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FULL PAPER

Regioselective Chlorination and Suzuki-Miyaura Cross-Coupling of 4-Alkoxy-2-Coumarins, 2-Pyrones and Related Heterocycles

Aisling M. Prendergast[a] and Gerard P. McGlacken*[a]

Abstract: Chlorination of the 2-coumarin framework is achieved using trichloroisocyanuric acid in ethyl acetate, which offers several advantages over *N*-chlorosuccinimide, particularly with respect to cost-effectiveness and toxicity. The Suzuki-Miyaura cross-coupling of the chlorinated 4-alkoxy-2-coumarins with a range of aryl and heteroaryl boronic acids using $Pd(OAc)_2$ and SPhos in an environmentally benign solvent was developed, with yields up to 99%. Sensitive functional groups such as aldehydes and nitriles are tolerated, and the conditions were demonstrated on gram scale. Extension of the cross-coupling methodology to the related 2-pyrone, 2-pyridone and 2-quinolone moieties was highly successful and yields of up to 96% were achieved, which is the first time cross-coupling conditions have been demonstrated to be general across this range of heterocyclic substrates. Demethylation of the Suzuki-Miyaura products allows access to 3-aryl-4-hydroxy-2-coumarins.

Introduction

The formation of aryl-heteroaryl (Ar-HetAr) bonds is an important transformation in organic synthesis[1] due to the abundance of the Ar-HetAr moiety in natural products and pharmaceuticals.[2] Despite the development of modern methods such as direct arylation,[3] the Suzuki-Miyaura reaction remains, by far, the most common cross-coupling reaction for large-scale synthesis (>100 mmol scale),[4] and usually involves the cross-coupling of an organohalide and an organoboron species.[5] Iodides and bromides have been largely preferred as the organohalide partner due to their propensity for oxidative addition. However, organochlorides are more attractive substrates from a cost and availability viewpoint.[6] In addition, top pharmaceutical companies are seeking to execute these reactions in more benign solvents.[7] This report focuses on the application of these principles to regioselective chlorination and Suzuki-Miyaura cross-coupling of 2-coumarins (Figure 1), which as a substrate class, has been shown to display a remarkable biological profile including anticancer, antimicrobial, anti-inflammatory, antithrombotic and antipsychotic effects.[8] Previous work on Suzuki-Miyaura reactions at the C-3 position of 4-alkoxy-2-coumarins has involved bromides.[9]

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Supporting Information for this article is given via a link at the end of the document. It contains ^{1}H, ^{13}C and ^{19}F spectra for all novel compounds, key intermediates and final products; optimization table for Suzuki-Miyaura cross-coupling of **4a**.

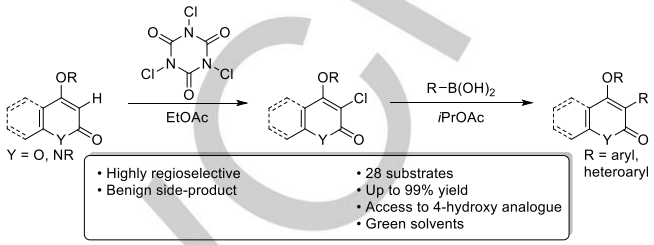
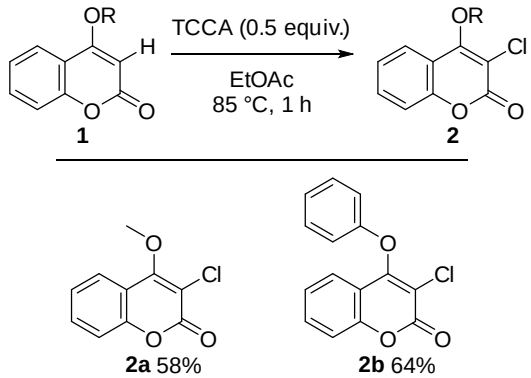


Figure 1. Regioselective chlorination and Suzuki-Miyaura cross-coupling.

Results and Discussion

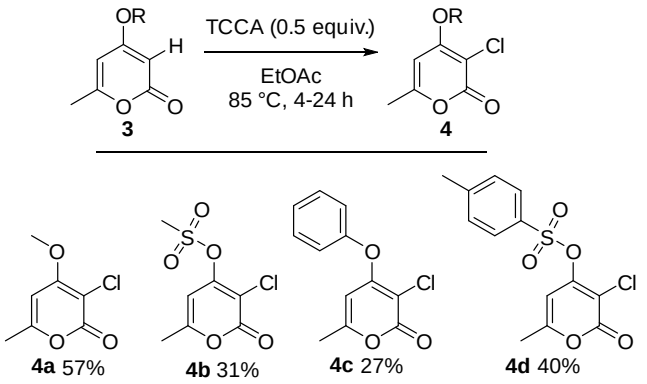
While *N*-chlorosuccinimide (NCS) is the reagent of choice in many cases for introducing chloride to heteroaromatic compounds, trichloroisocyanuric acid (TCCA) is more atom-economic, more soluble, less toxic and cheaper.[10] Using TCCA, the optimal conditions for the chlorination of 2-coumarins from **1** to **2** were found to involve refluxing in EtOAc for 1 h (Scheme 1). While TCCA is soluble in the reaction mixture, the by-product cyanuric acid is largely insoluble. Thus the products can be purified via a simple filtration, followed by recrystallization from EtOH.[11] The use of TCCA to chlorinate 2-coumarins represents a significant improvement in efficiency over the previously reported conditions,[12] for example, 2-coumarin **2b** was previously synthesized in 67% isolated yield after 72 h at 55 °C using a combination of NCS and trifluoroacetic acid (TFA)[12] whereas here, using TCCA, **2b** can be produced in 64% isolated yield after 1 h at 85 °C.



Scheme 1. Chlorination of 2-coumarins.

This procedure can be extended to the related 2-pyrone framework (Scheme 2).[11] 2-Pyrones are a less robust substrate than the corresponding 2-coumarins, which may explain the lower

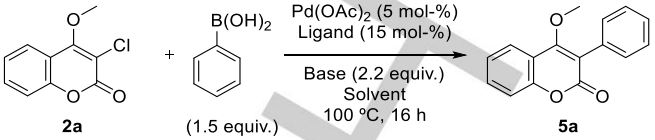
yields. It is pleasing, however, that chlorination proceeds cleanly, even in the presence of mesyl (**4b**) and tosyl (**4d**) groups.



Scheme 2. Chlorination of 2-pyrones.

With the desired 3-chloro-2-coumarins **2** in hand, we sought reaction conditions which would allow the Suzuki-Miyaura reaction to occur at this challenging site[13] (Table 1). Suzuki-Miyaura reactions involving a chloride at the C-3 position of 2-coumarins have been reported for 4-hydro-[14] and 4-alkyl-2-coumarins,[15] however, we have observed that the electronic changes caused by introducing 4-alkoxy groups can cause these reported conditions to fail.[16] We used a solvent selection guide to limit our solvent choices to greener options.[7b] The use of EtOH as solvent (Table 1, entry 1) allowed the full consumption of starting material **2a**, with a low, 22% yield of desired product **5a** along with a 45% yield of dechlorinated side-product **1a**. Switching to an aprotic polar solvent, 2-MeTHF gave a 54% yield of the desired product without significant dechlorination (Table 1, entry 2). The optimal solvent was determined to be isopropyl acetate (*i*PrOAc) which gave **5a** in 80% yield (Table 1, entry 3). Changing to a palladium(0) source reduced both conversion and yield (Table 1, entry 4), while changing to the bulkier RuPhos ligand (Table 1, entry 5) or PPh_3 (Table 1, entry 6) offered no advantages over SPhos. Employing KOAc as base hindered the reaction (Table 1, entry 7). The best conditions for the reaction were found when K_2CO_3 was used as the base, which gave 100% conversion to the desired product in 82% isolated yield (Table 1, entry 8). With our optimized conditions in hand, we sought to demonstrate the variety of aryl boronic acids which were tolerated by our reaction conditions (Scheme 3). A range of *para*-substituted phenylboronic acids were tested, and no significant electronic effects were observed, with *p*-OMe phenylboronic acid giving **5c** in 79% yield, while *p*-CF_3 phenylboronic acid gave **5d** in 76% yield.

Table 1. Optimisation of reaction conditions.

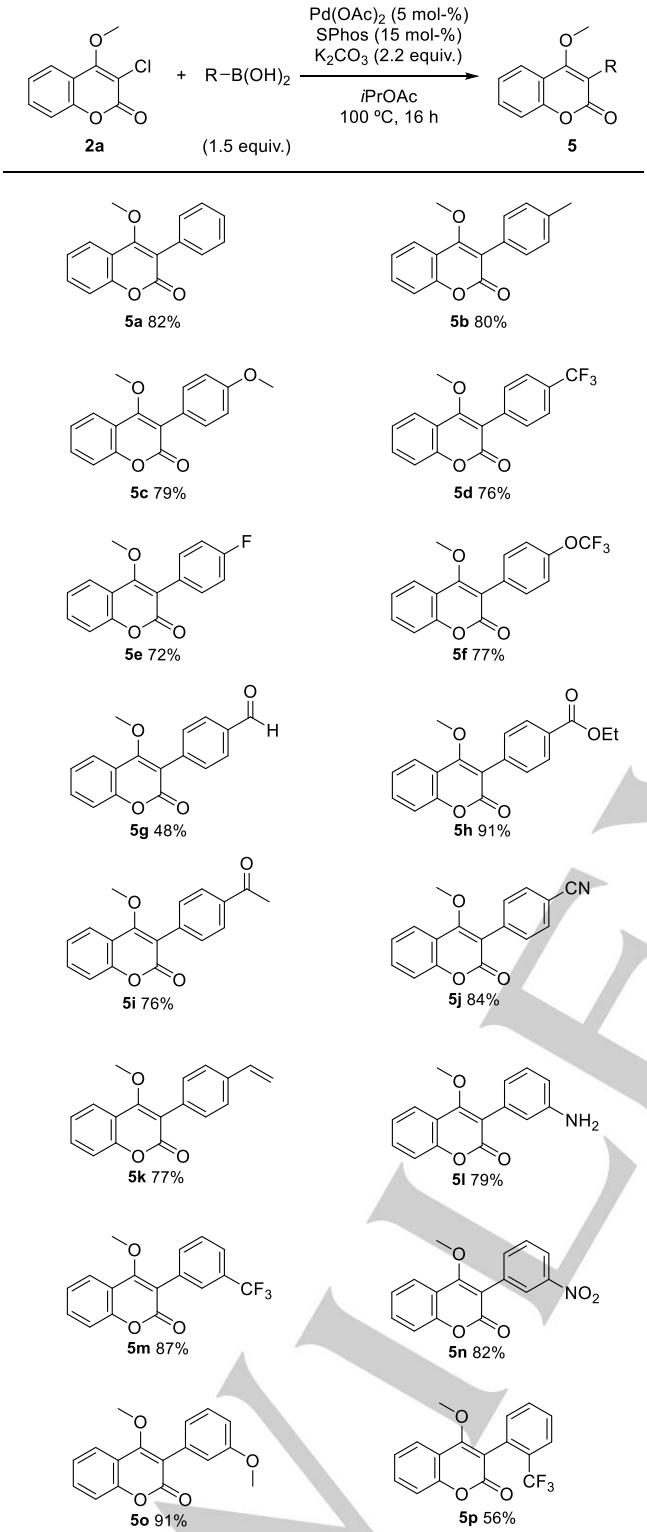


2a (1.5 equiv.) **5a**

Entry	Ligand	Base	Solvent	Conversion (%)	Yield (%)[a]
1	SPhos	Na_2CO_3	EtOH[b]	100	22[c]
2	SPhos	Na_2CO_3	2-MeTHF[b]	63	54
3	SPhos	Na_2CO_3	*i*PrOAc	97	80
4	SPhos[d]	Na_2CO_3	*i*PrOAc	90	70
5	RuPhos	Na_2CO_3	*i*PrOAc	100	80
6	PPh_3	Na_2CO_3	*i*PrOAc	14	12
7	SPhos	KOAc	*i*PrOAc	36	29
8	**SPhos**	**K_2CO_3**	***i*PrOAc**	**100**	**84 (82)**

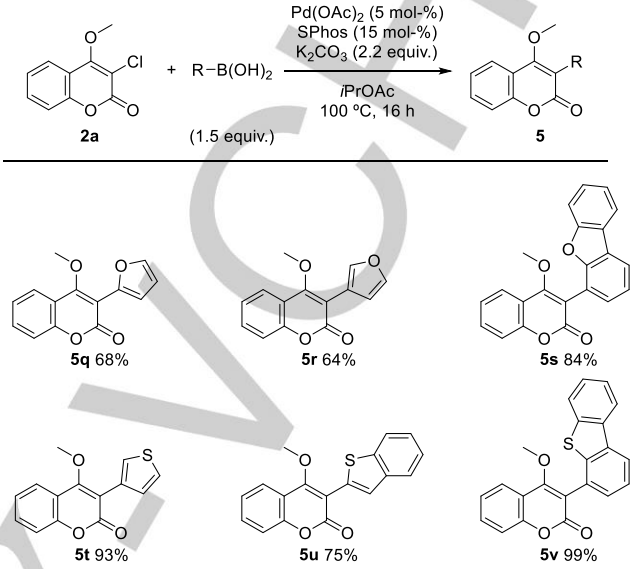
[a] Yields were determined using ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard for quantification. Isolated yields in parenthesis. [b] Temperature was 90 °C. [c] A 45% yield of dechlorinated side-product **1a** was determined from the ^{1}H NMR spectrum of the crude reaction mixture. [d] $Pd_2(dba)_3$ (5 mol-%) was used instead of $Pd(OAc)_2$.

Sensitive functional groups such as aldehydes and esters also survived the coupling conditions, with **5g** and **5h** being isolated in 48% and 91% yield respectively. Substituents which could potential ligate to Pd and inhibit the reaction were well-tolerated, giving products such as nitrile **5j**, primary amine **5l** and the nitro **5n** in good yields. 4-Styrylboronic acid coupled to give **5k** in 77% isolated yield, with the alkenyl functionality remaining untouched. *Meta*-substituted phenylboronic acids gave higher yields that the corresponding *para*-substituted phenylboronic acids, e.g. *m*-OMe phenylboronic acid gave **5o** in 91% yield. A somewhat sterically hindered *ortho*-substituted phenylboronic acid also coupled to give **5p** in 56% yield. Having achieved success with a wide range of substituted phenylboronic acids, we turned our attention towards more challenging heteroaryl boronic acids (Scheme 4). 2- and 3-Furanylboronic acids coupled successfully to give **5q** and **5r** in 68% and 64% yield respectively, with the 3-thiopheneboronic acid giving **5t** in 93% isolated yield.



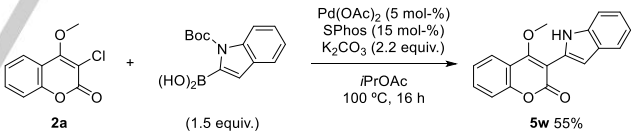
Scheme 3. Variety of phenylboronic acids tolerated under reaction conditions.

Benzothiophene **5u**, dibenzofuran **5s** and dibenzothiophene **5v** substituents were introduced at the 3-position using our conditions to give the Suzuki-Miyaura products in good to excellent yields, with the highest yield for this study obtained for **5v** in 99% yield.



Scheme 4. Variety of heteroaryl boronic acids tolerated under reaction conditions.

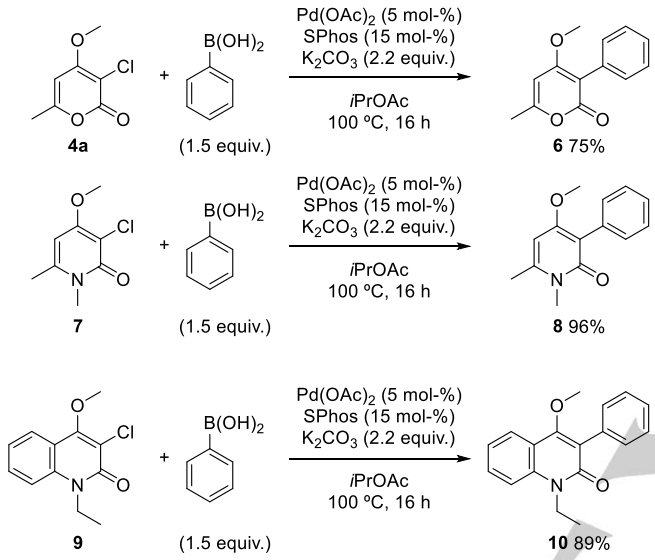
In addition, a Boc-protected indole boronic acid successfully underwent the Suzuki-Miyaura cross-coupling (Scheme 5). The Boc group was deprotected in situ to give **5w** as the main product of the reaction in 55% isolated yield.



Scheme 5. Successful Suzuki-Miyaura cross-coupling and in situ deprotection of an indole boronic acid.

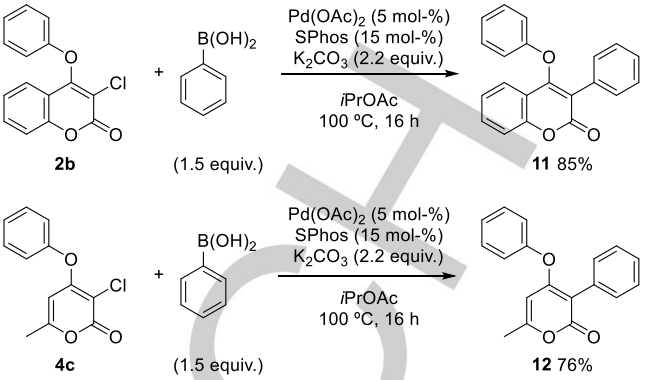
Given the diverse range of both aryl and heteroaryl boronic acids which are tolerated by these reaction conditions, we questioned whether the conditions might also be general for the structurally-related 3-chloro-2-pyrone, -2-pyridone and -2-quinolone. These heterocycles, while structurally-related, are chemically quite different. The nitrogen of the 2-quinolone could potentially ligate to Pd, inhibiting the reaction, while 2-pyrones and 2-pyridones are suspected to be less aromatic in character than the corresponding 2-coumarins and 2-quinolones. 2-Pyrones in particular have been demonstrated to have a rich variety of chemical properties and can behave like aromatics,[17] dienes[18] and enones.[19] Moreover, the framework can ring-open under certain cross-coupling conditions.[20] Thus, 2-pyrones in particular, present significant chemoselectivity challenges.

In the face of these potential challenges, 2-pyrone **4a** was subjected to the Suzuki-Miyaura conditions which had been developed for 2-coumarin **2a** and, to our satisfaction, 2-pyrone **6** could be isolated in 75% yield. 2-Pyridone **7** and 2-quinolone **9** were also coupled in excellent yields,[21] and were isolated in 96% and 89% respectively (Scheme 6). As far as we are aware, this is the first time that Suzuki-Miyaura conditions optimized for one of these heterocyclic substrates has demonstrated generality across the range of difficult 2-coumarins, 2-pyrones, 2-pyridones and 2-quinolones substrates.



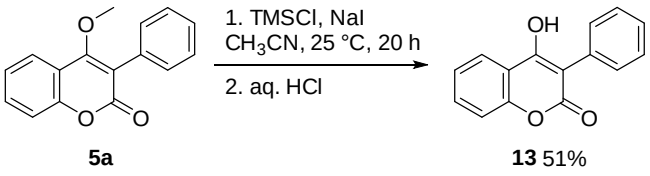
Scheme 6. Variety of 3-chloro heterocycles tolerated under reaction conditions.

Next, we tested the effect of varying the 4-OR group. The 4-OPh group can prove more sterically demanding than the 4-OMe group, and yet it did not hinder the progress of the reaction (Scheme 7). Compounds **2b** and **4c** were coupled with phenylboronic acid to give **11** and **12** in 85% and 76% yields respectively. It is particularly interesting that no products as a result of an intramolecular direct arylation process[12] were observed in the crude reaction mixture. Unfortunately, attempts to couple **4b** and **4d** gave a mixture of mono- and di-arylated products. Interestingly, **4d** gave the 3-Ph-4-OTs-2-pyrone as the major product, with both the 3-Cl-4-Ph-2-pyrone and the 3,4-diarylated product also observed. These preliminary results are under further development, and any successes will be reported in due course.



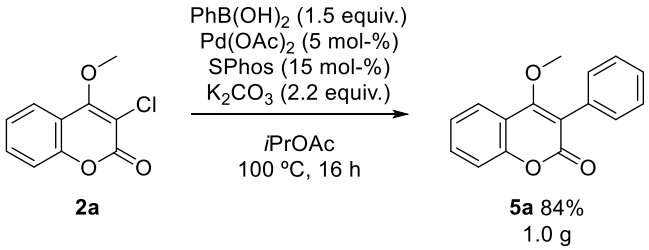
Scheme 7. Variation of 4-OR groups.

In addition to the important biological activity of 4-alkoxy-2-coumarins and related heterocycles,[22] many important coumarins contain a 4-hydroxy-2-coumarin motif, e.g. the anti-coagulant warfarin. Thus, we sought to gain access to 3-aryl-4-hydroxy coumarins via –OH protection, chlorination, Suzuki-Miyaura coupling and deprotection. However, several common hydroxyl protecting groups (e.g. benzyl and silyl), when present on our substrates, either shut down the desired chlorination, or the subsequent Suzuki-Miyaura coupling (see SI for details). Pleasingly however, a remarkably facile method to cleave the methyl ether of compound **5a** at room temperature was discovered. Thus arylated coumarin **5a** was converted to the hydroxyl compound **13** in 51% yield using TMSI[23] (formed in situ from TMSCl and NaI[24]), followed by an acidic workup. It is noteworthy that previous routes to compound such as **13** require cyclisation of the appropriate diester,[25] reactions of diaryliodonium salts[26] or hazardous diazo compounds.[27] It is our opinion that the presented conditions represent the best route to diverse substrates of this class.



Scheme 8. Demethylation to give 4-hydroxy-2-coumarin.

To further demonstrate the utility and practicality of these conditions, the synthesis of **5a** was performed on a gram-scale, giving **5a** in an isolated yield of 84% without chromatography (Scheme 9). This constitutes a successful 20x scale-up from the demonstrated reaction conditions, and no loss of yield is observed.



Scheme 9. Gram-scale synthesis of **5a** via Suzuki-Miyaura cross-coupling.

Conclusions

We have developed the Suzuki-Miyaura cross-coupling of 4-alkoxy-3-chloro-2-coumarins in *i*PrOAc with excellent yields. Chlorination of the 2-coumarin and 2-pyrone framework is achieved through reaction with TCCA, a cheap and environmentally-friendly chlorinating agent. The presented Suzuki-Miyaura reaction conditions are tolerant of a diverse range of aryl and heteroaryl boronic acids. Conditions can be applied to the 2-pyrone, 2-pyridone and 2-quinolone frameworks with equal success. Demethylation of the Suzuki-Miyaura products allows access to 3-aryl-4-hydroxy-2-coumarins. A Suzuki-Miyaura reaction was successfully scaled up to gram quantities.

Experimental Section

1. General Information: Melting point determinations were performed by the open capillary method and are reported uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 25 ºC in $CDCl_3$ at 300, 75 and 282 MHz unless otherwise specified, with TMS as the internal standard for calibration. Chemical shifts (δH, δC and δF) 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. Literature citations are provided for known compounds and representative characterization data. IR spectra were recorded on an FT-IR spectrometer as a thin film (liquid samples) or applied as a solution in dichloromethane, and the dichloromethane was allowed to evaporate (solid samples). Column chromatography was carried out using 60 Å (35-70 µm) silica. TLC was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV light. Reagents were used as purchased from commercial sources. Isopropyl acetate was distilled over potassium carbonate and stored under nitrogen prior to use. HPLC grade CH_3CN was stored over 4Å molecular sieves prior to use in reactions. Temperatures (°C) are reported as the temperature set-point of the oil bath.

2. Experimental Procedures

2.1 Synthesis of 4-alkoxy-2-coumarins, 2-pyrones, 2-pyridone and 2-quinolone

4-Methoxy-2-coumarin (1a):[28] A mixture of 4-hydroxy-2-coumarin (5.0 g, 30.84 mmol), trimethylphosphate (7.6 mL, 64.76 mmol) and K_2CO_3 (5.1 g, 37.01 mmol) was stirred at 140 °C for 1 h. While still warm, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from EtOH to yield the product as an off-white solid (4.693 g, 86%); m.p. 116-118 °C (lit.[28] 122-124 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.5, 1H), 7.55 (ddd, *J* = 8.6, 7.4, 1.6, 1H), 7.36 – 7.22 (m, 2H), 5.70 (s, 1H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 162.9, 153.3, 132.4, 123.9, 123.0, 116.8, 115.6, 90.1, 56.4; *m/z* (ES+): 177 ($[M+H]^+$ 100%).

4-Phenoxy-2-coumarin (1b). See ref.[12]

4-Methoxy-6-methyl-2-pyrone (3a). See ref.[29]

4-Mesyloxy-6-Methyl-2-pyrone (3b):[30] A stirring suspension of 4-hydroxy-2-pyrone (2.0 g, 15.86 mmol) and K_2CO_3 (2.6 g, 19.03 mmol) in acetone (50 mL) was stirred at ambient temperature for 10 min. Mesyl chloride (1.5 mL, 19.03 mmol) was added, and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from EtOH to give the product as an off-white solid (2.619 g, 81%); m.p. 84-85 ºC; IRv_{max} (film) 1720, 1646, 1571, 1372, 1319; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, 2H), 3.28 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 162.7, 161.4, 100.2, 100.2, 39.0, 20.2; *m/z* (ES+): 205 ($(M+H)^+$ 30%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_7H_9O_5S$ 205.0171; Found 205.0168.

6-Methyl-4-phenoxy-2-pyrone (3c). See ref.[31]

6-Methyl-4-tosyloxy-2-pyrone (3d). See ref.[32]

4-Methoxy-1,6-dimethyl-2-pyridone:[33] A mixture of 4-hydroxy-1,6-dimethyl-2-pyridone (5.0 g, 35.93 mmol), trimethylphosphate (8.8 mL, 75.46 mmol) and K_2CO_3 (6.0 g, 43.12 mmol) was stirred at 140 °C for 18 h. While still warm, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from DCM/hexanes to yield the product as a yellow solid (3.194 g, 58%); m.p. 56-58 °C (lit.[33] 115-116 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (d, *J* = 2.8, 1H), 5.79 – 5.74 (m, 1H), 3.74 (s, 3H), 3.46 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 165.4, 146.0, 100.7, 94.5, 55.2, 30.5, 20.9; *m/z* (ES+): 154 ($[M+H]^+$ 100%).

1-Ethyl-4-methoxy-2-quinolone: A mixture of 1-ethyl-4-hydroxy-2-quinolone (0.5 g, 2.64 mmol), trimethylphosphate (0.7 mL, 5.55 mmol) and K_2CO_3 (0.4 g, 3.17 mmol) was stirred at 140 °C for 2 h. While still warm, the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from EtOH to yield the product as an orange solid (0.353 g, 66%); m.p. 60-63 °C; IRv_{max} (film) 2981, 1634, 1575, 1324, 1122; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.5, 1H), 7.58 (ddd, *J* = 9.6, 7.2, 1.6, 1H), 7.36 (d, *J* = 8.6, 1H), 7.21 (td, *J* = 7.6, 0.7, 1H), 6.03 (s, 1H), 4.33 (q, *J* = 7.1, 2H), 3.94 (s, 3H), 1.34 (t, *J* = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 162.6, 138.7, 131.2, 123.6, 121.4, 116.7, 113.9, 96.5, 55.8, 36.8, 12.9; *m/z* (ES+): 204 ($[M+H]^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{14}O_2N$ 204.1025; Found 204.1023.

2.2 Typical procedure for chlorination of 2-coumarins (1) and 2-pyrones (3): To a mixture of 2-coumarin or 2-pyrone (1.0 equiv.) and trichloroisocyanuric acid (0.5 equiv.) was slowly added EtOAc (3 mL/mmol substrate). The mixture was stirred at 85 °C until judged to be complete by TLC analysis (1 h for 2-coumarins **1**, 6-24 h for 2-pyrones **3**), then cooled to ambient temperature. The reaction mixture was filtered through fluted filter paper to remove the insoluble material, and the filtrate was concentrated under reduced pressure. The residues were recrystallized from EtOH to yield the products.

3-Chloro-4-methoxy-2-coumarin (2a):[34] Cream solid (1.112 g, 47% [from 2.0 g (11.35 mmol) **1a**]); m.p. 84-85 °C (lit.[34] 87.9-88.6 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.75 (m, 1H), 7.63 – 7.51 (m, 1H), 7.38 – 7.28 (m, 2H), 4.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 159.6, 151.2, 132.4, 124.6, 123.4, 117.2, 116.7, 106.0, 61.6; *m/z* (ES+) 211 (^{35}Cl (M+H)$^+$ 100%), 213 (^{37}Cl (M+H)$^+$ 32%).

3-Chloro-4-phenoxy-2-coumarin (2b):[12] Pale orange solid (0.727 g, 64% [from 1.0 g (4.20 mmol) **1b**]); m.p. 70-75 °C (lit.[12] 74-75 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.53 (m, 2H), 7.47 – 7.24 (m, 4H), 7.14 (t, *J* = 7.4, 1H), 7.05 – 6.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 158.4, 155.6, 151.7, 132.8, 130.1, 125.0, 124.1, 123.8, 117.0, 116.7, 116.1, 112.0; *m/z* (ES+) 273 (^{35}Cl (M+H)$^+$ 58%), 275 (^{37}Cl (M+H)$^+$ 18%).

3-Chloro-4-methoxy-6-methyl-2-pyrone (4a):[35] Yellow solid (1.534 g, 57% [from 2.17 g (15.48 mmol) **3a**]); m.p. 140-142 °C (lit.[35] 147-148 °C); IRν_{max} (film) 1704 , 1537, 1322, 1233, 737; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 0.6, 1H), 4.00 (s, 3H), 2.31 (d, *J* = 0.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 161.9, 160.9, 99.3, 95.2, 57.3, 20.3; *m/z* (ES+) 175 (^{35}Cl (M+H)$^+$ 100%), 177 (^{37}Cl (M+H)$^+$ 40%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_7H_8ClO_3$ 175.0162; Found 175.0154; Anal. Calc. for $C_7H_7ClO_3$: C, 48.16; H, 4.04; Found: C, 48.27; H, 4.08.

3-Chloro-4-mesyloxy-6-methyl-2-pyrone (4b): Off-white solid (0.736 g, 31% [from 2.0 g (9.79 mmol) **3b**]); m.p. 107-110 ºC; IRν_{max} (film) 1738, 1642, 1556, 1376, 1189, 790; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, *J* = 0.7, 1H), 3.37 (d, *J* = 0.5, 3H), 2.32 (d, *J* = 0.6, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 159.7, 156.2, 109.6, 101.7, 40.1, 20.0; *m/z* (ES+): 239 (^{35}Cl (M+H)$^+$ 50%), 241 (^{37}Cl (M+H)$^+$ 26%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_7H_8O_5SCl$ 238.9781; Found 238.9787.

3-Chloro-6-methyl-4-phenoxy-2-pyrone (4c):[12] Purified by column chromatography (EtOAc:hexanes 30:70), pale yellow solid (0.078 g, 27% [from 0.16 g (0.80 mmol) **3c**]); m.p. 100-103 °C (lit.[12] 96-97 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.41 (m, 2H), 7.40-7.26 (m, 1H), 7.16-7.04 (m, 2H), 5.68 (s, 1H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 161.4, 160.9, 152.8, 130.4, 126.5, 120.8, 101.7, 97.6, 20.1; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{12}H_{10}ClO_3$ 237.0318; Found 237.0312.

3-Chloro-6-methyl-4-tosyloxy-2-pyrone (4d): Pale yellow solid (0.673 g, 40% [from 1.5 g (5.35 mmol) **3d**]); m.p. 144-147 °C; IRν_{max} (film) 1741, 1547, 1386, 1195, 666; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4, 2H), 7.39 (d, *J* = 8.1, 2H), 6.43 (d, *J* = 0.8, 1H), 2.48 (s, 3H), 2.30 (d, *J* = 0.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 159.8, 156.5, 147.0, 131.9, 130.3, 128.5, 110.0, 101.6, 21.9, 19.9; *m/z* (ES+) 315 (^{35}Cl (M+H)$^+$ 100%), 317 (^{37}Cl (M+H)$^+$ 40%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{13}H_{12}ClSO_5$ 315.0094; Found 315.0086.

2.3 Typical procedure for chlorination of 2-pyridone (7) and 2-quinolone (9): To a stirring solution of substrate (1.0 equiv.) and *N*-chlorosuccinimide (1.2 equiv.) in $CHCl_3$ (5 mL/mmol substrate) in a round-bottomed flask was added trifluoroacetic acid (1.2 equiv.). The flask was covered in aluminium foil and the reaction mixture was stirred at 55 °C overnight. The reaction mixture was allowed to cool to ambient temperature. The mixture was washed with saturated aqueous $NaHCO_3$ (1 x 20 mL) and H_2O (2 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (eluent in parenthesis) to yield the title products.

3-Chloro-4-methoxy-1,6-dimethyl-2-pyridone (7): (DCM), white solid (0.445 g, 30% [from 1.2 g (7.83 mmol) 4-methoxy-1,6-dimethyl-2-pyridone]); m.p. 180-182 °C; IRν_{max} (film) 1647, 1589, 1535, 1083, 751; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (s, 1H), 3.92 (s, 3H), 3.54 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 160.7, 145.3, 105.2, 94.7, 56.4, 31.9, 21.4; *m/z* (ES+): 188 (^{35}Cl (M+H)$^+$) 78%, 190 (^{37}Cl (M+H)$^+$) 26%; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_8H_{11}NO_2Cl$ 188.0478; Found 188.0480.

3-Chloro-1-ethyl-4-methoxy-2-quinolone (9): (EtOAc:hexanes 50:50), yellow solid (1.033 g, 68% [from 1.3 g (6.40 mmol) 4-methoxy-1-ethyl-2-quinolone]); m.p. 73-76 °C; IRν_{max} (film) 1652, 1615, 1598, 1113, 755; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.0, 1.4, 1H), 7.60 (ddd, *J* = 8.7, 7.2, 1.6, 1H), 7.40 (d, *J* = 8.5, 1H), 7.33 – 7.22 (m, 1H), 4.40 (q, *J* = 7.1, 2H), 4.12 (s, 3H), 1.37 (t, *J* = 7.1, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 159.4, 137.1, 131.3, 123.8, 122.4, 117.8, 115.0, 114.2, 61.1, 38.6, 12.7; *m/z* (ES+) 238 (^{35}Cl (M+H)+ 14%), 240 (^{37}Cl (M+H)+ 6%); HRMS (ESI-TOF) *m/z*: [M+H]+ Calcd for $C_{12}H_{13}O_2NCl$ 238.0635; Found 238.0632.

2.4 Typical procedure for Suzuki-Miyaura cross-coupling (synthesis of compounds 5, 8, 10, 11, 12): A Schlenk tube was heated under vacuum and refilled with N_2 three times, then the Schlenk tube was allowed to cool. Substrate **2**, **4c**, **7** or **9** (0.237 mmol), boronic acid (0.356 mmol), $Pd(OAc)_2$ (0.012 mmol), SPhos (0.036 mmol) and K_2CO_3 (0.521 mmol) were added. The Schlenk tube was evacuated and refilled with N_2 three times. *i*PrOAc (7 mL) was added *via* syringe. The Schlenk tube was placed in an oil bath preheated to 100 °C. The reaction was stirred at this temperature for 16 h, then cooled to ambient temperature. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (eluent in parenthesis) to afford the title compounds.

4-Methoxy-3-phenyl-2-coumarin (5a):[36] (DCM), yellow solid (0.049 g, 82%); m.p. 111-114 °C (lit.[36] 117-119 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.3, 1H), 7.60 – 7.51 (m, 1H), 7.50 – 7.26 (m, 7H), 3.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 162.9, 152.5, 132.4, 132.0, 131.0, 128.4, 128.3, 124.0, 123.9, 117.8, 116.5, 111.1, 61.3; *m/z* (ES+) 253 ((M+H)$^+$ 12%).

4-Methoxy-3-tolyl-2-coumarin (5b): (DCM), white solid (0.056 g, 89%); m.p. 128-130 °C; IR ν_{max} (film) 1702, 1608, 1571, 1345, 1106; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.4, 1H), 7.54 (ddd, *J* = 8.4, 7.3, 1.6, 1H), 7.40 – 7.20 (m, 6H), 3.57 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 162.7, 152.4, 138.3, 131.8, 130.8, 129.3, 129.1, 124.0, 123.8, 117.8, 116.4, 111.0, 61.2, 21.4; *m/z* (ES+) 267 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{15}O_3$ 267.1021; Found 267.1011.

4-Methoxy-3-(4-methoxyphenyl)-2-coumarin (5c): (DCM), yellow solid (0.053 g, 79%); m.p. 134-138 °C; IR ν_{max} (film) 1710, 1606, 1512, 1347, 1246, 1109; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.4, 1H), 7.60 – 7.47 (m, 1H), 7.45 – 7.36 (m, 2H), 7.36 – 7.24 (m, 2H), 7.06 – 6.90 (m, 2H), 3.85 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 162.7, 159.6, 152.4, 132.1, 131.8, 124.3, 124.0, 123.8, 117.9, 116.4, 113.8, 111.0, 61.1, 55.3; *m/z* (ES+) 283 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{15}O_4$ 283.0970; Found 283.0970.

4-Methoxy-3-(4-(trifluoromethyl)phenyl)-2-coumarin (5d): (DCM), yellow solid (0.058 g, 76%); m.p. 153-156 °C; IR ν_{max} 1700, 1612, 1567, 1327, 1121; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.5, 1H), 7.71 (d, *J* = 8.2, 2H), 7.67 – 7.53 (m, 3H), 7.41 – 7.28 (m, 2H), 3.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 162.9, 152.6, 136.2, 132.5, 131.4, 130.5 (q, *J* = 32), 125.2 (q, *J* = 4), 124.3, 124.0, 124.0 (q, *J* = 272), 117.4, 116.6, 110.2, 61.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63; *m/z* (ES+) 321 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{12}O_3F_3$ 321.0739; Found 321.0735.

4-Methoxy-3-(4-fluorophenyl)-2-coumarin (5e): (DCM), yellow solid (0.046 g, 72%); m.p. 135-137 °C; IR ν_{max} (film) 1699, 1609, 1570, 1222, 1161; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.9, 1.6, 1H), 7.56 (ddd, J = 8.4, 7.3, 1.6, 1H), 7.51 – 7.41 (m, 2H), 7.39 – 7.27 (m, 2H), 7.21 – 7.08 (m, 2H), 3.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 163.2, 162.6 (d, J = 248), 152.5, 132.8 (d, J = 8), 132.2, 128.1 (d, J = 4), 124.1, 123.9, 117.6, 116.5, 115.4 (d, J = 22), 110.4, 61.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113; *m/z* (ES+) 271 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_{12}O_3F$ 271.0770; Found 271.0770.

4-Methoxy-3-(4-(trifluoromethoxy)phenyl)-2-coumarin (5f): (DCM), pale yellow solid (0.061 g, 77%); m.p. 145-146 °C; IR ν_{max} (film) 1700, 1616, 1570, 1351, 1258, 1211; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.9, 1.4, 1H), 7.62 – 7.48 (m, 3H), 7.41 – 7.27 (m, 4H), 3.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 163.1, 152.6, 149.1 (q, J = 2), 132.5, 132.3, 130.9, 124.2, 123.9, 120.6, 120.5 (q, J = 258), 117.5, 116.6, 110.2, 61.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -58; *m/z* (ES+) 337 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{12}O_4F_3$ 337.0688; Found 337.0671.

4-Methoxy-3-(4-formylphenyl)-2-coumarin (5g): (DCM:MeOH 99:1), yellow solid (0.032 g, 48%); m.p. 154-155 °C; IR ν_{max} (film) 2729, 1701, 1607, 1567, 1348, 1207; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.02 – 7.93 (m, 2H), 7.89 (dd, J = 8.0, 1.3, 1H), 7.74 – 7.65 (m, 2H), 7.64 – 7.53 (m, 1H), 7.42 – 7.28 (m, 2H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 163.8, 162.7, 152.7, 138.9, 136.0, 132.6, 131.8, 129.5, 124.3, 124.0, 117.4, 116.6, 110.3, 61.7; *m/z* (ES+) 281 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{13}O_4$ 281.0814; Found 281.0815.

Ethyl 4-(4-methoxy-2-oxo-2*H*-chromen-3-yl)benzoate (5h): (DCM), yellow solid (0.070 g, 91%); m.p. 131-133 °C; IR ν_{max} (film) 1715, 1610, 1573, 1348, 1274; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 – 8.07 (m, 2H), 7.88 (dd, J = 8.0, 1.3, 1H), 7.64 – 7.52 (m, 3H), 7.41 – 7.28 (m, 2H), 4.41 (q, J = 7.1, 2H), 3.57 (s, 3H), 1.41 (t, J = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 163.5, 162.9, 152.6, 137.2, 132.4, 131.1, 130.4, 129.4, 124.2, 124.0, 117.5, 116.6, 110.4, 61.5, 61.1, 14.3; *m/z* (ES+) 325 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{19}H_{17}O_5$ 325.1076; Found 325.1079.

3-(4-Acetylphenyl)-4-methoxy-2-coumarin (5i): (DCM), white solid (0.053 g, 76%); m.p. 183-187 °C; IR ν_{max} (film) 1712, 1682, 1611, 1571, 1347, 1267; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 2H), 7.89 (dd, J = 7.9, 1.5, 1H), 7.65 – 7.52 (m, 3H), 7.41 – 7.28 (m, 2H), 3.59 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 163.6, 162.9, 152.6, 137.5, 136.8, 132.5, 131.3, 128.2, 124.2, 124.0, 117.5, 116.6, 110.3, 61.6, 26.7; *m/z* (ES+) 295 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{15}O_4$ 295.0970; Found 295.0952.

3-(4-Cyanophenyl)-4-methoxy-2-coumarin (5j): (DCM), white solid (0.055 g, 83%); m.p. 199-202 °C; IR ν_{max} (film) 2225, 1699, 1610, 1454, 1351; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.0, 1.3, 1H), 7.79 – 7.71 (m, 2H), 7.68 – 7.56 (m, 3H), 7.41 – 7.30 (m, 2H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 162.5, 152.7, 137.4, 132.8, 132.0, 131.8, 124.4, 124.1, 118.5, 117.2, 116.7, 112.2, 110.0, 61.8; *m/z* (ES+) 278 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{12}NO_3$ 278.0817; Found 278.0808.

4-Methoxy-3-(4-vinylphenyl)-2-coumarin (5k): (DCM), yellow solid (0.051 g, 77%); m.p. 102-104 °C; IR ν_{max} (film) 1713, 1608, 1571, 1346; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 1H), 7.60 – 7.41 (m, 5H), 7.39 – 7.26 (m, 2H), 6.76 (dd, J = 17.6, 10.9, 1H), 5.81 (dd, J = 17.6, 0.8, 1H), 5.30 (dd, J = 10.9, 0.8, 1H), 3.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 163.0, 152.5, 137.7, 136.4, 132.0, 131.7, 131.1, 126.1, 124.1, 123.9, 117.7, 116.5, 114.6, 110.9, 61.3; *m/z* (ES+) 279 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{15}O_3$ 279.1021; Found 279.1025.

3-(3-Aminophenyl)-4-methoxy-2-coumarin (5l): (DCM), orange solid (0.050 g, 79%); m.p. 131-136 °C; IR ν_{max} (film) 3367, 1712, 1645, 1610, 1570, 1266, 738; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 1H), 7.53 (ddd, J = 8.4, 7.3, 1.6, 1H), 7.38 – 7.14 (m, 3H), 6.86 – 6.76 (m, 2H), 6.71 (ddd, J = 8.0, 2.4, 1.0, 1H), 3.63 (s, 3H), 3.53 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 162.6, 152.4, 146.4, 133.3, 131.9, 129.2, 124.0, 123.9, 121.5, 117.8, 117.7, 116.4, 115.4, 110.8, 61.1; *m/z* (ES+) 268 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_{14}NO_3$ 268.0974; Found 268.0961.

4-Methoxy-3-(3-(trifluoromethyl)phenyl)-2-coumarin (5m): (DCM), yellow solid (0.066 g, 87%); m.p. 95-97 °C; IR ν_{max} (film) 1716, 1610, 1570, 1330, 1125; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 1H), 7.79 – 7.53 (m, 5H), 7.40 – 7.28 (m, 2H), 3.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 162.9, 152.6, 134.4, 133.2, 132.5, 130.8 (q, J = 33), 128.8, 127.8 (q, J = 4), 125.2 (q, J = 4), 124.3, 124.0, 124.0 (q, J = 273), 117.4, 116.6, 110.1, 61.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63; *m/z* (ES+) 321 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{12}O_3F_3$ 321.0739 Found 321.0734.

4-Methoxy-3-(3-nitrophenyl)-2-coumarin (5n): (DCM), yellow solid (0.058 g, 82%); m.p. 153-155 °C; IR ν_{max} (film) 1714, 1611, 1570, 1528, 1349, 1298, 1106; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (t, J = 1.9, 1H), 8.26 (ddd, J = 8.3, 2.3, 1.1, 1H), 7.95 – 7.82 (m, 2H), 7.69 – 7.57 (m, 2H), 7.42 – 7.31 (m, 2H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 162.7, 152.7, 148.2, 137.1, 134.1, 132.8, 129.3, 125.9, 124.5, 124.1, 123.3, 117.2, 116.7, 109.6, 61.9; *m/z* (ES+) 298 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_{12}NO_5$ 298.0715; Found 298.0720.

4-Methoxy-3-(3-methoxyphenyl)-2-coumarin (5o): (DCM), yellow oil (0.061 g, 91%); IR ν_{max} (film) 1715, 1611, 1572, 1347, 1214, 1106; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.9, 1.4, 1H), 7.55 (ddd, J = 8.6, 7.4, 1.6, 1H), 7.44 – 7.22 (m, 3H), 7.10 – 6.87 (m, 3H), 3.83 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.8, 159.4, 152.5, 133.7, 132.0, 129.3, 124.0, 123.9, 123.5, 117.7, 116.6, 116.4, 114.1, 110.7, 61.1, 55.3; *m/z* (ES+) 283 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{15}O_4$ 283.0970; Found 283.0961.

4-Methoxy-3-(2-(trifluoromethyl)phenyl)-2-coumarin (5p): (DCM), yellow oil (0.042 g, 56%); IR ν_{max} (film) 1716, 1613, 1573, 1350, 1315; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.0, 1.3, 1H), 7.82 – 7.74 (m, 1H), 7.68 – 7.45 (m, 4H), 7.41 – 7.27 (m, 2H), 3.56 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0, 161.5, 152.6, 133.7, 132.5 (q, J = 29), 132.3, 131.7, 130.7 (q, J = 30), 129.2, 126.6 (q, J = 5), 124.2, 124.1, 123.9 (d, J = 274), 116.9, 116.6, 105.7, 60.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -61; *m/z* (ES+) 321 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{12}O_3F_3$ 321.0739; Found 321.0726.

3-(Furan-2-yl)-4-methoxy-2-coumarin (5q): (DCM), yellow oil (0.039 g, 68%); IR ν_{max} (film) 1723, 1625, 1610, 1549, 1348, 1328, 1124; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 1H), 7.61 – 7.51 (m, 2H), 7.37 – 7.27 (m, 2H), 6.82 (dd, J = 3.3, 0.8, 1H), 6.55 (dd, J = 3.3, 1.9, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 161.9, 152.4, 144.5, 142.9, 132.5, 124.2, 124.0, 117.3, 116.6, 113.9, 111.6, 101.4, 60.5; *m/z* (ES+) 243 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{14}H_{11}O_4$ 243.0657; Found 243.0652.

3-(Furan-3-yl)-4-methoxy-2-coumarin (5r): (EtOAc:hexanes 10:90), white solid (0.037 g, 64%); m.p. 97-99 °C; IR ν_{max} (film) 1710, 1614, 1602, 1538, 1329, 1161; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 0.6, 1H), 7.80

(dd, *J* = 7.9, 1.4, 1H), 7.54 (ddd, *J* = 10.2, 5.3, 1.6, 2H), 7.42 – 7.28 (m, 2H), 7.10 – 6.92 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 162.7, 162.1, 152.2, 144.3, 142.5, 131.7, 124.3, 123.4, 117.5, 116.6, 115.8, 111.2, 108.1, 60.8; *m/z* (ES+) 243 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{14}H_{11}O_4$ 243.0657; Found 243.0656.

3-(Dibenzo[*b,d*]furan-4-yl)-4-methoxy-2-coumarin (5s): (DCM), white solid (0.068 g, 84%); m.p. 196-198 °C; IR ν_{max} (film) 1714, 1645, 1570, 1349; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.05 – 7.90 (m, 3H), 7.64 – 7.49 (m, 3H), 7.49 – 7.29 (m, 5H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 163.7, 162.8, 156.2, 154.7, 152.7, 132.3, 130.0, 127.4, 124.5, 124.2, 124.1, 124.1, 123.0, 122.8, 121.2, 120.8, 117.6, 117.3, 116.6, 112.0, 104.3, 60.6; *m/z* (ES+) 343 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{22}H_{15}O_4$ 343.0970; Found 343.0960.

4-Methoxy-3-(thiophen-3-yl)-2-coumarin (5t): (DCM), yellow oil (0.057 g, 93%); IR ν_{max} (film) 1717, 1610, 1573, 1341, 1326, 756; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.85 (dd, *J* = 7.9, 1.6, 1H), 7.68 – 7.63 (m, 1H), 7.54 (ddd, *J* = 8.7, 7.3, 1.6, 1H), 7.43 – 7.27 (m, 4H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 163.4, 162.8, 152.3, 132.0, 131.2, 129.6, 126.9, 124.9, 124.2, 123.8, 117.7, 116.5, 107.9, 60.8; *m/z* (ES+) 259 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{14}H_{11}O_3S$ 259.0429; Found 259.0432.

3-(Benzo[*b*]thiophen-2-yl)-4-methoxy-2-coumarin (5u): (DCM), yellow solid (0.055 g, 75%); m.p. 132-136 °C; IR ν_{max} (film) 1720, 1608, 1554, 1351, 1328, 749; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.95 (d, *J* = 0.6, 1H), 7.90 – 7.75 (m, 3H), 7.57 (ddd, *J* = 8.4, 7.3, 1.6, 1H), 7.41 – 7.28 (m, 4H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 163.8, 161.8, 152.4, 140.9, 139.1, 132.6, 132.5, 127.6, 125.0, 124.4, 124.4, 124.1, 124.0, 121.9, 117.2, 116.7, 107.8, 61.3; *m/z* (ES+) 309 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{13}O_3S$ 309.0585; Found 309.0590.

3-(Dibenzo[*b,d*]thiophen-4-yl)-4-methoxy-2-coumarin (5v): (DCM), yellow solid (0.840 g, 99%); m.p. 191-196 °C; IR ν_{max} (film) 1713, 1611, 1566, 1349, 754; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.27 – 8.12 (m, 2H), 7.94 (dd, *J* = 8.0, 1.5, 1H), 7.86 – 7.75 (m, 1H), 7.65 – 7.28 (m, 7H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 163.2, 162.5, 152.7, 141.7, 139.4, 135.8, 135.8, 132.4, 129.8, 127.9, 127.0, 124.7, 124.6, 124.2, 124.1, 122.9, 121.9, 121.8, 117.3, 116.6, 107.1, 60.3; *m/z* (ES+) 359 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{22}H_{15}O_3S$ 359.0742; Found 359.0746.

3-(1*H*-Indol-2-yl)-4-methoxy-2-coumarin (5w): (DCM), yellow solid (0.038 g, 55%); m.p. 169-174 °C; IR ν_{max} (film) 3403, 1645, 1454, 1346, 1266, 1112; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 10.43 (br s, 1H), 7.89 – 7.81 (m, 1H), 7.67 (dd, *J* = 7.9, 0.9, 1H), 7.60 – 7.52 (m, 1H), 7.45 (dd, *J* = 8.1, 0.9, 1H), 7.42 – 7.28 (m, 3H), 7.23 (ddd, *J* = 8.2, 7.0, 1.2, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 163.4, 163.0, 152.0, 135.6, 132.0, 128.2, 128.1, 124.7, 123.7, 123.1, 120.8, 120.1, 117.6, 116.7, 111.4, 108.1, 106.6, 60.5; *m/z* (ES+) 292 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{14}NO_3$ 292.0974; Found 292.0979.

4-Methoxy-6-methyl-3-phenyl-2-pyrone (6):[37] (DCM), yellow solid (0.028 g, 75% [from 30.0 mg (0.172 mmol) **4a**]); m.p. 155-159 °C (lit.[37] 156-157 °C); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.46 – 7.33 (m, 4H), 7.32 – 7.24 (m, 1H), 6.13 (d, *J* = 0.8, 1H), 3.82 (s, 3H), 2.32 (d, *J* = 0.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 165.9, 164.3, 162.7, 131.4, 130.5, 127.9, 127.4, 105.3, 95.3, 56.5, 20.5; *m/z* (ES+) 217 ((M+H)$^+$ 22%).

4-Methoxy-1,6-dimethyl-3-phenyl-2-pyridone (8):[38] (DCM:MeOH 99.5:0.5), yellow semi-solid (0.052 g, 96%); IR ν_{max} (film) 1634, 1558, 1362, 1266; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.45 – 7.20 (m, 5H), 6.02 (d, *J* = 0.5, 1H), 3.75 (s, 3H), 3.54 (s, 3H), 2.40 (d, *J* = 0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 163.7, 162.8, 146.1, 133.6, 130.8, 127.7, 126.8, 111.8, 95.3, 55.8, 31.4, 21.6; *m/z* (ES+) 230 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{14}H_{16}NO_2$ 230.1181; Found 230.1180.

1-Ethyl-4-methoxy-3-phenyl-2-quinolone (10): (EtOAc:hexanes 10:90), clear colourless oil (0.032 g, 91%); IR ν_{max} (film) 1635, 1593, 1356, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.03 (dd, *J* = 8.0, 1.3, 1H), 7.66 – 7.56 (m, 1H), 7.55 – 7.48 (m, 2H), 7.48 – 7.31 (m, 4H), 7.30 – 7.20 (m, 1H), 4.39 (q, *J* = 7.1, 2H), 3.50 (s, 3H), 1.38 (t, *J* = 7.1, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 162.9, 160.4, 138.4, 133.5, 130.9, 130.9, 128.1, 127.7, 124.4, 121.7, 119.3, 118.5, 113.8, 60.8, 37.8, 12.8; *m/z* (ES+) 280 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1338; Found 280.1335.

4-Phenoxy-3-phenyl-2-coumarin (11): (EtOAc:hexanes 10:90), white solid (0.063 g, 85%); m.p. 191-194 °C; IR ν_{max} (film) 1723 1625, 1483, 1350, 1207; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.63 (dd, *J* = 8.0, 1.5, 1H), 7.56 (ddd, *J* = 8.8, 7.3, 1.6, 1H), 7.47 – 7.32 (m, 3H), 7.31 – 7.10 (m, 6H), 7.00 – 6.90 (m, 1H), 6.84 – 6.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 162.4, 158.6, 156.5, 153.1, 132.3, 130.4, 130.1, 129.7, 128.4, 128.0, 124.4, 124.3, 123.2, 118.3, 117.0, 116.8, 116.3; *m/z* (ES+) 315 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{21}H_{15}O_3$ 315.1021; Found 315.1013.

6-Methyl-4-phenoxy-3-phenyl-2-pyrone (12): (EtOAc:hexanes 8:92), off-white solid (0.050 g, 76%); m.p. 129-133 °C; IR ν_{max} (film) 1716, 1647, 1566, 1489, 1345, 1220; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.59 – 7.50 (m, 2H), 7.44 – 7.33 (m, 4H), 7.33 – 7.19 (m, 2H), 7.07 – 6.98 (m, 2H), 5.72 (d, *J* = 0.8, 1H), 2.20 (d, *J* = 0.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 164.2, 163.9, 162.1, 153.7, 130.8, 130.4, 130.2, 128.0, 127.8, 125.6, 120.5, 108.7, 98.4, 20.2; *m/z* (ES+) 279 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{15}O_3$ 279.1021; Found 279.1018.

2.5 Demethylation of Suzuki-Miyaura product (5a)

4-Hydroxy-3-phenyl-2-coumarin (13):[39] To an oven-dried 5 mL reaction tube was added NaI (120 mg, 0.792 mmol) and CH_3CN (1 mL), and the mixture was stirred at ambient temperature. To the stirring mixture was added TMSCl (0.05 mL, 0.396 mmol). The mixture was stirred at ambient temperature for 1 h. 4-Methoxy-3-phenyl-2-coumarin **5a** (50 mg, 0.198 mmol) was added to the stirring mixture. The mixture was stirred at 25 °C overnight with the reaction tube open to the air, then poured into a beaker containing cold 1M HCl (15 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with 5% aqueous sodium thiosulfate (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (gradient EtOAc:hexanes 20:80 to 50:50) to yield the product as a pale pink solid (0.024 g, 51%); m.p. 232-233 °C (lit.[39] 232-233 °C); ^{1}H NMR (300 MHz, DMSO-d_6) *δ* 8.02 (dd, *J* = 7.9, 1.2, 1H), 7.72 – 7.61 (m, 1H), 7.49–7.31 (m, 7H); ^{13}C NMR (75 MHz, DMSO-d_6) *δ* 162.4, 160.7, 152.8, 132.8, 132.5, 131.5, 128.5, 127.9, 124.4, 124.2, 116.9, 116.7, 106.6; *m/z* (ES–) 237 ((M–H)$^-$ 100%).

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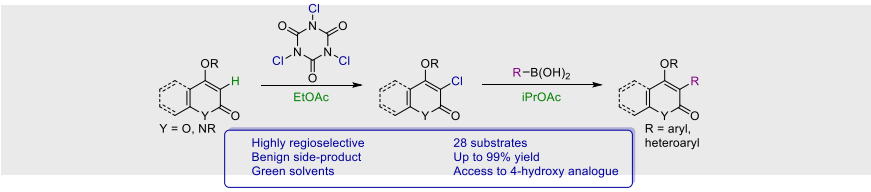

Chlorination of biologically important 4-alkoxy-2-coumarins is achieved with trichloroisocyanuric acid, a favourable alternative to *N*-chlorosuccinimide. The Suzuki-Miyaura cross-coupling of the chlorinated 2-coumarins was developed, with yields up to 99%, and successfully applied to the related 2-pyrone, 2-pyridone and 2-quinolone. Demethylation allows access to a 3-aryl-4-hydroxy-2-coumarin.

Cross-Coupling

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Regioselective Chlorination and Suzuki-Miyaura Cross-Coupling of 4-Alkoxy-2-Coumarins, 2-Pyrones and Related Heterocycles