

Generation of diverse 2-pyrones *via* palladium-catalyzed site-selective Suzuki-Miyaura couplings of 3-bromo-4-tosyloxy-2-pyrone†Xiaoli Lei,^a Liang Gao,^a Qiuping Ding,^a Yiyuan Peng^{*a} and Jie Wu^{*b}

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Based on different reactivity of the (pseudo)halide substituents in the 2-pyrone (3-Br and 4-OTs), palladium-catalyzed sequential site-selective Suzuki–Miyaura cross-coupling reactions of 3-bromo-6-methyl-4-tosyloxy-2-pyrone are described, which afford the diverse 2-pyrones in good yields.

Introduction

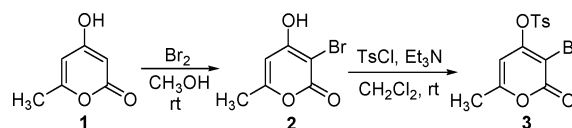
2-Pyrone is the structural unit in various biologically active natural products.¹ Compounds with different substitutions on the 2-pyrone scaffold show diverse biological activities (such as anticancer and antimicrobial agents, HIV-protease inhibitor and selective cyclooxygenase-2 inhibitor).² Meanwhile, 2-pyrone is a versatile building block in organic synthesis.³ For example, it has been utilized as a diene component in Diels–Alder reactions,⁴ and as a precursor for the synthesis of other heterocyclic systems.⁵ So far, various methods have been developed for the synthesis of substituted 2-pyrones. However, the formation of substituted 2-pyrones usually suffered from multi-steps, harsh reaction conditions and generally low yields.⁶ Alternatively, halogenated 2-pyrones have been used for direct couplings.^{7–10} Additionally, they can be converted into organometallic reagents (such as tin,¹¹ boron,¹² zinc,¹³ and copper-based reagents¹⁴) for couplings with electrophilic partners. Although the above research has focused on the use of palladium-catalyzed C–C bond formation for introduction of substituent 2-pyrones, most of these methods are centered on mono-substituted 2-pyrones. Applications of transition metal-catalyzed reactions for the synthesis of 3,4-disubstituted 2-pyrones are limited, which is due to the restrictions of regioselectivity problems. Therefore, the development of an effective strategy for the synthesis of diverse 2-pyrones, especially for 3,4-disubstituted 2-pyrones is highly desirable.

Recently, transition-metal-catalyzed site-selective cross-coupling reactions have been developed for the compounds bearing two or more leaving groups, especially dihaloheteroarenes.^{15,16} We also applied the palladium-catalyzed

site-selective cross-coupling reactions for the synthesis of 3,4-disubstituted coumarins, which include 3,4-diaryl-coumarins, 3-amino-4-aryl-coumarins, and 3-aryl-4-aminocoumarins.^{16f} Prompted by these results, we conceived that the generation of differentially 3,4-disubstituted 2-pyrones could be accessed by using the similar strategy. Thus, the key step in our program is to introduce leaving groups with different reactivities to the electronically different C-3 and C-4 positions of 2-pyrones. We envisioned that based on the controllable chemoselectivity of two leaving groups, substituents would be expected to be successively installed into the 2-pyrone moiety. Herein, we would like to describe our recent efforts for the synthesis of 3,4-disubstituted 2-pyrones through palladium-catalyzed site-selective couplings of 3-bromo-4-tosyloxy-2-pyrone.

Results and discussion

As mentioned above, our strategy is based on the elaboration of the readily available 2-pyrone core structure using site-selective cross-coupling reactions. Thus, 4-hydroxy-2-pyrone **1** was selected as the target for further development due to its easy availability. After halogenation and sulfonation of 4-hydroxy-2-pyrone, 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** could be prepared easily with a total yield of 86% (Scheme 1).



Scheme 1 Synthesis of 3-bromo-4-tosyloxy-2-pyrone **3** from 4-hydroxy-2-pyrone **1**.

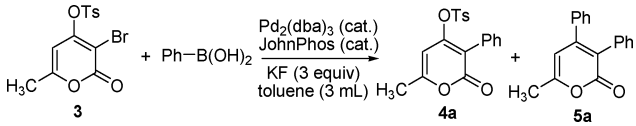
Due to the great functional group tolerance of Suzuki–Miyaura cross-coupling reaction,¹⁷ initial studies were performed for the palladium-catalyzed reaction of 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** with phenylboronic acid (Table 1). To test the C3 and C4 selectivity, the reaction was carried out in the presence of Pd₂(dba)₃, JohnPhos, and KF in toluene. A mixture of mono-coupled product **4a** and di-coupled product **5a** were obtained

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† Electronic supplementary information (ESI) available: General experimental information, characterization data, ¹H and ¹³C NMR spectra of compounds **4–6**. See DOI: 10.1039/c1ob05783a

Table 1 Initial studies for palladium-catalyzed reaction of 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** with phenylboronic acid

					
Entry	Pd ₂ (dba) ₃ (mol%)	JohnPhos (mol%)	PhB(OH) ₂ (equiv.)	T/°C	Yield (%) ^a (4a / 5a)
1	2.5	5	1.5	85	38/10
2	2.5	5	1.5	75	35/6
3	2.5	5	1.5	60	49/0
4	2.5	5	1.5	40	15/0
5	2.5	5	1.5	rt	5/0
6	2.5	5	1.1	60	40/0
7	2.5	5	2.0	60	45/0
8	2.5	5	3.0	60	46/0
9	5.0	10	1.5	60	40/0
10	7.5	15	1.5	60	50/0

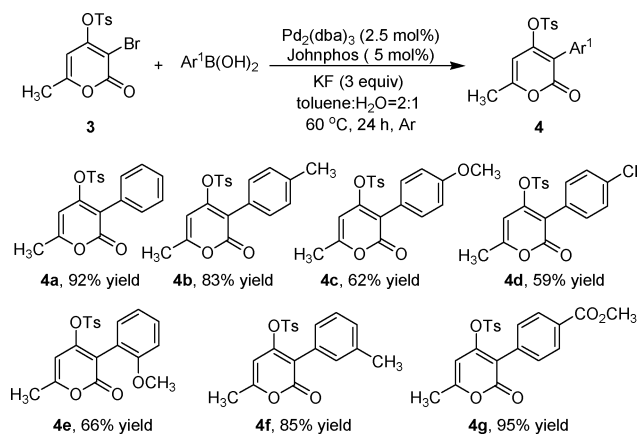
^a Isolated yield based on 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3**.

in 38% and 10% yield, respectively (Table 1, entry 1) when the reaction occurred at 85 °C catalyzed by 2.5 mol% of Pd₂(dba)₃ and 5 mol% of JohnPhos. The amount of compound **5a** was reduced when the temperature decreased (Table 1, entry 2). Only product **4a** was generated when the reaction was performed at 60 °C with a 49% isolated yield (Table 1, entry 3). However, the reaction was retarded when the temperature was lower (Table 1, entries 4 and 5). No obvious influence was observed when the amount of phenylboronic acid or palladium catalyst was changed (Table 1, entries 6–10).

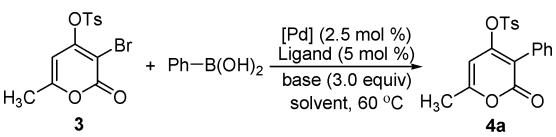
To further improve the reaction, we investigated other reaction parameters, such as palladium catalyst, ligand, base, and solvent (Table 2). To our delight, screening of solvents (Table 2, entries 1–13) revealed that mono-coupled product **4a** was generated in 92% yield when toluene/water (v/v: 2/1) was used as the co-solvent in the presence of Pd₂(dba)₃, JohnPhos, and KF (Table 2, entries 13), and no formation of 4-position coupled product was observed. Reactions employing other palladium catalysts such as Pd(OAc)₂, Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, and Pd/C gave rise to the corresponding product **4a** in lower yields (Table 2, 14–17). Inferior results were displayed when other ligands such as PPh₃, Josiphos, Xantphos, DPPF, and DIPF were examined (Table 2, entries 18–23). No better results were obtained when different bases (Na₂CO₃, K₂CO₃, Cs₂CO₃, NaHCO₃, K₃PO₄·3H₂O, K₂HPO₄·3H₂O, and Et₃N) were used in the reaction (Table 2, entries 24–30).

With this promising result in hands, we investigated the cross-coupling reactions between 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** and various arylboronic acids under optimized reaction conditions [Pd₂(dba)₃ (2.5 mol%), JohnPhos (5 mol%), KF (3.0 equiv.), toluene/H₂O = 2/1, 60 °C]. The results indicated that arylboronic acids containing electron-donating or -withdrawing groups could be successfully employed in the reaction, leading to the corresponding 2-pyrone derivatives in good to excellent isolated yields (Scheme 2). For instance, 4-methylphenyl-boronic acid reacted with compound **3**, giving rise to the desired product **4b** in 83% yield. It is noteworthy that the ester group could be tolerated under the standard conditions, and compound **4g** was isolated in 95% yield.

To further diversify the monocoupled 2-pyrones, we then explored the reactivity of the remaining tosyloxy group at the C4

**Scheme 2** Synthesis of 3-aryl-4-tosyloxy-2-pyrone **4**.

position. Our investigation began with the reaction of 6-methyl-3-phenyl-4-tosyloxy-2-pyrone **4a** with phenylboronic acid under the above optimized reaction conditions. The expected product **5a** was generated only in 28% yield. After screening of different conditions, the best result (89% yield) was obtained when the reaction was catalyzed by 5 mol% of Pd(OAc)₂ and 10 mol% of PCy₃ in the presence of 3.0 equiv. of K₂HPO₄·3H₂O in MeOH at 90 °C. To test the effectiveness of the 4-position couplings of 6-methyl-3-aryl-4-tosyloxy-2-pyrone **4**, a range of arylboronic acids were examined under the optimized reaction conditions (Table 3). As shown, various arylboronic acids bearing electron-withdrawing as well as electron-donating substituents underwent the 4-position cross-coupling reactions, providing 3,4-diarylated 2-pyrones in fair to excellent yields. For example, 6-methyl-3-phenyl-4-tosyloxy-2-pyrone **4a** coupled with 4-tolylboronic acid gave the desired product **5b** in 95% yield (Table 3, entry 2). Reaction of compound **4c** with 4-chlorophenylboronic acid afforded the corresponding product **5k** in 80% yield (Table 3, entry 11). Various symmetrical or unsymmetrical 3,4-diarylated 2-pyrones **5** could be generated as well under the standard conditions. Again, when ester-substituted phenylboronic acid was used in the reaction of 6-methyl-3-phenyl-4-tosyloxy-2-pyrone **4a**, the desired product **5l** could be formed with a 66% yield (Table 3, entry 12). However, only a trace

Table 2 Condition screening for palladium-catalyzed reaction of 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** with phenylboronic acid


Entry	[Pd]	Ligand	Base	Solvent	Yield ^a (%)
1	Pd ₂ (dba) ₃	JohnPhos	KF	Toluene	49
2	Pd ₂ (dba) ₃	JohnPhos	KF	THF	5
3	Pd ₂ (dba) ₃	JohnPhos	KF	MeCN	27
4	Pd ₂ (dba) ₃	JohnPhos	KF	Dioxane	Trace
5	Pd ₂ (dba) ₃	JohnPhos	KF	DCE	41
6	Pd ₂ (dba) ₃	JohnPhos	KF	DMF	nr
7	Pd ₂ (dba) ₃	JohnPhos	KF	NMP	nr
8	Pd ₂ (dba) ₃	JohnPhos	KF	DMSO	nr
9	Pd ₂ (dba) ₃	JohnPhos	KF	Acetone	19
10	Pd ₂ (dba) ₃	JohnPhos	KF	MeOH	21
11	Pd ₂ (dba) ₃	JohnPhos	KF	^t BuOH	Trace
12	Pd ₂ (dba) ₃	JohnPhos	KF	H ₂ O	nr
13	Pd ₂ (dba) ₃	JohnPhos	KF	Toluene/H ₂ O	92
14	Pd(OAc) ₂	JohnPhos	KF	Toluene/H ₂ O	49
15	Pd(PPh ₃) ₄	JohnPhos	KF	Toluene/H ₂ O	58
16	Pd(PPh ₃) ₂ Cl ₂	JohnPhos	KF	Toluene/H ₂ O	64
17	Pd/C	JohnPhos	KF	Toluene/H ₂ O	24
18	Pd ₂ (dba) ₃	—	KF	Toluene/H ₂ O	44
19	Pd ₂ (dba) ₃	PPh ₃	KF	Toluene/H ₂ O	45
20	Pd ₂ (dba) ₃	Josiphos	KF	Toluene/H ₂ O	52
21	Pd ₂ (dba) ₃	Xantphos	KF	Toluene/H ₂ O	33
22	Pd ₂ (dba) ₃	DPPF	KF	Toluene/H ₂ O	42
23	Pd ₂ (dba) ₃	DIPF	KF	Toluene/H ₂ O	51
24	Pd ₂ (dba) ₃	JohnPhos	Na ₂ CO ₃	Toluene/H ₂ O	43
25	Pd ₂ (dba) ₃	JohnPhos	K ₂ CO ₃	Toluene/H ₂ O	33
26	Pd ₂ (dba) ₃	JohnPhos	Cs ₂ CO ₃	Toluene/H ₂ O	45
27	Pd ₂ (dba) ₃	JohnPhos	NaHCO ₃	Toluene/H ₂ O	66
28	Pd ₂ (dba) ₃	JohnPhos	K ₃ PO ₄ ·3H ₂ O	Toluene/H ₂ O	38
29	Pd ₂ (dba) ₃	JohnPhos	K ₂ HPO ₄ ·3H ₂ O	Toluene/H ₂ O	49
30	Pd ₂ (dba) ₃	JohnPhos	Et ₃ N	Toluene/H ₂ O	56

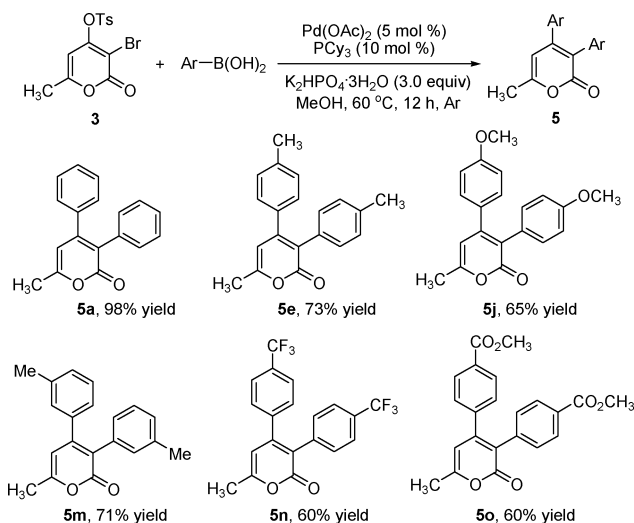
^a Isolated yield based on 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3**.

amount of product was observed when compound **4** with electron-withdrawing group attached to the aromatic ring in the 3-position was used (Table 3, entries 13–15).

We also tried the one-pot synthesis of symmetrical 3,4-diarylated 2-pyrone derivatives from 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** under the conditions shown in Table 2 (Scheme 3). Good yields were observed for the transformation when arylboronic acids bearing electron-donating or -withdrawing substituents were used, by increasing the amount of arylboronic acid to 3.0 equiv. compared to substrate **3**. For instance, reaction of compound **3** with 4-methylphenylboronic acid led to 2-pyrone **5e** in 73% yield. Trifluoromethyl- or ester-substituted phenylboronic acid was a good partner as well in the conversion.

Conclusions

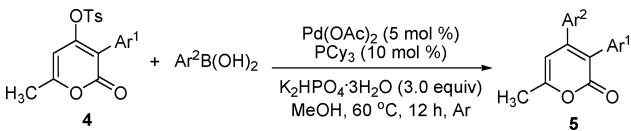
In summary, we have developed an efficient synthetic method for the synthesis of 3,4-disubstituted 2-pyrones *via* a sequential site-selective Pd-catalyzed Suzuki cross-coupling reactions of 3-bromo-6-methyl-4-tosyloxy-2-pyrone. This approach has the potential for the rapid synthesis of bioactive substituted 2-pyrone derivatives. Further studies for generation of diverse 2-pyrones are currently underway in our laboratory.

**Scheme 3** One-pot synthesis of symmetrical 3,4-diarylated 2-pyrones **5**.

Experimental Section

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All solvents were dried

Table 3 Palladium-catalyzed cross-coupling reactions of compound **4** with arylboronic acids^a

				
Entry	4/Ar ¹	Ar ²	Product 5	Yield (%) ^b
1	4a /C ₆ H ₅	C ₆ H ₅	5a	89
2	4a /C ₆ H ₅	4-MeC ₆ H ₄	5b	95
3	4a /C ₆ H ₅	4-MeOC ₆ H ₄	5c	94
4	4a /C ₆ H ₅	4-ClC ₆ H ₄	5d	73
5	4b /4-MeC ₆ H ₄	4-MeC ₆ H ₅	5e	82
6	4b /4-MeC ₆ H ₄	4-MeOC ₆ H ₄	5f	70
7	4b /4-MeC ₆ H ₄	4-ClC ₆ H ₄	5g	64
8	4c /4-MeOC ₆ H ₄	C ₆ H ₅	5h	55
9	4c /4-MeOC ₆ H ₄	4-MeC ₆ H ₄	5i	67
10	4c /4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	5j	80
11	4c /4-MeOC ₆ H ₄	4-ClC ₆ H ₄	5k	80
12	4a /C ₆ H ₅	4-MeO ₂ CC ₆ H ₄	5l	66
13	4d /4-ClC ₆ H ₄	4-MeOC ₆ H ₄	—	Trace
14	4d /4-ClC ₆ H ₄	4-ClC ₆ H ₄	—	Trace
15	4g /4-MeO ₂ CC ₆ H ₄	4-MeOC ₆ H ₄	—	Trace

^a Reaction conditions: substrate **4** (0.30 mmol), arylboronic acid (1.5 equiv.), Pd(OAc)₂ (5 mol%), PCy₃ (10 mol%), K₂HPO₄·3H₂O (3.0 equiv.), methanol (2.0 mL), 60 °C, 12 h, Ar. ^b Isolated yield based on compound **4**.

and distilled according to standard procedures. All reactions were performed in reaction tubes under Ar. The flash column chromatography was performed using silica gel (60–Å pore size, 32–63 µm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane (TMS) on the δ scale.

General procedure for the synthesis of compound **4** through palladium-catalyzed reaction of compound **3** with arylboronic acids: A mixture of compound **3** (0.3 mmol), arylboronic acid (1.5 equiv.), Pd₂(dba)₃ (2.5 mol%), JohnPhos (5 mol%), and KF (3.0 equiv.) in 3.0 mL of toluene/H₂O (v/v:2/1) was stirred at 60 °C for 24 h. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to produce the corresponding product **4**.

6-Methyl-4-(4-methylbenzenesulfonyloxy)-3-phenyl-2-pyrone **4a**. White solid (92% yield), mp: 125.7–127.0 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, *J* = 7.2 Hz, 2H), 7.26–7.18 (m, 3H), 7.08–7.05 (m, *J* = 8 Hz, 4 Hz, 4H), 6.45 (s, 1H), 2.39 (s, 3H), 2.34 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.2, 161.8, 156.4, 145.8, 131.5, 130.0, 129.7, 128.5, 128.1, 127.9, 127.7, 116.1, 102.3, 21.69, 20.1; HRMS (ESI) Calcd for C₁₉H₁₆O₅SNa (M+Na⁺), 379.0616; Found, 379.0622.

6-Methyl-4-(4-methylbenzenesulfonyloxy)-3-(4-methylphenyl)-2-pyrone **4b**. Yellow oil (83% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.06–6.96 (m, 6H), 6.42 (s, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.4, 161.5, 156.2, 145.8, 138.1, 131.6, 129.9, 129.5, 128.4, 127.9,

126.0, 116.2, 102.4, 21.74, 21.34, 20.09; HRMS (ESI) Calcd for C₂₀H₁₈O₅SH (M+H⁺) 371.0953; Found, 371.0951.

3-(4-Methoxyphenyl)-6-methyl-4-(4-methylbenzenesulfonyloxy)-2-pyrone **4c**. Yellow oil (62% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.43 (s, 1H), 3.81 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.2, 161.2, 159.4, 155.9, 145.7, 131.3, 129.6, 127.9, 121.1, 115.1, 113.2, 102.5, 55.2, 21.7, 20.0; HRMS (ESI) Calcd for C₂₀H₁₈O₆SNa (M+Na⁺) 409.0722; Found, 409.0714.

3-(4-Chlorophenyl)-6-methyl-4-(4-methylbenzenesulfonyloxy)-2-pyrone **4d**. Yellow solid (59% yield), mp: 108.1–109.3 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.43 (s, 1H), 2.34 (s, 3H), 2.23 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.0, 162.3, 156.8, 146.2, 134.3, 131.5, 129.7, 127.9, 127.8, 127.5, 114.9, 102.7, 21.7, 20.2; HRMS (ESI) Calcd for C₁₉H₁₅ClO₅Na (M+Na), 413.0226; Found, 413.0219.

3-(2-Methoxyphenyl)-6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate **4e**. Yellow solid (66% yield), mp: 134.9–136.2 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 12.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.44 (s, 1H), 3.65 (s, 3H), 2.42 (s, 3H), 2.34 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 162.8, 161.8, 157.1, 157.0, 145.5, 132.0, 131.3, 130.3, 130.0, 129.7, 128.4, 127.9, 120.1, 118.3, 113.5, 110.8, 101.8, 55.4, 21.7, 20.1; HRMS (ESI) Calcd for C₂₀H₁₈NaO₆S (M+Na), 409.0722; Found, 409.0710.

6-Methyl-2-oxo-3-*m*-tolyl-2H-pyran-4-yl 4-methylbenzenesulfonate **4f**. Yellow oil (85% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.12–7.04 (m, 4H), 6.91 (d, *J* = 4.0 Hz, 1H), 6.81 (s, 1H), 6.45 (s, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.3, 161.7, 156.3, 145.7, 137.3, 131.6, 130.4, 129.6, 128.9, 128.5, 127.9, 127.7, 127.2, 116.3, 102.4, 21.7, 21.3, 20.1; HRMS (ESI) Calcd for C₂₀H₁₉O₅S (M+H), 371.0953; Found, 371.0958.

Methyl 4-(6-methyl-2-oxo-4-(tosyloxy)-2H-pyran-3-yl)benzoate **4g**. Yellow solid (95% yield), mp: 152.1–153.8 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.47 (s, 1H), 3.94 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 166.6, 162.8, 162.7, 157.1, 146.2, 133.9, 131.3, 130.1, 129.8, 129.6, 128.8, 127.8, 115.0, 102.5, 52.2, 21.6, 20.2; HRMS (ESI) Calcd for C₂₁H₁₈NaO₇S (M+Na), 437.0671; Found, 437.0678.

General procedure for the generation of 3,4-disubstituted 2-pyrones **5** through palladium-catalyzed reaction of compound **4** with arylboronic acids: A mixture of substrate **4** (0.3 mmol), arylboronic acid (1.5 equiv.), Pd(OAc)₂ (5 mol%), PCy₃ (10 mol%), and K₂HPO₄·3H₂O (3.0 equiv.) in methanol (2.0 mL) was stirred at 60 °C for 12 h. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to produce the corresponding product **5**.

3,4-Diphenyl-6-methyl-2-pyrone **5a**. Yellow solid (89% yield), mp: 130.1–130.7 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.24–7.20 (m, 6H), 7.14–7.12 (m, 2H), 7.09–7.07 (m, 2H), 6.17 (s, 1H), 2.33 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 160.1, 152.6, 137.5, 133.8, 130.8, 128.7, 128.6, 128.2, 127.9, 127.5, 122.0, 107.1, 19.9; HRMS (ESI) Calcd for C₁₈H₁₄NaO₂ (M+Na) 285.0891; Found, 285.0895.

6-Methyl-4-(4-methylphenyl)-3-phenyl-2-pyrone **5b**. Yellow solid (95% yield), mp: 109.2–110.7 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.22–7.15 (m, 3H), 7.15–7.13 (m, 2H), 7.02–6.96 (m, 4H), 6.16 (s, 1H), 2.31 (s, 3H), 2.28 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.7, 159.9, 152.7, 138.8, 134.5, 134.2, 130.8, 128.9, 128.7, 128.0, 127.4, 121.6, 107.2, 21.3, 19.9; HRMS (ESI) Calcd for C₁₉H₁₆O₂Na (M+Na⁺) 299.1048; Found, 299.1044.

4-(4-Methoxyphenyl)-6-methyl-3-phenyl-2-pyrone **5c**. Yellow solid (94% yield), mp: 109.3–110.0 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.24–7.22 (m, 3H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.17 (s, 1H), 3.75 (s, 3H), 2.31 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.7, 159.9, 152.2, 134.3, 130.9, 130.4, 129.5, 128.1, 127.5, 121.1, 113.7, 107.1, 55.2, 19.9; HRMS (ESI) Calcd for C₁₉H₁₆O₃Na (M+Na) 315.0997; Found, 315.0997.

4-(4-Chlorophenyl)-6-methyl-3-phenyl-2-pyrone **5d**. Yellow solid (73% yield), mp: 120.9–122.0 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.11 (m, 8H), 7.03–7.01 (m, 1H), 6.13 (s, 1H), 2.33 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.1, 160.4, 151.4, 135.9, 134.8, 133.5, 130.8, 130.1, 128.6, 128.2, 127.8, 122.2, 106.7, 19.9; HRMS (ESI) Calcd for C₁₈H₁₃ClO₂Na (M+Na⁺) 319.0502; Found, 319.0495.

3,4-Di(4-methylphenyl)-6-methyl-2-pyrone **5e**. Yellow oil (82% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.03–6.97 (m, 8H), 6.14 (s, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.8, 159.6, 152.3, 138.7, 137.2, 134.7, 131.1, 130.6, 128.9, 128.8, 128.6, 121.6, 107.2, 21.3, 19.9; HRMS (ESI) Calcd for C₂₀H₁₈NO₂Na (M+Na⁺) 313.1204; Found, 313.1204.

4-(4-Methoxyphenyl)-6-methyl-3-(4-methylphenyl)-2-pyrone **5f**. Yellow solid (70% yield), mp: 135.7–137.1 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.05–7.29 (m, 6H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.15 (s, 1H), 3.76 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.9, 159.8, 159.6, 151.8, 137.1, 131.2, 130.7, 130.3, 129.8, 128.8, 121.2, 113.7, 107.1, 55.2, 21.3, 19.9; HRMS (ESI) Calcd for C₂₀H₁₈O₃Na (M+Na⁺) 329.1154; Found, 329.1160.

4-(4-Chlorophenyl)-6-methyl-3-(4-methylphenyl)-2-pyrone **5g**. White solid (64% yield), mp: 131.6–132.6 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, *J* = 8.4 Hz, 2H), 7.05–7.03 (m, 4H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.11 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.5, 160.1, 150.9, 137.6, 136.1, 134.7, 130.6, 130.4, 130.1, 128.9, 128.6, 122.2, 106.7, 21.3, 19.9; HRMS (ESI) Calcd for C₁₉H₁₅ClO₂Na (M+Na⁺) 333.0658; Found, 333.0664.

3-(4-Methoxyphenyl)-6-methyl-4-phenyl-2-pyrone **5h**. Yellow oil (55% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.24–7.22 (m, 3H), 7.11–7.05 (m, 4H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.15 (s, 1H), 3.75 (s, 3H), 2.32 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.8, 159.6, 158.8, 152.1, 137.8, 132.0, 128.6, 128.5, 128.3, 125.9, 113.5, 107.1, 55.1, 19.8; HRMS (ESI) Calcd for C₁₉H₁₇O₃ (M+H⁺) 293.1178; Found, 293.1170.

3-(4-Methoxyphenyl)-6-methyl-4-(4-methylphenyl)-2-pyrone **5i**. Yellow oil (67% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.08–6.98 (m, 6H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.13 (s, 1H), 3.76 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.9, 159.4, 158.8, 152.1, 138.6, 134.8, 132.0, 129.0, 128.6, 126.2, 121.2, 113.5, 107.2, 55.1, 21.2, 19.8; HRMS (ESI) Calcd for C₂₀H₁₉O₃ (M+H⁺) 307.1334; Found, 307.1329.

3,4-Di(4-methoxyphenyl)-6-methyl-2-pyrone **5j**. Yellow oil (80% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.75 (d,

J = 8.8 Hz, 2H) 6.30 (s, 1H), 3.77 (s, 6H), 2.30 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.7, 161.8, 158.7, 151.70, 132.0, 130.3, 128.2, 126.4, 120.8, 114.6, 113.7, 107.1, 103.2, 55.5, 55.2, 19.9. HRMS (ESI) Calcd for C₂₀H₁₈O₄Na (M+Na⁺), 345.1103; Found, 345.1088.

4-(4-Chlorophenyl)-3-(4-methoxyphenyl)-6-methyl-2-pyrone **5k**. Yellow oil (80% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, *J* = 8.8 Hz, 2H), 7.06–7.03 (m, 4H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.10 (s, 1H), 3.76 (s, 3H), 2.31 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.6, 159.9, 159.0, 150.8, 136.2, 134.6, 132.0, 130.1, 128.6, 125.6, 121.8, 113.7, 106.7, 55.2, 19.9; HRMS (ESI) Calcd for C₁₉H₁₅ClO₃Na (M+Na⁺) 349.0607; Found, 349.0601.

Methyl 4-(6-methyl-2-oxo-3-phenyl-2H-pyran-4-yl)benzoate **5l**. Yellow solid (66% yield), mp: 195.0–196.1 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 4.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 4.0 Hz, 2H), 6.17 (s, 1H), 3.89 (s, 3H), 2.35 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 166.4, 163.2, 160.5, 151.5, 142.1, 133.3, 130.7, 130.1, 129.5, 128.7, 128.1, 127.8, 122.6, 106.5, 52.2, 19.9; HRMS (ESI) Calcd for C₂₀H₁₆NaO₄ (M+Na⁺) 343.0946; Found, 343.0931.

6-Methyl-3,4-dim-tolyl-2H-pyran-2-one **5m**. Yellow oil (71% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.07–7.00 (m, 5H), 6.93 (s, 1H), 6.88–6.82 (m, 2H), 6.16 (s, 1H), 2.31 (s, 3H), 2.23 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 163.7, 159.8, 152.7, 137.8, 137.4, 137.3, 133.8, 131.3, 129.3, 129.2, 128.3, 128.0, 127.9, 127.8, 125.8, 122.0, 107.1, 21.4, 21.3, 19.9; HRMS (ESI) Calcd for C₂₀H₁₈NaO₂ (M+Na⁺) 313.1204; Found, 313.1215.

6-Methyl-3,4-bis(4-(trifluoromethyl)phenyl)-2H-pyran-2-one **5n**. White crystal (60% yield), mp: 125.8–126.8 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.54–7.49 (m, 4H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.18 (s, 1H), 2.37 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 162.6, 161.6, 152.0, 140.6, 137.0, 131.5, 130.9, 129.7, 128.9, 125.6 (dd), 125.2 (dd), 122.5, 122.2, 121.2, 106.6, 20.0; HRMS (ESI) Calcd for C₂₀H₁₂F₆NaO₂ (M+Na⁺) 421.0639; Found, 421.0651.

6-Methyl-2-pyrone **5o**. Yellow solid (60% yield), mp: 54.9–55.9 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.90–7.87 (m, 4H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.20 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.36 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 166.6, 166.2, 162.6, 161.3, 152.4, 141.5, 138.3, 130.9, 130.4, 129.6, 129.3, 129.2, 128.6, 121.5, 106.6, 52.2, 52.1, 20.0; HRMS (ESI) Calcd for C₂₂H₁₈NaO₆ (M+Na⁺) 401.1001; Found, 401.1012.

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