

SUPPORTING INFORMATION

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Regioselective Synthesis of 3,4-Disubstituted Isocoumarins by Pd-Catalyzed Annulation of 2-Iodoaromatic Acids with Ynamides

authored by

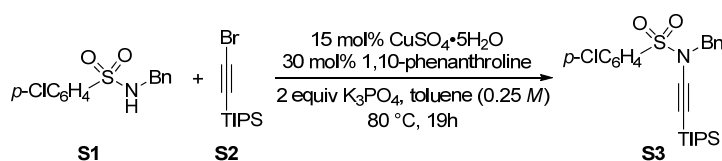
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GENERAL EXPERIMENTAL INFORMATION

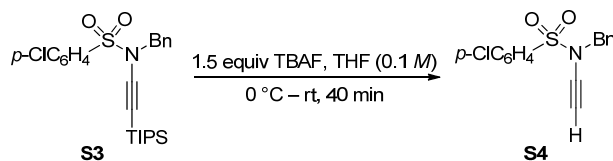
All reactions were performed in oven-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Chromatographic separations were performed using 200–300 mesh silica gel. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker's AscendTM 400 NMR spectrometer using CDCl_3 as solvent with TMS or residual solvent as standard unless otherwise noted. ^{13}C NMR (100 MHz) spectra were reported in ppm with the internal chloroform signal at 77.2 ppm as a standard. Infrared spectra were obtained on a Bruker ALPHA FT/IR spectrophotometer and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using 254 nm polyester-backed plates and visualized using UV and KMnO_4 stain. High-resolution mass spectra (HRMS) was performed on a Bruker MicrOTOF-Q II mass spectrometer. All spectral data obtained for new compounds are reported here.

Procedure for Synthesis of Ynamides **2c**.



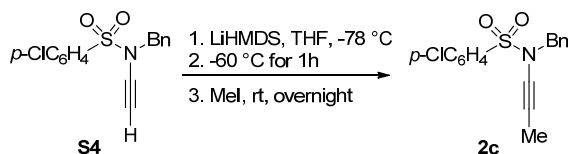
To a oven-dried screw-cap vial were added (in the following order) amide **S1** (752.5 mg, 2.67 mmol), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (100.0 mg, 0.40 mmol), 1,10-phenanthroline (144.3 mg, 0.80 mmol) and K_3PO_4 (1.13 g, 5.34 mmol), toluene (10.7 mL, amide *concn* = 0.25 M), and the alkyne bromide **S2** (837.3 mg, 3.20 mmol). The vial was evacuated under vacuum and flushed with nitrogen gas for three times, then sealed under nitrogen and heated to 80 °C. When the reaction was judged to be complete by TLC after 19 hours, the mixture was cooled to rt, filtered through a pad of silica gel, and purified by silica gel flash column chromatography [isocratic eluent: 20:1 petroleum ether/EtOAc + 3% NEt_3] to afford ynamide **S3** (1.13 g, 2.45 mmol, 92% yield).

S3: R_f = 0.47 [20:1 petroleum ether/EtOAc]; white solid; mp = 49–50 °C; ^1H NMR (400 MHz, CDCl_3) δ 0.96 (s, 21H), 4.53 (s, 2H), 7.27–7.31 (m, 5H), 7.41–7.45 (m, 2H), 7.73–7.77 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 11.4, 18.7, 55.9, 70.9, 96.1, 128.6, 128.7, 129.1, 129.3, 129.4, 134.2, 136.2, 140.3; IR (KBr) (cm^{-1}) 2943s, 2865s, 2163s, 1586w, 1477m, 1458m, 1373s, 1170s, 1094s, 1011s; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{32}\text{ClNO}_2\text{SSiNa}$ [$\text{M}+\text{Na}$]⁺: 484.1504; found 484.1504.



To an oven-dried flask were added ynamide **S3** (1.13 g, 2.45 mmol) and THF (24.5 mL, ynamide *concn* = 0.10 M). The solution was cooled to 0 °C, and TBAF (3.67 mL, 3.67 mmol, 1.0 M in THF) was added dropwise via syringe. After the addition was complete, the mixture was allowed to warm to rt. The reaction was judged to be complete by TLC analysis after 40 min, and saturated NH₄Cl solution (20 mL) was added to quench the reaction. The quenched mixture was extracted with EtOAc, dried over anhydrous Na₂SO₄, filtered, concentrated *in vacuo* and purified by silica gel flash column chromatography [isocratic eluent: 20:1 petroleum ether/EtOAc + 3% NEt₃] to afford crude product. After washed with 10:1 petroleum ether/EtOAc, pure ynamide **S4** (618.0 mg, 2.02 mmol, 82% yield) was obtained.

S4: R_f = 0.27 [20:1 petroleum ether/EtOAc]; white solid; mp = 96–97 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.71 (s, 1H), 4.53 (s, 2H), 7.27–7.31 (m, 5H), 7.44–7.47 (m, 2H), 7.73–7.77 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 55.7, 60.1, 76.1, 128.7, 128.78, 128.84, 129.2, 129.6, 134.1, 136.2, 140.5; IR (KBr) (cm⁻¹) 3280s, 2138m, 1584m, 1475m, 1452m, 1367s, 1283m, 1169s, 1095s, 1085s, 1012s; HRMS (ESI): *m/z* calcd for C₁₅H₁₂ClNO₂SNa [M+Na]⁺: 328.0169; found 328.0165.

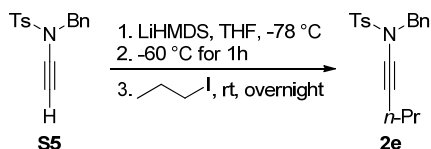


To an oven-dried flask were charged with ynamide **S4** (244.6 mg, 0.80 mmol) and THF (5 mL, ynamide *concn* = 0.16 M). To this solution at -78 °C was added LHMDS (1.20 mL, 1.0 M in THF), and then the mixture was allowed to warm to -60 °C. After the reaction was stirred at -60 °C for 1 h, MeI (0.10 mL, 1.60 mmol) was added, the resulting mixture was warmed to rt slowly, stirred overnight (12 h) and monitored using TLC analysis, water (10 mL) was added to quench the reaction. The quench mixture was extracted with EtOAc, dried over anhydrous Na₂SO₄, filtered, concentrated *in vacuo* and purified by silica gel flash column chromatography [isocratic eluent: 20:1 petroleum ether/EtOAc + 3% NEt₃] to afford ynamide **2c** (250.7 mg, 0.78 mmol) in 98% yield.

2c: R_f = 0.26 [20:1 petroleum ether/EtOAc]; yellow solid; mp = 76–77 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.83 (s, 3H), 4.48 (s, 2H), 7.27–7.31 (m, 5H), 7.44–7.48 (m, 2H), 7.73–7.76 (m, 2H); ¹³C NMR (100

MHz, CDCl₃) δ 3.4, 55.9, 66.7, 72.1, 128.4, 128.6, 128.7, 129.1, 129.4, 134.7, 136.4, 140.1; IR (KBr) (cm⁻¹) 3088m, 2917w, 2265w, 1583m, 1476m, 1455m, 1375s, 1184s, 1172s, 1091s, 1084s; HRMS (ESI): *m/z* calcd for C₁₆H₁₄ClNO₂SNa [M+Na]⁺: 342.0326; found 342.0311.

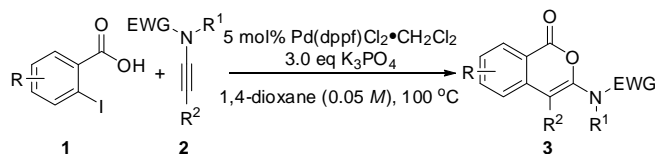
Procedure for Synthesis of Ynamides **2e**.



To a oven-dried flask was added ynamide **S5**¹ (285.4 mg, 1.00 mmol) and THF (7 mL, ynamide *concn* = 0.14 M). To this solution at -78 °C was added LHMDS (1.50 mL, 1.0 M in THF), and then the mixture was allowed to warm to -60 °C. After the reaction was stirred at -60 °C for 1 h, *n*-propyl iodide (0.19 mL, 2.00 mmol) was added, the resulting mixture was warmed to rt slowly, stirred overnight (12 h) and monitored using TLC analysis, water (10 mL) was added to quench the reaction. The quench mixture was extracted with EtOAc, dried over anhydrous Na₂SO₄, filtrated, concentrated *in vacuo* and purified by silica gel flash column chromatography [isocratic eluent: 20:1 petroleum ether/EtOAc + 3% NEt₃] to afford ynamide **2e** (223.3 mg, 0.68 mmol) in 68% yield.

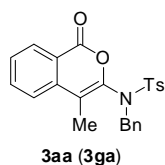
2e: *R_f* = 0.23 [20:1 petroleum ether/EtOAc]; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 0.82 (t, 3H, *J* = 7.4 Hz), 1.35-1.44 (m, 2H), 2.13 (t, 2H, *J* = 6.9 Hz), 2.43 (s, 3H), 4.44 (s, 2H), 7.27-7.31 (m, 7H), 7.74 (d, 2H, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.4, 20.5, 21.7, 22.4, 55.7, 70.9, 73.6, 127.8, 128.2, 128.5, 128.8, 129.7, 134.9, 135.0, 144.4; IR (film) (cm⁻¹) 2963m, 2932m, 2872w, 2253w, 2044w, 1597m, 1496m, 1456m, 1363s, 1168s; HRMS (ESI): *m/z* calcd for C₁₉H₂₁NO₂SNa [M+Na]⁺: 350.1185; found 350.1193.

General Procedure for the Synthesis of 3,4-Disubstituted Isocoumarins **3**.



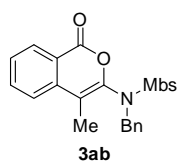
To an oven-dried sealed tube were added 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol), ynamide **2a**¹ (59.9 mg, 0.20 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (8.2 mg, 0.01 mmol), K₃PO₄ (127.4 mg, 0.60 mmol) and 1,4-dioxane (4.0 mL, ynamide *concn* = 0.05 M) in sequence at rt. The reaction vessel was then capped and directly heated to 100 °C. After stirring at 100 °C for 16.0 h, the reaction mixture was cooled to rt, filtered through a short plug of silica gel, concentrated *in vacuo*, and purified using silica gel flash

column chromatography [gradient eluent: 20:1~10:1 petroleum ether/EtOAc] to afford isocoumarin **3aa** (82.1 mg, 0.196 mmol) in 98% yield.



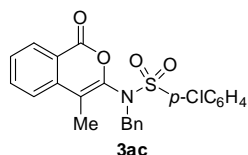
3ga: Isocoumarin **3ha** (39.2 mg, 0.093 mmol) was prepared from 2-bromobenzoic acid **1g** (80.4 mg, 0.40 mmol) and ynamide **2a** (59.9 mg, 0.20 mmol) in 47% yields after stirring at 100 °C for 34.0 h.

3aa (3ga): $R_f = 0.17$ [10:1 petroleum ether/EtOAc]; white solid; mp = 144–145 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.05 (s, 3H), 2.46 (s, 3H), 4.23 (s, 1H), 4.86 (s, 1H), 7.20-7.24 (m, 3H), 7.28-7.30 (m, 2H), 7.37 (d, 2H, $J = 8.1$ Hz), 7.47-7.52 (m, 2H), 7.71 (t, 1H, $J = 7.7$ Hz), 7.77 (d, 2H, $J = 8.2$ Hz), 8.24 (d, 1H, $J = 7.8$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 12.7, 21.8, 52.4, 115.1, 121.0, 124.4, 128.1, 128.4, 128.6, 128.7, 129.4, 129.9, 130.1, 134.3, 135.0, 135.5, 138.1, 140.9, 144.7, 161.8; IR (KBr) (cm^{-1}) 2920w, 1741s, 1656s, 1597m, 1485m, 1455m, 1353s, 1345s, 1242m, 1166s; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 442.1083; found 442.1073.



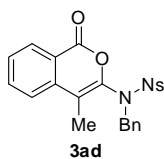
Isocoumarin **3ab** (42.0 mg, 0.096 mmol) was prepared from 2-iodobenzoic acid **1a** (49.6 mg, 0.20 mmol) and ynamide **2b**² (31.5 mg, 0.10 mmol) in 96% yields after stirring at 100 °C for 22.0 h.

3ab: $R_f = 0.31$ [4:1 petroleum ether/EtOAc]; white solid; mp = 153–154 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.05 (s, 3H), 3.90 (s, 3H), 4.23 (s, 1H), 4.85 (s, 1H), 7.04 (d, 2H, $J = 8.9$ Hz), 7.21-7.25 (m, 3H), 7.28-7.31 (m, 2H), 7.48-7.54 (m, 2H), 7.72 (t, 1H, $J = 7.6$ Hz), 7.80-7.84 (m, 2H), 8.25 (d, 1H, $J = 7.8$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 12.7, 52.4, 55.8, 114.6, 115.1, 121.0, 124.4, 128.4, 128.6, 128.8, 129.5, 129.9, 130.0, 130.4, 134.3, 135.1, 138.1, 141.0, 161.9, 163.7; IR (KBr) (cm^{-1}) 2926w, 1723s, 1651s, 1596s, 1497s, 1455m, 1352s, 1265s, 1165s; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$: 458.1033; found 458.1023.



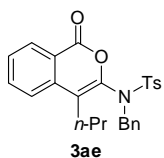
Isocoumarin **3ac** (79.5 mg, 0.181 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2c** (64.0 mg, 0.20 mmol) in 90% yield after stirred at 100 °C for 17.0 h.

3ac: $R_f = 0.20$ [10:1 petroleum ether/EtOAc]; white solid; mp = 160–161 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.02 (s, 3H), 4.25 (s, 1H), 4.86 (s, 1H), 7.21-7.24 (m, 3H), 7.27-7.30 (m, 2H), 7.48-7.56 (m, 4H), 7.73 (t, 1H, $J = 7.5$ Hz), 7.82 (d, 2H, $J = 8.5$ Hz), 8.26 (d, 1H, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.7, 52.7, 115.4, 121.0, 124.5, 128.6, 128.7, 129.0, 129.5, 129.6, 129.8, 130.0, 133.9, 135.1, 137.0, 137.9, 140.4, 140.5, 161.7; IR (KBr) (cm^{-1}) 3090w, 2924w, 1740s, 1658s, 1605m, 1587m, 1485s, 1356s, 1241s, 1169s; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{18}\text{ClNO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 462.0537; found 462.0536.



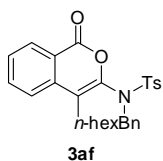
Isocoumarin **3ad** (73.5 mg, 0.163 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2d**² (66.1 mg, 0.20 mmol) in 82% yield after stirred at 100 °C for 26.0 h.

3ad: $R_f = 0.12$ [10:1 petroleum ether/EtOAc]; pale yellow solid; mp = 170–171 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.01 (s, 3H), 4.29 (s, 1H), 4.92 (s, 1H), 7.23-7.30 (m, 5H), 7.51-7.59 (m, 2H), 7.74-7.79 (m, 1H), 8.07 (d, 2H, $J = 8.7$ Hz), 8.27 (d, 1H, $J = 7.8$ Hz), 8.42 (d, 2H, $J = 8.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.6, 53.2, 115.8, 121.1, 124.6, 124.7, 128.8, 129.3, 129.5, 129.6, 130.1, 133.4, 135.3, 137.7, 140.1, 144.3, 150.7, 161.5; IR (KBr) (cm^{-1}) 3039w, 2927w, 1743s, 1655m, 1607m, 1530s, 1484m, 1458m, 1360s, 1242m, 1172s; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$: 473.0778; found 473.0774.



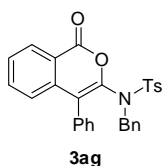
Isocoumarin **3ae** (57.4 mg, 0.128 mmol) was prepared from 2-iodobenzoic acid **1a** (68.2 mg, 0.27 mmol) and ynamide **2e** (45.0 mg, 0.14 mmol) in 93% yield after stirred at 100 °C for 12.0 h.

3ae: $R_f = 0.20$ [10:1 petroleum ether/EtOAc]; white solid; mp = 132–133 °C; ^1H NMR (400 MHz, CDCl_3) δ 0.44 (s, 1H), 0.85 (t, 3H, $J = 7.3$ Hz), 1.41 (s, 1H), 2.43-2.62 (m, 5H), 4.21 (d, 1H, $J = 10.0$ Hz), 4.85 (d, 1H, $J = 9.6$ Hz), 7.20-7.25 (m, 3H), 7.28-7.31 (m, 2H), 7.37 (d, 2H, $J = 8.0$ Hz), 7.49-7.52 (m, 2H), 7.69-7.73 (m, 1H), 7.77 (d, 2H, $J = 8.3$ Hz), 8.27 (dd, 1H, $J = 1.3, 8.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.7, 21.8, 22.2, 28.8, 52.6, 119.7, 121.5, 124.8, 128.3, 128.4, 128.67, 128.70, 129.7, 130.0, 130.1, 134.6, 134.9, 135.4, 137.4, 140.7, 144.7, 161.8; IR (KBr) (cm^{-1}) 3063w, 2963s, 2877m, 1736s, 1647s, 1597s, 1487s, 1455s, 1348s, 1240s, 1163s; HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{25}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 470.1397; found 470.1384.



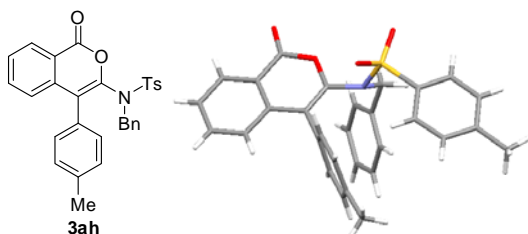
Isocoumarin **3af** (94.5 mg, 0.193 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2f**¹ (73.9 mg, 0.20 mmol) in 97% yield after stirred at 100 °C for 17.5 h.

3af: R_f = 0.22 [10:1 petroleum ether/EtOAc]; white solid; mp = 123–124 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.38 (s, 1H), 0.90 (t, 3H, J = 7.2 Hz), 1.13-1.32 (m, 7H), 2.46-2.62 (m, 5H), 4.20 (d, 1H, J = 12.5 Hz), 4.85 (d, 1H, J = 12.7 Hz), 7.21-7.25 (m, 3H), 7.28-7.32 (m, 2H), 7.37 (d, 2H, J = 8.2 Hz), 7.49-7.53 (m, 2H), 7.70-7.74 (m, 1H), 7.77 (d, 2H, J = 8.2 Hz), 8.27 (d, 1H, J = 7.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 21.8, 22.8, 26.9, 28.9, 30.0, 31.6, 52.5, 119.8, 121.6, 124.8, 128.3, 128.5, 128.6, 128.7, 129.7, 130.0, 130.1, 134.6, 134.9, 135.4, 137.4, 140.6, 144.7, 161.8; IR (KBr) (cm⁻¹) 3061w, 2929s, 2860s, 1732s, 1645s, 1597s, 1562m, 1485s, 1456s, 1359s, 1241s, 1164s; HRMS (ESI): m/z calcd for C₂₉H₃₁NO₄SNa [M+Na]⁺: 512.1866; found 512.1865.



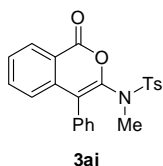
Isocoumarin **3ag** (80.3 mg, 0.167 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2g**¹ (72.2 mg, 0.20 mmol) in 83% yield after stirred at 100 °C for 64.0 h.

3ag: R_f = 0.16 [10:1 petroleum ether/EtOAc]; white solid; mp = 153–154 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.46 (s, 3H), 4.29 (s, 2H), 6.80-7.03 (m, 5H), 7.11 (t, 2H, J = 7.5 Hz), 7.20 (t, 1H, J = 7.3 Hz), 7.31-7.35 (m, 4H), 7.40 (t, 1H, J = 7.3 Hz), 7.49-7.58 (m, 2H), 7.71 (d, 2H, J = 8.2 Hz), 8.32 (d, 1H, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.8, 52.8, 121.0, 126.4, 128.2, 128.26, 128.28, 128.6, 128.8, 128.9, 129.6, 129.8, 129.9, 130.8, 131.6, 133.8, 134.9, 135.6, 138.6, 141.7, 144.6, 161.7; IR (KBr) (cm⁻¹) 3062w, 3033w, 2924w, 1739s, 1647m, 1598m, 1564w, 1482m, 1458w, 1340s, 1247m, 1167s; HRMS (ESI): m/z calcd for C₂₉H₂₃NO₄SNa [M+Na]⁺: 504.1240; found 504.1239.



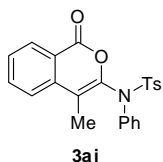
Isocoumarin **3ah** (74.5 mg, 0.150 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2h**³ (75.1 mg, 0.20 mmol) in 75% yield after stirred at 100 °C for 118.0 h.

3ah: R_f = 0.20 [10:1 petroleum ether/EtOAc]; white solid; mp = 190–191 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.43 (s, 3H), 2.46 (s, 3H), 4.29 (s, 2H), 6.70-6.90 (m, 4H), 7.05-7.21 (m, 6H), 7.34 (d, 2H, J = 8.1 Hz), 7.48-7.58 (m, 2H), 7.73 (d, 2H, J = 8.1 Hz), 8.31 (d, 1H, J = 7.7 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 21.8, 52.9, 120.9, 121.1, 126.5, 128.2, 128.51, 128.54, 128.8, 128.9, 129.0, 129.6, 129.8, 129.9, 130.7, 133.9, 134.8, 135.7, 138.0, 138.8, 141.8, 144.6, 161.8; IR (KBr) (cm^{-1}) 3031w, 2921w, 1736s, 1644s, 1596m, 1514m, 1482m, 1339s, 1246m, 1171s; HRMS (ESI): m/z calcd for $\text{C}_{30}\text{H}_{25}\text{NO}_4\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 518.1397; found 518.1372.



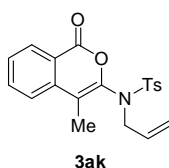
Isocoumarin **3ai** (63.8 mg, 0.157 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2i**⁴ (57.1 mg, 0.20 mmol) in 79% yield after stirred at 100 °C for 43.0 h.

3ai: R_f = 0.12 [10:1 petroleum ether/EtOAc]; white solid; mp = 176–177 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.44 (s, 3H), 2.87 (s, 3H), 7.22 (d, 1H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.0 Hz), 7.43-7.51 (m, 4H), 7.52-7.57 (m, 2H), 7.63-7.70 (m, 3H), 8.35 (dd, 1H, J = 1.0, 7.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.8, 36.8, 119.2, 121.3, 126.2, 128.5, 128.6, 128.9, 129.0, 129.8, 130.0, 130.5, 132.2, 135.0, 135.1, 138.5, 144.3, 144.4, 161.7; IR (KBr) (cm^{-1}) 3069w, 2922w, 1746s, 1650m, 1597w, 1494w, 1352s, 1243m, 1164s; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_4\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 428.0927; found 428.0931.



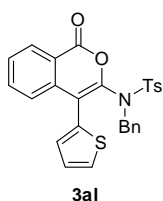
Isocoumarin **3aj** (48.4 mg, 0.119 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2j**⁵ (57.1 mg, 0.20 mmol) in 59% yield after stirred at 100 °C for 69.0 h.

3aj: R_f = 0.15 [10:1 petroleum ether/EtOAc]; pale yellow solid; mp = 177–178 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.428 (s, 3H), 2.435 (s, 3H), 7.26-7.31 (m, 5H), 7.38-7.41 (m, 2H), 7.55 (t, 1H, J = 7.6 Hz), 7.62-7.65 (m, 3H), 7.77 (t, 1H, J = 7.6 Hz), 8.32 (d, 1H, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.4, 21.8, 113.5, 121.5, 124.4, 128.2, 128.6, 128.7, 128.9, 129.5, 129.7, 130.1, 135.1, 135.5, 138.4, 138.6, 143.0, 144.6, 161.9; IR (KBr) (cm^{-1}) 2921m, 2851w, 1736s, 1655s, 1596m, 1484s, 1455m, 1359s, 1238s, 1168s; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_4\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 428.0927; found 428.0927.



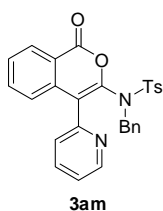
Isocoumarin **3ak** (24.6 mg, 0.067 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2k**⁶ (49.9 mg, 0.20 mmol) in 33% yield after stirred at 100 °C for 5.5 h.

3ak: $R_f = 0.20$ [10:1 petroleum ether/EtOAc]; white solid; mp = 134–135 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.39 (s, 3H), 2.45 (s, 3H), 3.86 (s, 1H), 4.20 (s, 1H), 5.08–5.18 (m, 2H), 5.74–5.84 (m, 1H), 7.35 (d, 2H, $J = 8.1$ Hz), 7.57 (t, 1H, $J = 7.5$ Hz), 7.67 (d, 1H, $J = 8.0$ Hz), 7.73 (d, 2H, $J = 8.2$ Hz), 7.79–7.83 (m, 1H), 8.30 (d, 1H, $J = 7.7$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.1, 21.8, 51.7, 114.9, 120.8, 121.3, 124.5, 128.2, 128.9, 130.05, 130.07, 131.3, 135.2, 135.5, 138.3, 141.4, 144.7, 161.9; IR (KBr) (cm⁻¹) 2921w, 1731s, 1657m, 1595w, 1487m, 1349s, 1244m, 1211m, 1164s; HRMS (ESI): m/z calcd for C₂₀H₁₉NO₄SNa [M+Na]⁺: 392.0927; found 392.0914.



Isocoumarin **3al** (70.0 mg, 0.144 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2l**⁷ (73.5 mg, 0.20 mmol) in 72% yield after stirred at 100 °C for 47.0 h.

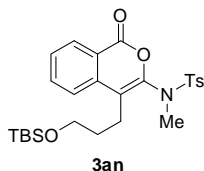
3al: $R_f = 0.18$ [10:1 petroleum ether/EtOAc]; white solid; mp = 156–157 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.47 (s, 3H), 4.35 (s, 2H), 6.81 (d, 1H, $J = 3.0$ Hz), 6.94 (d, 2H, $J = 7.4$ Hz), 7.06–7.19 (m, 4H), 7.29 (d, 1H, $J = 8.0$ Hz), 7.37 (d, 2H, $J = 8.2$ Hz), 7.44 (d, 1H, $J = 5.1$ Hz), 7.53 (t, 1H, $J = 7.5$ Hz), 7.63 (t, 1H, $J = 7.6$ Hz), 7.78 (d, 2H, $J = 8.2$ Hz), 8.29 (d, 1H, $J = 7.8$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.8, 53.0, 114.9, 120.7, 126.4, 126.9, 127.5, 128.3, 128.6, 128.8, 129.2, 129.4, 129.8, 130.0, 130.7, 131.3, 133.8, 135.1, 135.6, 138.6, 143.3, 144.7, 161.3; IR (KBr) (cm⁻¹) 3035w, 2927w, 1742s, 1643m, 1566w, 1480m, 1456m, 1356s, 1244m, 1163s; HRMS (ESI): m/z calcd for C₂₇H₂₁NO₄S₂Na [M+Na]⁺: 510.0804; found 510.0790.



Isocoumarin **3am** (22.7 mg, 0.047 mmol) was prepared from 2-iodobenzoic acid **1a** (49.6 mg, 0.20 mmol) and ynamide **2m**⁷ (36.2 mg, 0.10 mmol) in 47% yield after stirred at 100 °C for 30.0 h.

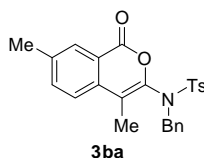
3am: $R_f = 0.22$ [2:1 petroleum ether/EtOAc]; pale yellow solid; mp = 154–155 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.48 (s, 3H), 4.30 (s, 2H), 6.87 (d, 2H, $J = 7.3$ Hz), 7.06 (t, 2H, $J = 7.4$ Hz), 7.13–7.19 (m, 2H), 7.30–7.38 (m, 3H), 7.51–7.63 (m, 3H), 7.80–7.85 (m, 3H), 8.31 (d, 1H, $J = 7.6$ Hz), 8.54 (d, 1H, $J = 3.8$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.9, 53.6, 120.0, 121.2, 123.1, 126.5, 126.7, 128.2, 128.6, 128.8,

129.2, 129.9, 130.0, 133.7, 135.1, 135.7, 137.1, 137.5, 143.5, 144.8, 149.3, 151.7, 161.6; IR (KBr) (cm^{-1}) 2923w, 1737s, 1650w, 1586w, 1484w, 1456w, 1350m, 1248w, 1161s; HRMS (ESI): m/z calcd for $\text{C}_{28}\text{H}_{22}\text{N}_2\text{O}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 505.1192; found 505.1183.



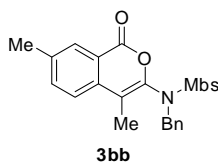
Isocoumarin **3an** (65.9 mg, 0.131 mmol) was prepared from 2-iodobenzoic acid **1a** (99.2 mg, 0.40 mmol) and ynamide **2n**⁸ (76.3 mg, 0.20 mmol) in 66% yield after stirred at 100 °C for 22.0 h.

3an: R_f = 0.18 [10:1 petroleum ether/EtOAc]; white solid; mp = 114–115 °C; ^1H NMR (400 MHz, CDCl_3) δ 0.11 (s, 6H), 0.96 (s, 9H), 1.90 (s, 2H), 2.46 (s, 3H), 2.98 (s, 2H), 3.09 (s, 3H), 3.77 (t, 2H, J = 5.8 Hz), 7.36 (d, 2H, J = 8.1 Hz), 7.53–7.57 (m, 1H), 7.75–7.80 (m, 3H), 7.86 (d, 1H, J = 8.0 Hz), 8.30 (dd, 1H, J = 1.0, 7.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ -5.2, 18.5, 21.8, 23.0, 26.1, 32.2, 36.8, 62.8, 117.2, 121.8, 125.0, 128.6, 128.8, 129.9, 130.2, 134.5, 135.0, 137.6, 143.6, 144.6, 161.9; IR (KBr) (cm^{-1}) 2954s, 2928s, 2857s, 1743s, 1654m, 1598w, 1490m, 1460m, 1354s, 1253s, 1164s; HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{35}\text{NO}_5\text{SSiNa}$ $[\text{M}+\text{Na}]^+$: 524.1897; found 524.1891.



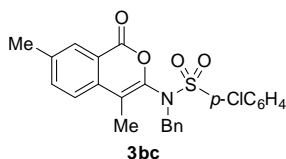
Isocoumarin **3ba** (74.5 mg, 0.172 mmol) was prepared from 2-iodoaromatic acid **1b** (104.8 mg, 0.40 mmol) and ynamide **2a** (59.9 mg, 0.20 mmol) in 86% yield after stirred at 100 °C for 12.0 h.

3ba: R_f = 0.20 [10:1 petroleum ether/EtOAc]; white solid; mp = 114–115 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.02 (s, 3H), 2.44 (s, 3H), 2.46 (s, 3H), 4.22 (s, 1H), 4.86 (s, 1H), 7.19–7.24 (m, 3H), 7.26–7.30 (m, 2H), 7.35–7.39 (m, 3H), 7.52 (dd, 1H, J = 1.4, 8.2 Hz), 7.76 (d, 2H, J = 8.3 Hz), 8.05 (d, 1H, J = 0.5 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.7, 21.3, 21.8, 52.4, 115.1, 120.9, 124.4, 128.2, 128.4, 128.6, 129.5, 129.7, 130.0, 134.4, 135.58, 135.63, 136.2, 139.2, 140.1, 144.6, 162.0; IR (KBr) (cm^{-1}) 2924w, 1732s, 1656m, 1597w, 1502m, 1456w, 1353s, 1247m, 1165s; HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 456.1240; found 456.1231.



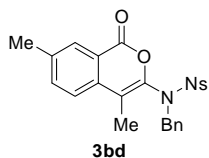
Isocoumarin **3bb** (83.7 mg, 0.186 mmol) was prepared from 2-iodoaromatic acid **1b** (104.8 mg, 0.40 mmol) and ynamide **2b** (63.1 mg, 0.20 mmol) in 93% yield after stirred at 100 °C for 10.0 h.

3bb: $R_f = 0.33$ [4:1 petroleum ether/EtOAc]; white solid; mp = 65–66 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.02 (s, 3H), 2.44 (s, 3H), 3.89 (s, 3H), 4.23 (s, 1H), 4.84 (s, 1H), 7.01-7.05 (m, 2H), 7.19-7.24 (m, 3H), 7.27-7.30 (m, 2H), 7.38 (d, 1H, $J = 8.2$ Hz), 7.52 (dd, 1H, $J = 1.6, 8.2$ Hz), 7.80-7.84 (m, 2H), 8.05 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 12.6, 21.3, 52.4, 55.8, 114.6, 115.1, 120.9, 124.3, 128.3, 128.6, 129.4, 129.7, 130.1, 130.3, 134.4, 135.6, 136.2, 139.1, 140.3, 162.1, 163.7; IR (KBr) (cm^{-1}) 2925w, 1731s, 1655s, 1596s, 1498s, 1456m, 1352s, 1263s, 1162s; HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$: 472.1189; found 472.1196.



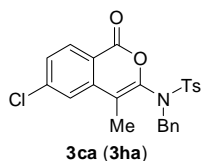
Isocoumarin **3bc** (80.2 mg, 0.177 mmol) was prepared from 2-iodoaromatic acid **1b** (104.8 mg, 0.40 mmol) and ynamide **2c** (64.0 mg, 0.20 mmol) in 88% yield after stirred at 100 °C for 22.0 h.

3bc: $R_f = 0.21$ [10:1 petroleum ether/EtOAc]; white solid; mp = 61–62 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.99 (s, 3H), 2.45 (s, 3H), 4.24 (s, 1H), 4.85 (s, 1H), 7.21-7.23 (m, 3H), 7.27-7.29 (m, 2H), 7.38 (d, 1H, $J = 8.2$ Hz), 7.53-7.56 (m, 3H), 7.80-7.84 (m, 2H), 8.07 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 12.6, 21.4, 52.7, 115.4, 121.0, 124.4, 128.6, 128.7, 129.5, 129.6, 129.78, 129.83, 134.0, 135.5, 136.3, 137.1, 139.4, 139.8, 140.3, 161.9; IR (KBr) (cm^{-1}) 2924w, 1735s, 1656m, 1586w, 1502m, 1360s, 1246m, 1168s; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{20}\text{ClNO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 476.0694; found 476.0680.



Isocoumarin **3bd** (75.2 mg, 0.162 mmol) was prepared from 2-iodoaromatic acid **1b** (104.8 mg, 0.40 mmol) and ynamide **2d** (67.6 mg, 0.20 mmol) in 81% yield after stirred at 100 °C for 12.0 h.

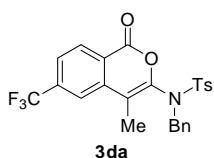
3bd: $R_f = 0.15$ [10:1 petroleum ether/EtOAc]; green yellow solid; mp = 67–68 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.99 (s, 3H), 2.46 (s, 3H), 4.28 (s, 1H), 4.91 (s, 1H), 7.22-7.29 (m, 5H), 7.40 (d, 1H, $J = 8.2$ Hz), 7.56 (dd, 1H, $J = 1.4, 8.2$ Hz), 8.05-8.08 (m, 3H), 8.39-8.42 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 12.5, 21.4, 53.1, 115.7, 120.9, 124.5, 124.6, 128.8, 129.5, 129.6, 129.9, 133.5, 135.2, 136.5, 139.3, 139.7, 144.4, 150.6, 161.6; IR (KBr) (cm^{-1}) 2923w, 1735s, 1655m, 1531s, 1502m, 1456w, 1349s, 1247m, 1168s; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$: 487.0934; found 487.0923.



3ca: Isocoumarin **3da** (76.1 mg, 0.168 mmol) was prepared from 2-iodoaromatic acid **1d** (113.0 mg, 0.40 mmol) and ynamide **2a** (59.9 mg, 0.20 mmol) in 84% yields after stirred at 100 °C for 21.0 h.

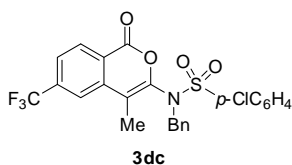
3ha: Isocoumarin **3ia** (34.4 mg, 0.076 mmol) was prepared from 2-bromoaromatic acid **1i** (94.2 mg, 0.40 mmol) and ynamide **2a** (59.9 mg, 0.20 mmol) in 38% yield after stirred at 100 °C for 85.0 h.

3ca (3ha): R_f = 0.21 [10:1 petroleum ether/EtOAc]; white solid; mp = 159–160 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.05 (s, 3H), 2.49 (s, 3H), 4.23 (s, 1H), 4.88 (s, 1H), 7.20-7.35 (m, 5H), 7.37-7.49 (m, 4H), 7.79 (d, 2H, J = 7.7 Hz), 8.19 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.8, 21.8, 52.5, 114.4, 119.3, 124.3, 128.2, 128.5, 128.7, 129.2, 129.4, 130.1, 131.5, 134.1, 135.4, 139.6, 142.0, 142.1, 144.8, 161.0; IR (KBr) (cm^{-1}) 2923w, 1749s, 1660m, 1599s, 1477w, 1356s, 1238w, 1169s; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{20}\text{ClNO}_4\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 476.0694; found 476.0696.



Isocoumarin **3da** (78.7 mg, 0.161 mmol) was prepared from 2-iodoaromatic acid **1d** (126.4 mg, 0.40 mmol) and ynamide **2a** (59.9 mg, 0.20 mmol) in 81% yield after stirred at 100 °C for 21.0 h.

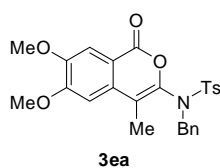
3da: R_f = 0.29 [10:1 petroleum ether/EtOAc]; white solid; mp = 156–157 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.10 (s, 3H), 2.48 (s, 3H), 4.23 (s, 1H), 4.88 (s, 1H), 7.22-7.39 (m, 7H), 7.73-7.78 (m, 4H), 8.36 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.8, 21.8, 52.5, 114.7, 121.6 (q, J = 3.8 Hz), 123.3 (q, J = 271.8 Hz), 123.5, 125.1 (q, J = 3.3 Hz), 128.2, 128.6, 128.7, 129.4, 130.2, 130.9, 134.0, 135.3, 136.5 (q, J = 32.7 Hz), 138.7, 142.3, 144.9, 160.7; IR (KBr) (cm^{-1}) 3078w, 3057w, 2918w, 1754s, 1654s, 1597m, 1574m, 1493m, 1430m, 1356s, 1287s, 1169s; HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{20}\text{F}_3\text{NO}_4\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 510.0957; found 510.0958.



Isocoumarin **3dc** (82.2 mg, 0.162 mmol) was prepared from 2-iodoaromatic acid **1d** (126.4 mg, 0.40 mmol) and ynamide **2c** (64.0 mg, 0.20 mmol) in 81% yield after stirred at 100 °C for 12.0 h.

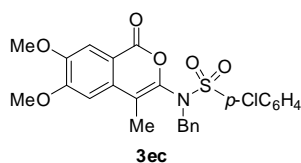
3ec: R_f = 0.43 [10:1 petroleum ether/EtOAc]; white solid; mp = 158–159 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.07 (s, 3H), 4.26 (s, 1H), 4.87 (s, 1H), 7.22-7.30 (m, 5H), 7.56 (d, 2H, J = 8.5 Hz), 7.71-7.77 (m, 2H), 7.83 (d, 2H, J = 8.5 Hz), 8.37 (d, 1H, J = 8.1 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.7, 52.8, 114.9, 121.7 (q, J = 3.8 Hz), 123.3 (q, J = 271.8 Hz), 123.5, 125.3 (q, J = 3.2 Hz), 128.80, 128.83, 129.5, 129.6, 129.9, 131.0, 133.6, 136.6 (q, J = 32.8 Hz), 136.9, 138.5, 140.6, 141.9, 160.5; IR (KBr)

(cm^{-1}) 3090w, 1754s, 1655m, 1575w, 1476w, 1362s, 1288s, 1171s; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{27}\text{ClF}_3\text{NO}_4\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 530.0411; found 530.0407.



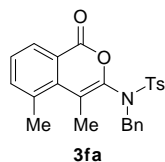
Isocoumarin **3ea** (73.1 mg, 0.152 mmol) was prepared from 2-iodoaromatic acid **1e** (123.2 mg, 0.40 mmol) and ynamide **2a** (59.9 mg, 0.20 mmol) in 76% yield after stirred at 100 °C for 4.0 h.

3ea: R_f = 0.18 [4:1 petroleum ether/EtOAc]; white solid; mp = 203–204 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.04 (s, 3H), 2.47 (s, 3H), 3.96 (s, 6H), 4.23 (s, 1H), 4.86 (s, 1H), 6.82 (s, 1H), 7.22–7.38 (m, 7H), 7.62 (s, 1H), 7.76 (d, 2H, J = 6.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 13.0, 21.8, 52.4, 56.3, 56.4, 105.2, 109.8, 114.2, 114.8, 128.1, 128.4, 128.6, 129.5, 130.1, 133.8, 134.4, 135.5, 140.1, 144.6, 150.0, 155.1, 161.7; IR (KBr) (cm^{-1}) 2924w, 1716s, 1655w, 1604m, 1513s, 1457w, 1392m, 1355s, 1269s, 1172s; HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{25}\text{NO}_6\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 502.1295; found 502.1274.



Isocoumarin **3ec** (71.8 mg, 0.144 mmol) was prepared from 2-iodoaromatic acid **1e** (123.2 mg, 0.40 mmol) and ynamide **2c** (64.0 mg, 0.20 mmol) in 72% yield after stirred at 100 °C for 4.0 h.

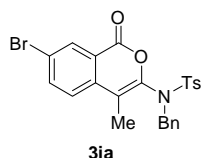
3ec: R_f = 0.18 [4:1 petroleum ether/EtOAc]; pale yellow solid; mp = 184–185 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.01 (s, 3H), 3.97 (s, 3H), 4.24 (d, 1H, J = 8.2 Hz), 4.87 (d, 1H, J = 8.2 Hz), 6.81 (s, 1H), 7.22–7.30 (m, 5H), 7.55 (d, 2H, J = 8.5 Hz), 7.62 (s, 1H), 7.81 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.9, 52.7, 56.4, 56.5, 105.3, 109.9, 114.3, 115.1, 128.6, 128.7, 129.5, 129.6, 129.8, 133.6, 134.0, 137.1, 139.7, 140.4, 150.2, 155.2, 161.5; IR (KBr) (cm^{-1}) 2924w, 1717s, 1656m, 1604s, 1512s, 1457m, 1360s, 1269s, 1175s; HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{22}\text{ClNO}_6\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 522.0749; found 522.0761.



Isocoumarin **3fa** (39.8 mg, 0.092 mmol) was prepared from 2-iodoaromatic acid **1f** (104.8 mg, 0.40 mmol) and ynamide **2a** (59.9 mg, 0.20 mmol) in 46% yield after stirred at 100 °C for 12.0 h.

3fa: R_f = 0.18 [10:1 petroleum ether/EtOAc]; white solid; mp = 139–140 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.22 (s, 3H), 2.46 (s, 3H), 2.61 (s, 3H), 4.22 (d, 1H, J = 13.1 Hz), 4.87 (d, 1H, J = 13.1 Hz),

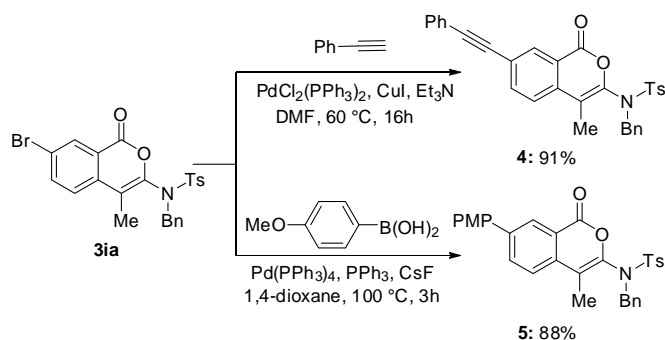
7.20-7.24 (m, 3H), 7.28-7.31 (m, 2H), 7.34-7.38 (m, 3H), 7.47 (d, 1H, $J = 7.2$ Hz), 7.77 (d, 2H, $J = 8.2$ Hz), 8.16 (d, 1H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 17.8, 21.8, 24.3, 52.5, 116.1, 122.5, 128.2, 128.5, 128.55, 128.65, 129.7, 130.1, 134.2, 135.6, 136.2, 137.1, 139.3, 140.9, 144.7, 162.2; IR (KBr) (cm^{-1}) 2921w, 1728s, 1636m, 1595m, 1495w, 1456m, 1357s, 1260w, 1168s; HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 456.1240; found 456.1223.



Isocoumarin **3ia** (45.5 mg, 0.091 mmol) was prepared from 2-iodoaromatic acid **1i** (130.8 mg, 0.40 mmol) and ynamide **2a** (59.9 mg, 0.20 mmol) in 46% yield after stirred at 100 °C for 7.5 h.

3ia: $R_f = 0.28$ [10:1 petroleum ether/EtOAc]; white solid; mp = 149–150 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.03 (s, 3H), 2.47 (s, 3H), 4.20 (s, 1H), 4.86 (s, 1H), 7.20-7.23 (m, 3H), 7.26-7.29 (m, 2H), 7.35-7.39 (m, 3H), 7.75 (d, 2H, $J = 8.3$ Hz), 7.80 (dd, 1H, $J = 2.2, 8.6$ Hz), 8.37 (d, 1H, $J = 2.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.8, 21.8, 52.5, 114.8, 122.5, 122.7, 126.2, 128.2, 128.5, 128.7, 129.5, 130.2, 132.5, 134.1, 135.4, 136.9, 138.1, 141.3, 144.9, 160.6; IR (KBr) (cm^{-1}) 2924w, 1729s, 1654m, 1596w, 1481w, 1353s, 1232w, 1164s; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{20}\text{BrNO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 522.0171; found 476.0161.

Procedures for the Synthesis of Isocoumarins **4** and **5**.^{9,10}



To an oven-dried sealed tube were added isocoumarin **3ia** (99.7 mg, 0.20 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (7.0 mg, 0.01 mmol), CuI (2.0 mg, 0.01 mmol), DMF (1.5 mL, isocoumarin *concn* = 0.13 M), phenylacetylene (32.9 μL , 0.30 mmol) and NEt_3 (0.5 mL) in sequence. The reaction was heated to 60 °C and stirred for 16 h. After consumption of the starting material, the mixture was cooled to rt, filtered through a short silica pad, concentrated *in vacuo*, and purified using silica gel flash column chromatography [gradient eluent: 20:1~10:1 petroleum ether/EtOAc] to afford isocoumarin **4** (94.8 mg, 0.182 mmol) in 91% yield.

4: R_f = 0.22 [10:1 petroleum ether/EtOAc]; orange solid; mp = 170–171 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.05 (s, 3H), 2.46 (s, 3H), 4.22 (s, 1H), 4.86 (s, 1H), 7.21-7.30 (m, 5H), 7.34-7.38 (m, 5H), 7.45 (d, 1H, J = 8.3 Hz), 7.52-7.54 (m, 2H), 7.76-7.81 (m, 3H), 8.38 (d, 1H, J = 1.4 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.8, 21.8, 52.5, 87.9, 92.2, 115.0, 121.2, 122.6, 124.2, 124.6, 128.2, 128.5, 128.6, 128.7, 129.0, 129.4, 130.1, 131.9, 132.9, 134.2, 135.4, 137.4, 137.5, 141.4, 144.8, 161.1; IR (KBr) (cm^{-1}) 2923w, 1741s, 1651m, 1596w, 1503m, 1456w, 1444w, 1356s, 1226w, 1166s; HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{25}\text{NO}_4\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 542.1397; found 542.1372.

To an oven-dried sealed tube were added isocoumarin **3ia** (78.0 mg, 0.16 mmol), 4-methoxyphenylboronic acid (71.4 mg, 0.47), Pd (PPh_3) $_4$ (18.1 mg, 0.016 mmol), PPh_3 (8.2 mg, 0.031 mmol), CsF (95.1 mg, 0.63 mmol) and 1,4-dioxane (5.0 mL, isocoumarin *concn* = 0.03 M) in sequence. The solution was heated to 100 °C and monitored by TLC analysis. When the reaction was judged to be completed after 3 h, the reaction mixture was cooled to rt, filtered through a short silica pad, concentrated *in vacuo*, and purified using silica gel flash column chromatography [gradient eluent: 6:1~4:1 petroleum ether/EtOAc] to afford isocoumarin **5** (72.3 mg, 0.138 mmol) in 88% yield.

5: R_f = 0.32 [4:1 petroleum ether/EtOAc]; yellow solid; mp = 172–173 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.07 (s, 3H), 2.47 (s, 3H), 3.85 (s, 3H), 4.24 (s, 1H), 4.88 (s, 1H), 6.97-7.01 (m, 2H), 7.21-7.25 (m, 3H), 7.29-7.32 (m, 2H), 7.37 (d, 2H, J = 8.2 Hz), 7.52 (d, 1H, J = 8.4 Hz), 7.56-7.59 (m, 2H), 7.78 (d, 2H, J = 8.3 Hz), 7.91 (dd, 1H, J = 2.0, 8.4 Hz), 8.43 (d, 1H, J = 1.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 12.8, 21.8, 52.5, 55.6, 114.7, 115.2, 121.5, 125.0, 127.2, 128.2, 128.3, 128.4, 128.7, 129.5, 130.1, 131.5, 133.2, 134.4, 135.6, 136.3, 140.6, 141.4, 144.7, 160.1, 162.1; IR (KBr) (cm^{-1}) 2925w, 1735s, 1655w, 1607m, 1494m, 1458w, 1351m, 1251m, 1165s; HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{27}\text{NO}_5\text{SNa}$ [$\text{M}+\text{Na}$] $^+$: 548.1502; found 548.1505.

Further explanation of the mechanism for the annulation.^{11,12}

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