 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.30–7.25 (m, 1 H), 7.14–7.06 (m, 2 H), 6.40 (s, 1 H), 5.28 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (C), 160.3 (C), 155.7 (C), 134.8 (C), 129.3 (CH), 129.0 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.0 (C), 126.6 (C),124.2 (CH), 123.8 (CH), 100.7 (C), 96.5 (CH), 69.4 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1711 cm^{-1}. MS (M^+, ES^+) m/z (%) 282 (10), 42 (100). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{16}H_{11}O_3S$ 283.0429, found 283.0415.

3-(Furan-2-yl)pyrano[4,3-*c*]isochromen-1(6*H*)-one (16): Yellow solid (0.0342 g, 98%), m.p. 153–155 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, J = 8.3 Hz, 1 H) 7.50 (d, J = 1.1 Hz, 1 H), 7.42–7.37 (m, 1 H), 7.30–7.25 (m, 1 H), 7.08–7.05 (m, 2 H), 6.57–6.55 (m, 1 H), 6.48 (s, 1 H), 5.28 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (C), 160.2 (C), 151.9 (C), 146.3 (C), 127.7 (C), 127.0 (C), 145.1 (CH), 129.0 (CH), 127.7 (CH), 124.2 (CH), 123.8 (CH), 112.6 (CH), 112.5 (CH), 100.9 (C), 95.9 (CH), 69.4 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1712 cm^{-1}. MS (M^+, ES^+) m/z (%) 266 (12), 42 (100). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{16}H_{11}O_4$ 267.0657, found 267.0652.

3-[4-(Trifluoromethyl)phenyl]pyrano[4,3-*c*]isochromen-1(6*H*)-one (17): Yellow solid (0.0208 g, 96%).[39]

3-(*o*-Tolyl)pyrano[4,3-*c*]isochromen-1(6*H*)-one (18): White solid (0.0220 g, 58%), m.p. 124–126 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, J = 7.7 Hz, 1 H), 7.58–7.49 (m, 1 H), 7.49–7.11 (m, 5 H), 7.07 (d, J = 7.7 Hz, 1 H), 6.25 (s, 1 H), 5.30 (s, 2 H), 2.52 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8 (C), 162.3 (C), 161.2 (C), 136.8 (C), 131.8 (C), 131.4 (CH), 130.5 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 127.8 (CH), 127.1 (C), 126.5 (C), 124.3 (CH), 123.8 (CH), 101.7 (CH), 100.7 (C), 69.4 (CH_2), 20.9 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1712 cm^{-1}. HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{19}H_{15}O_3$ 291.1017, found 291.1021.

3-(4-Methoxyphenyl)pyrano[4,3-*c*]isochromen-1(6*H*)-one (19): Yellow solid (0.0250 g, 81%), m.p. >230 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 7.6 Hz, 1 H), 7.81 (d, J = 10.0 Hz, 2 H), 7.39 (t, J = 7.9 Hz, 1 H), 7.26 (t, J = 7.9 Hz, 1 H), 7.07 (d, J = 7.6 Hz, 1 H), 6.97 (d, J = 10.0 Hz, 2 H), 6.45 (s, 1 H),

5.28 (s, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (C), 162.0 (C), 161.1 (C), 160.3 (C), 129.0 (CH), 127.5 (CH), 127.4 (CH), 127.0 (C), 126.7 (C), 124.1 (CH), 123.8 (CH), 123.5 (C), 114.4 (CH), 100.2 (C), 95.9 (CH), 69.4 (CH_2), 55.5 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1706 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 306 (64), 262 (100), 206 (38). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{19}H_{15}O_4$ 307.0970, found 307.0973.

3-(3,4,5-Trimethoxyphenyl)pyrano[4,3-*c*]isochromen-1(6*H*)-one (20): (0.0179 g, 54%).[39]

3-Isobutylpyrano[4,3-*c*]isochromen-1(6*H*)-one (22): Yellow oil (0.0144 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 7.9 Hz, 1 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 7.04 (d, *J* = 7.4 Hz, 1 H), 5.89 (s, 1 H), 5.24 (s, 2 H), 2.35 (d, *J* = 7.2 Hz, 2 H), 2.18–2.09 (m, 1 H), 0.97 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (C), 165.4 (C), 161.7 (C), 128.8 (CH), 127.5 (CH), 126.8 (C), 126.6 (C), 124.0 (CH), 123.7 (CH), 100.4 (CH), 100.0 (C), 69.3 (CH_2), 43.0 (CH_2), 26.8 (CH), 22.2 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1708 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 256 (8). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{16}H_{17}O_3$ 257.1174, found 257.1178.

3-(4-Chlorophenyl)pyrano[4,3-*c*]isochromen-1(6*H*)-one (24): Yellow solid (0.0280 g, 90%), m.p. 182–184 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 2 H), 7.53–7.22 (m, 4 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 6.31 (s, 1 H), 5.29 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8 (C), 160.6 (C), 158.8 (C), 137.3 (C), 129.4 (C), 129.3 (CH), 129.0 (CH), 128.4 (C), 127.9 (CH), 127.1 (C), 126.9 (CH), 124.3 (CH), 123.8 (CH), 101.4 (C), 97.8 (CH), 69.5 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1694 cm^{-1}. HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{18}H_{12}O_3Cl$ 311.0475, found 311.0471.

8-Methoxy-3-methylpyrano[4,3-*c*]isochromen-1(6*H*)-one (42): White solid (0.0023 g, 8%).[37] This compound could not be fully separated from the residual starting material by chromatographic methods.

8-Fluoro-3-methylpyrano[4,3-*c*]isochromen-1(6*H*)-one (43): White solid (0.0200 g, 54%), m.p. 150–154 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (dd, *J* = 8.8, 5.6 Hz, 1 H), 7.05 (td, *J* = 8.8, 2.7 Hz, 1 H), 6.77 (dd, *J* = 8.3, 2.7 Hz, 1 H), 5.92 (d, *J* = 0.9 Hz, 1 H), 5.22 (s, 2 H), 2.27 (d, *J* = 0.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6 (C), 163.6 (C), 161.6 (d, *J* = 156.0 Hz, C-F), 160.4 (C), 129.0 (d, *J* = 7.4 Hz, F-C), 126.2 (d, *J* = 8.0 Hz, F-CH), 122.5 (C), 115.5 (d, *J* = 20.9 Hz, F-CH), 111.1 (d, *J* = 23.2 Hz, F-CH), 100.1 (CH), 99.4 (C), 68.8 (CH_2), 20.1 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1703 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 233 (80), 102 (35), 64 (48). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{13}H_{10}O_3F$ 233.0614, found 233.0619.

8-Fluoro-1-methylpyrano[4,3-*c*]isochromen-3(6*H*)-one (44): White solid (0.0131 g, 35%). 178–180 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 8.7, 5.1 Hz, 1 H), 7.14 (td, *J* = 8.6, 2.7 Hz, 1 H), 6.97 (dd, *J* = 8.1, 2.6 Hz, 1 H), 5.77 (s, 1 H), 5.02 (s, 2 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4 (C), 163.3 (C), 162.7 (C), 160.7 (C), 159.2 (C), 133.7 (d, *J* = 7.5 Hz, F-C), 127.6 (d, *J* = 8.2 Hz, F-CH), 122.3 (C), 115.9 (d, *J* = 21.8 Hz, F-CH), 112.6 (d, *J* = 22.6 Hz, F-CH), 93.7 (CH), 68.9 (CH_2), 20.5 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1722 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 232 (100), 102 (69), 64 (34), 42 (14). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{13}H_{10}O_3F$ 233.0614, found 233.0609.

Isochromeno[4,3-*c*]chromen-11(6*H*)-one (45): White solid (0.0281 g, 86%).[39]

3-Methylisochromeno[4,3-*c*]chromen-11(6*H*)-one (46): Yellow solid (0.0198 g, 76%).[65]

3-Ethyl-6*H*,11*H*-isochromeno[4,3-*c*]chromen-11-one (47): Orange solid (0.0500 g, 71%), m.p. 72–75 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 7.9, 0.8 Hz, 1 H), 7.64 (d, *J* = 2.0 Hz, 1 H), 7.43–7.18 (m, 4 H), 7.14–7.06 (m, 1 H), 5.36 (s, 2 H), 2.70 (q, *J* = 7.6 Hz, 2 H), 1.27 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3 (C), 160.3 (C), 151.2 (C), 140.2 (C), 132.5 (CH), 129.0 (CH), 128.1 (CH), 127.4 (C), 126.8 (CH), 124.9 (C), 123.9 (CH), 121.5 (CH), 116.3 (CH), 114.9 (C), 102.4 (C), 69.7 (CH_2), 28.4 (CH_2), 15.6 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1710 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 279 (2). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{18}H_{15}O_3$ 279.1021, found 279.1019.

3-Methoxyisochromeno[4,3-*c*]chromen-11(6*H*)-one (48): Yellow solid (0.0282 g, 82%), m.p. 178–179 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 7.8 Hz, 1 H), 7.48–7.22 (m, 4 H), 7.19–7.07 (m, 2 H), 5.40 (s, 2 H) 3.87 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9 (C), 160.3 (C), 156.0 (C), 147.5 (C), 129.0 (CH), 128.2 (CH), 127.4 (C), 126.7 (C), 125.0 (CH), 123.9 (CH), 121.0 (CH), 117.7 (CH), 115.5 (C), 104.5 (CH), 102.8 (C), 69.7 (CH_2), 55.9 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1713 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 280 (100), 42 (10). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{17}H_{13}O_4$ 281.0814, found 281.0810.

2-Fluoroisochromeno[4,3-*c*]chromen-11(6*H*)-one (49): White solid (0.0190 g, 71%), m.p. 178–179 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 7.9, 0.8 Hz, 1 H), 7.86 (ddd, *J* = 8.4, 6.1, 0.7 Hz, 1 H), 7.45–7.38 (m, 1 H), 7.32 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.21–6.97 (m, 3 H), 5.41 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C), 163.4 (d, *J* = 279.9 Hz, C-F), 160.8 (C), 159.8 (C), 154.5 (d, *J* = 13.2 Hz, C-F), 129.0 (CH), 128.3 (CH), 127.2 (C), 126.8 (C), 125.1 (d, *J* = 10.4 Hz, F-CH), 124.8 (CH), 123.9 (CH), 112.3 (d, *J* = 23.0 Hz, F-CH), 111.8 (C), 104.0 (d, *J* = 25.6 Hz, F-CH), 69.8 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 1704 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 268 (50), 235 (100), 102 (44), 64 (50), 42 (38). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{16}H_{10}O_3F$ 269.0614, found 269.0611.

3-Methyl-2,6-dihydro-1*H*-isochromeno[4,3-*c*]pyridin-1-one (50): White solid (0.0250 g, 66%), m.p. 187–188 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.03 (br. s, 1 H), 8.79 (d, *J* = 7.9 Hz, 1 H), 7.38 (t, *J* = 7.5 Hz, 1 H), 7.25 (t, *J* = 7.3 Hz, 1 H), 7.09 (d, *J* = 7.4 Hz, 1 H), 5.90 (s, 1 H), 5.17 (s, 2 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3 (C), 163.8 (C), 145.3 (C), 128.6 (CH), 128.5 (C), 128.3 (C), 126.9 (CH), 124.3 (CH), 123.7 (CH), 105.4 (C), 99.8 (CH), 68.9 (CH_2), 19.1 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1728 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 213 (6). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{13}H_{12}NO_2$ 214.0868, found 214.0869. This product was subject to some degradation over time.

2,3-Dimethyl-2,6-dihydro-1*H*-isochromeno[4,3-*c*]pyridin-1-one (51):[66] White solid (0.0300 g, 74%).[39]

3-Methyl-2-phenyl-2,6-dihydro-1*H*-isochromeno[4,3-*c*]pyridin-1-one (52): White solid (0.0320 g, 82%), m.p. 172–174 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (dd, *J* = 7.9, 0.9 Hz, 1 H), 7.56–7.43 (m, 3 H), 7.33–7.18 (m, 4 H), 7.06 (dd, *J* = 7.3, 0.8 Hz, 1 H), 5.98 (d, *J* = 0.8 Hz, 1 H), 5.18 (s, 2 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4 (C), 162.6 (C), 146.2 (C), 138.9 (C), 129.7 (CH), 128.7 (CH), 128.5 (CH), 128.4 (C), 128.3 (CH), 126.9 (CH), 124.5 (CH), 123.5 (CH), 121.8 (C), 105.9 (C), 100.3 (CH), 69.0 (CH_2), 21.7 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1651 cm^{-1}. MS (M^+, ES^+) *m/z* (%) 289 (100). HRMS (ESI, $[M + H]^+$) *m/z* calcd. for $C_{19}H_{16}NO_2$ 290.1181, found 290.1171.

2-Benzyl-3-methyl-2,6-dihydro-1*H*-isochromeno[4,3-*c*]pyridin-1-one (53):[66] Yellow solid (0.0500 g, 77%).[39]

2-(4-Methoxyphenyl)-3-methyl-2,6-dihydro-1*H*-isochromeno[4,3-*c*]-pyridin-1-one (54): Orange solid (0.0254 g, 64%), m.p. 172–174 °C

(hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (dd, J = 7.9, 0.9 Hz, 1 H), 7.30 (td, J = 7.7, 1.4 Hz, 1 H), 7.21 (td, J = 7.4, 1.3 Hz, 1 H), 7.17–7.12 (m, 2 H), 7.08–7.00 (m, 3 H), 5.96 (d, J = 0.8 Hz, 1 H), 5.17 (s, 2 H), 3.86 (s, 3 H), 1.98 (d, J = 0.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3 (C), 162.8 (C), 159.6 (C), 146.7 (C), 131.5 (C), 129.2 (CH), 128.5 (CH), 127.8 (C), 126.8 (CH), 124.5 (CH), 123.5 (CH), 115.0 (CH), 105.9 (C), 100.2 (CH), 69.0 (CH_2), 55.5 (CH_3), 21.8 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1651 cm^{-1}. MS (M^+, ES^+) m/z (%) 319 (100). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{20}H_{18}NO_3$ 320.1287, found 320.1286.

2-(4-Fluorophenyl)-3-methyl-2,6-dihydro-1*H*-isochromeno[4,3-*c*]-pyridin-1-one (55): Yellow solid (0.0290 g, 80%), m.p. 187–188 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (d, J = 7.8 Hz, 1 H), 7.30 (t, J = 7.6 Hz, 1 H), 7.24–7.18 (m, 5 H), 7.06 (d, J = 7.3 Hz, 1 H), 5.98 (s, 1 H), 5.18 (s, 2 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4 (C), 162.6 (C), 162.4 (d, J = 248.3 Hz, F-C), 146.1 (C), 134.8 (d, J = 3.02 Hz, F-C), 130.1 (d, J = 8.3 Hz, F-CH), 128.6 (CH), 128.3 (C), 127.8 (C), 126.9 (CH), 124.5 (CH), 123.6 (CH), 116.8 (d, J = 23.4 Hz, F-CH), 105.9 (C), 100.6 (CH), 69.1 (CH_2), 21.7 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 1651 cm^{-1}. MS (M^+, ES^+) m/z (%) 307 (100). HRMS (ESI, $[M + H]^+$) m/z calcd. for for $C_{19}H_{15}FNO_2$ 308.1087, found 308.1081.

12-Methyl-6*H*-isochromeno[4,3-*c*]quinolin-11(12*H*)-one (56): Yellow solid (0.0400 g, 60%).[38]

Mechanistic Studies

($Pd\{[C_7H_6O\text{-}2\text{-}(C_9H_5O_2)]\}I(PPh_3)_2$) (57). A Schlenk tube was heated under vacuum and refilled with N_2 three times. $Pd_2(dba)_3$ (1.0 equiv.) and PPh_3 (8.0 equiv.) were then added. The Schlenk was then evacuated and refilled with N_2 three times. The vessel was then left under vacuum overnight. The Schlenk tube was refilled with N_2. 10 mL freshly distilled THF was added giving a brown solution. The reaction was stirred at ambient temperature for 15 min, resulting in a dark green solution. 4-[(2-iodobenzyl)oxy]-2 coumarin **28** (1 equiv.) was added to the THF solution. The coumarin dissolved and the solution remained dark green. The reaction mixture was heated to 70 °C and stirred at this temperature for 1 h. The vessel was cooled to room temperature and the reaction mixture concentrated under reduced pressure yielding a green residue. 5 mL Et_2O was added to the residue which dissolved. The solution was stored at 5–8 °C for 2 h. The resulting grey precipitate was isolated by suction filtration and dried under vacuum overnight to yield a grey powder **57** in 90% yield (0.0679 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.41 (m, 13 H), 7.35–7.14 (m, 20 H), 7.08–7.00 (m, 1 H), 6.87–6.81 (m, 1 H), 6.64–6.57 (m, 2 H), 6.37–6.30 (m, 1 H), 5.64 (s, 1 H), 4.85 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5 (C), 162.9 (C), 161.3 (C), 153.3 (C), 137.1 (C), 136.3 (t, $J_{P\text{-}C}$ = 5 Hz, CH), 134.7 (t, $J_{P\text{-}C}$ = 6 Hz, CH), 132.1 (CH), 131.9 (C), 131.6 (C), 131.3 (C), 130.0 (CH), 128.7 (CH), 127.9 (t, $J_{P\text{-}C}$ = 5 Hz, CH), 127.4 (CH), 123.5 (CH), 123.2 (CH), 123.0 (CH), 116.6 (CH), 115.7 (C), 90.4 (CH), 74.3 (CH_2) ppm. $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): δ = 22.8 ppm.

4-(Benzyloxy)-2*H*-chromen-2-one (*unhalogenated* variant of 28): Usual benzylation procedure from commercially available 4-hydroxy-2-coumarin and benzyl bromide. White solid (0.1510, 19%), m.p. 164–167 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, J = 1.4, 8.0 Hz, 1 H), 7.62–7.50 (m, 1 H), 7.49–7.21 (m, 7 H), 5.78 (s, 1 H), 5.20 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3 (C), 162.8 (C), 153.4 (C), 134.4 (C), 132.5 (CH), 128.9 (CH), 128.9 (CH), 127. 8 (CH), 123.9 (CH), 123.2 (CH), 116.8 (CH), 115.7 (C), 91.2 (CH), 71.2 (CH_2). IR (film): $\tilde{\nu}$ = 1730 cm^{-1}. MS (M^+, ES^+) m/z (%) 253 (94). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{16}H_{13}O_3$ 253.0857, found 253.0865.

Procedure for the Intermolecular Coupling Reaction. Compound 59: A solution of the coumarin **58** (2.0 equiv.), 2′-($PdPCy_3Cl$)-2-aminobiphenyl (**60**) (5 mol-%), pivalic acid (30 mol-%), K_2CO_3 (1.5 equiv.) and bromobenzene (1.0 equiv.) in toluene (3.0 mL/mmol starting material) was stirred in a Schlenk tube under N_2 at 140 °C. After 2.5 d, water (20 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried and the solvents evaporated. The crude obtained was purified by column chromatography (SiO_2, Hex/EtOAc, 99.5:0.5).

4-Methoxy-2*H*-chromen-2-one (58): See ref.[67]

4-Methoxy-3-phenyl-2*H*-chromen-2-one (59): White solid (0.050 g, 33%), m.p. 117–119 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (dd, J = 7.9, 1.2 Hz, 1 H), 7.59–7.53 (td, J = 7.2, 1.5 Hz, 1 H), 7.49–7.43 (m, 4 H), 7.42–7.39 (m, 1 H), 7.36 (dd, J = 8.4, 0.8 Hz, 1 H), 7.33–7.28 (m, 1 H), 3.56 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (C), 161.8 (C), 151.4 (C), 131.4 (C), 131.0 (CH), 130.0 (CH), 127.4 (CH), 127.3 (CH), 123.0 (CH), 122.9 (CH), 116.7 (C), 115.5 (CH), 110.0 (C), 60.2 (CH_3) ppm. MS (M^+, ES^+) m/z (%) 253 (100). HRMS (ESI, $[M + H]^+$) m/z calcd. for $C_{16}H_{13}O_3$ 253.0865, found 253.0869.

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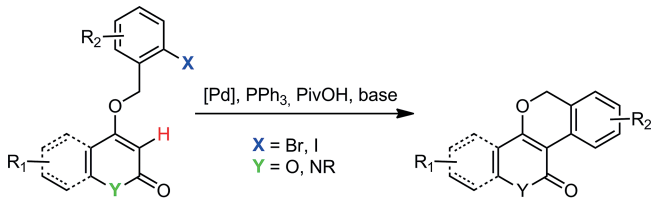

Direct arylation conditions optimised and applied to pyrones

Direct Arylation represents a favourable alternative to traditional cross-coupling reactions. However there are limited reports on application to more delicate, privileged biological motifs. Herein the intramolecular Pd/PivOH promoted direct arylation of 2-pyrones, 2-coumarins, 2-pyridones and 2-quinolones is reported. One intermolecular example is included along with preliminary mechanistic investigations.

Keywords: Synthetic methods / Homogeneous catalysis / Palladium / C–C bond formation / Arylation / Oxygen heterocycles

