Generation of diverse 2-pyrone via palladium-catalyzed site-selective Suzuki-Miyaura couplings of 3-bromo-4-tosyloxy-2-pyrole

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Supporting Information

1. General experimental methods (S2)
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General experimental methods

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

Synthesis of 3-bromo-6-methyl-4-tosyloxy-2-pyrone 3:¹

Br₂ (1.0 equiv) was added dropwise into a solution of 4-hydroxy-6-methyl-2-pyrone (8.0 mmol) in methanol at 0 °C. The resulting white solid was appeared in the process of addition of Br₂. After completion of the reaction as monitored by TLC, the mixture was then concentrated under reduced pressure to yield the crude 3-bromo-4-hydroxy-6-methyl-2-pyrone 2. Without purification, the crude was dissolved in CH₂Cl₂. Then Et₃N (3.0 equiv) and TsCl (1.2 equiv) were added to the suspension of compound 2 at 0 °C. The mixture was stirred at room temperature until the reaction was completed. After the solvent was evaporated under reduced pressure, the mixture was purified by flash column chromatography on silica gel to afford the desiring product 3 in 86% yield.

General procedure for the reaction of compound 3 with arylboronic acids (Scheme 2):
A mixture of compound 3 (0.3 mmol), arylboronic acid (1.5 equiv), Pd$_2$(dba)$_3$ (2.5 mol %), Johnphos (5 mol %), and KF (3.0 equiv) in 3.0 mL of toluene/H$_2$O (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.

General procedure for the reaction of compound 4 with arylboronic acids (Table 3):

A mixture of substrate 4 (0.3 mmol), arylboronic acid (1.5 equiv), Pd(OAc)$_2$ (5 mol %), PCy$_3$ (10 mol %), and K$_2$HPO$_4$·3H$_2$O (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.

General procedure for the Synthesis of symmetrically 3,4-diarylated 2-pyrones 5 (Scheme 3):

Following the same procedure above (increasing the amount of arylboronic acid to 3.0 equiv).
3-bromo-6-methyl-4-(4-methylbenzenesulfonyloxy)-2-pyrone 3. White solid (86% yield), mp: 165.3-166.2 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.88 (d, $J=8.4$ Hz, 2H), 7.40 (d, $J=8.0$ Hz, 2H), 6.44 (s, 1H), 2.49 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (400 MHz, CDCl$_3$) δ 161.9, 160.2, 158.8, 147.0, 131.9, 130.2, 128.5, 101.5, 99.8, 21.8, 19.9; HRMS (ESI) Calcd for C$_{13}$H$_{11}$BrO$_5$Na (M+Na), 380.9408; Found, 380.9408.

6-methyl-4-(4-methylbenzenesulfonyloxy)-3-phenyl-2-pyrone 4a. White solid (92% yield), mp: 125.7-127.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 (d, $J=7.2$ Hz, 2H), 7.26-7.18 (m, 3H), 7.08-7.05 (m, $J=8$ Hz, 4H), 6.45 (s, 1H), 2.39 (s, 3H), 2.34 (s, 3H); $^{13}$C NMR (400 MHz, CDCl$_3$) 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 C$_{19}$H$_{16}$O$_5$SNa (M+Na$^+$), 379.0616; Found, 379.0622.

6-methyl-4-(4-methylbenzenesulfonyloxy)-3-(4-methylphenyl)-2-pyrone 4b. Yellow oil (83% yield). $^1$H NMR (400 MHz, CDCl$_3$) 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); $^{13}$C NMR (400 MHz, CDCl$_3$) 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 C$_{20}$H$_{18}$O$_5$SH (M+H$^+$) 371.0953; Found, 371.0951.

3-(4-methoxylphenyl)-6-methyl-4-(4-methylbenzenesulfonyloxy)-2-pyrone 4c. Yellow oil (62% yield). $^1$H NMR (400 MHz, CDCl$_3$) 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); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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 C\(_{20}\)H\(_{18}\)O\(_6\)SNa (M+Na\(^+\)) 409.0722; Found, 409.0714.

![Structure 4d](image)

3-(4-chlorophenyl)-6-methyl-4-(4-methylbenzenesulfonyloxy)-2-pyrone 4d. Yellow solid (59% yield), mp: 108.1-109.3 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 163.0, 162.3, 156.8, 146.2, 134.3, 131.5, 129.7, 127.9, 127.8, 114.9, 102.7, 21.7, 20.2; HRMS (ESI) Calcd for C\(_{19}\)H\(_{15}\)ClO\(_5\)Na (M+Na), 413.0226; Found, 413.0219.

![Structure 4e](image)

3-(2-Methoxyphenyl)-6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate 4e. Yellow solid (66% yield), mp: 134.9-136.2 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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 C\(_{20}\)H\(_{18}\)NaO\(_6\)S (M+Na), 409.0722; Found, 409.0710.

![Structure 4f](image)

6-Methyl-2-oxo-3-\(m\)-tolyl-2H-pyran-4-yl 4-methylbenzenesulfonate 4f. Yellow oil (85% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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
Methyl 4-(6-methyl-2-oxo-4-(tosyloxy)-2H-pyran-3-yl)benzoate **4g**. Yellow solid (95% yield), mp: 152.1-153.8 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{21}$H$_{18}$NaO$_{3}$S (M+Na), 437.0671; Found, 437.0678.

3,4-diphenyl-6-methyl-2-pyrone **5a**. Yellow solid (89% yield), mp: 130.1-130.7 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{18}$H$_{14}$NaO$_{2}$ (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. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{19}$H$_{16}$O$_{2}$Na (M+Na$^+$) 299.1048; Found, 299.1044.
4-(4-methoxylphenyl)-6-methyl-3-phenyl-2-pyrone 5c. Yellow solid (94% yield), mp: 109.3-110.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{19}$H$_{16}$O$_3$Na (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. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26-7.11 (m, 8H), 7.03-7.01 (m, 1H), 6.13 (s, 1H), 2.33 (s, 3H); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{18}$H$_{13}$ClO$_2$Na (M+Na$^+$) 319.0502; Found, 319.0495.

3,4-di(4-methylphenyl)-6-methyl-2-pyrone 5e. Yellow oil (82% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.03-6.97 (m, 8H), 6.14 (s, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{20}$H$_{18}$NO$_2$Na (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. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{20}$H$_{18}$O$_3$Na (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. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{19}$H$_{15}$ClO$_2$Na (M+Na$^+$) 333.0658; Found, 333.0664.

3-(4-methoxyphenyl)-6-methyl-4-phenyl-2-pyrone 5h. Yellow oil (55% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C_{19}H_{17}O_{3} (M+H^{+}) 293.1178; Found, 293.1170.

![Structure of 3-(4-methoxylphenyl)-6-methyl-4-(4-methylphenyl)-2-pyrone 5i](image)

3-(4-methoxylphenyl)-6-methyl-4-(4-methylphenyl)-2-pyrone **5i**. Yellow oil (67% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 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 C$_{20}$H$_{19}$O$_3$ (M+H$^+$) 307.1334; Found, 307.1329.

![Structure of 3,4-di(4-methoxylphenyl)-6-methyl-2-pyrone 5j](image)

3,4-di(4-methoxylphenyl)-6-methyl-2-pyrone **5j**. Yellow oil (80% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 163.7, 161.8, 158.7, 151.7, 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 C$_{20}$H$_{18}$O$_4$Na (M+Na$^+$), 345.1103; Found, 345.1088.

![Structure of 4-(4-chlorophenyl)-3-(4-methoxylphenyl)-6-methyl-2-pyrone 5k](image)

4-(4-chlorophenyl)-3-(4-methoxylphenyl)-6-methyl-2-pyrone **5k**. Yellow oil (80% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (400 MHz,
Methyl 4-(6-methyl-2-oxo-3-phenyl-2H-pyran-4-yl)benzoate \(5\). Yellow solid (66\% yield), mp: 195.0-196.1 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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 C\(_{20}\)H\(_{16}\)NaO\(_4\) (M+Na\(^{+}\)) 343.0946; Found, 343.0931.

6-Methyl-3,4-di\(m\)-tolyl-2\(H\)-pyran-2-one \(5m\). Yellow oil (71\% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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 C\(_{20}\)H\(_{18}\)NaO\(_2\) (M+Na\(^{+}\)) 313.1204; Found, 313.1215.

6-Methyl-3,4-bis(4-(trifluoromethyl)phenyl)-2\(H\)-pyran-2-one \(5n\). White crystal (60\% yield). HRMS (ESI) Calcd for C\(_{20}\)H\(_{18}\)F\(_{14}\)NaO\(_2\) (M+Na\(^{+}\)) 495.1057; Found, 495.1052.
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 C₂₂H₁₆NaO₆ (M+Na⁺) 401.1001; Found, 401.1012.