Pd-Catalyzed Regioselectively Sequential Meta-, Ortho-C–H Functionalization of Arenes: A Predictable Approach to Synthesis

Polysubstituted β-Arylethylamines

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1. **Reagents:** Unless otherwise noted, all reagents were purchased from Acros, Alfa, Adamas and used without further purification. Column chromatography purifications were performed using 300–400 mesh silica gel.

2. **Instruments:** NMR spectra were recorded on Varian Inova-400 MHz, Inova-300 MHz, Bruker DRX-400 or Bruker DRX-500 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br s= broad singlet, m = multiplet. HRMS analysis were carried out using TOF-MS instrument with ESI source.

3. **Preparation of substrates**

![Chemical Structure Image]

3.1. **Preparation of N, N–Diisopropylxamoyl chloride S1**[^1]

A solution of Diisopropylamine (7.01 mL, 50 mmol, 1.0 eq) in CH$_2$Cl$_2$ (50 mL) was added dropwise to a solution of oxalyl chloride (6.44 ml, 75 mmol, 1.5 eq) in CH$_2$Cl$_2$ (100 mL) at 0 °C, after stirring for 5 min, triethylamine (7.30 mL, 52.5 mmol, 1.05 eq) was added dropwise. The solution was warmed to room temperature and stirred for 6 hours. The excess of oxalyl chloride and the solvent were removed under reduce pressure and CH$_2$Cl$_2$ (30 mL) was added and evaporated. This operation was performed twice to give S1 as a pale yellow solid. The crude product was used in the next step without any purification.

3.2. **General procedures for the preparation of oxalamide substrates**

A solution of amine (20 mmol, 1.0 eq) in CH$_2$Cl$_2$ (40 mL) was added dropwise to a solution of N,N–Diisopropylxamoyl chloride S1 (25 mmol, 1.25 eq) in CH$_2$Cl$_2$ (50 mL) at 0 °C, after stirring for 5 min, triethylamine (2.92 mL, 21 mmol, 1.05 eq) was added dropwise and then the mixture was stirred for 6 hours at room temperature before quenched by water (50 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (20 mL × 2). The combined organic phase was washed with brine (30 mL), and then dried over anhydrous Na$_2$SO$_4$. Evaporation and column chromatography on silica gel afforded corresponding amide substrates as white solid or colourless oil with >80% yield.

4. **General procedures for meta-arylation of β-Arylethylamide**

![Chemical Structure Image]

A mixture of oxalamide (0.2 mmol, 1.0 eq), ArI (0.6 mmol, 3.0 eq), Pd(OAc)$_2$ (4.5 mg, 10 mol%), AgOAc (50 mg, 0.3 mmol, 1.5 eq), norbornene (18.8 mg, 0.2 mmol, 1.0 eq), 1-AdCO$_2$H (18 mg, 0.1 mmol, 0.05 eq) and 1 mL mesitylene in a 15 mL glass vial was heated at 100 °C with vigorous stirring for 24 hours. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography.
chromatography on silica gel (Ethyl acetate/Petroleum ether = 1:15 to 1:3) to give meta-arylated product.

![Diagram](image)

1H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.04 (s, 1H), 6.99 (s, 2H), 6.76 (s, 1H), 4.68–4.62 (m, 1H), 3.86 (s, 3H), 3.63–3.58 (m, 2H), 3.52–3.45 (m, 1H), 2.90 (t, J = 7.1 Hz, 2H), 1.40 (d, J = 6.8 Hz, 6H), 1.18 (d, J = 6.7 Hz, 6H); 13C NMR (101 MHz, CDCl₃) δ 162.41, 162.13, 159.32, 142.14, 140.08, 139.51, 127.85, 126.61, 126.36, 119.32, 112.25, 110.35, 54.49, 48.78, 45.64, 39.43, 34.77, 19.95, 19.18; HRMS Calcd for C₂₃H₃₀N₂O₃NaO₃ [M+Na⁺]: 405.2154; Found: 405.2157.

![Diagram](image)

1H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 7.2 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 7.03 (s, 1H), 6.98 (br s, 1H), 4.69–4.62 (m, 1H), 3.62–3.57 (m, 2H), 3.52–3.45 (m, 1H), 2.89 (t, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 1.18 (d, J = 6.7 Hz, 6H); 13C NMR (101 MHz, CDCl₃) δ 162.39, 162.15, 140.75, 140.27, 138.02, 137.81, 127.81, 126.36, 126.34, 125.45, 123.90, 48.76, 45.64, 39.57, 34.57, 39.57, 34.57, 20.58, 19.96, 19.18; HRMS Calcd for C₂₃H₃₀N₂O₂ [M+Na⁺]: 389.2205; Found: 389.2206.

![Diagram](image)

1H NMR (400 MHz, CDCl₃) δ 7.88 (dd, J = 7.8, 1.1 Hz, 1H), 7.57–7.53 (m, 1H), 7.46–7.39 (m, 2H), 7.01 (br s, 1H), 6.70 (dd, J = 5.9, 1.5 Hz, 2H), 5.90 (s, 2H), 4.71–4.65 (m, 1H), 3.74 (s, 3H), 3.57–3.46 (m, 3H), 1.41 (d, J = 6.8 Hz, 6H), 1.19 (d, J = 6.7 Hz, 6H); 13C NMR (101 MHz, CDCl₃) δ 168.51, 163.37, 163.11, 147.43, 143.57, 136.42, 132.37, 131.88, 131.20, 130.86, 130.22, 127.88, 122.85, 122.47, 108.51, 101.13, 52.23, 49.76, 46.64, 40.76, 35.39, 20.95, 20.18; HRMS Calcd for C₂₅H₃₆N₂O₆ [M+Na⁺]: 477.2002; Found: 477.2000.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.55–7.53 (m, 2H), 7.42–7.38 (m, 2H), 7.35–7.31 (m, 1H), 7.00 (br s, 1H), 6.78 (s, 2H), 4.72–4.65 (m, 1H), 3.91 (s, 3H), 3.60–3.54 (m, 5H), 3.53–3.46 (m, 1H), 2.84 (t, \(J = 7.1\) Hz, 2H), 1.40 (t, \(J = 6.2\) Hz, 6H), 1.19 (d, \(J = 6.7\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.35, 162.06, 152.22, 144.28, 137.25, 134.95, 133.43, 128.36, 127.22, 126.27, 121.87, 111.08, 59.73, 55.13, 48.75, 45.67, 39.55, 34.53, 19.96, 19.18; HRMS Calcd for C\(_{24}\)H\(_{32}\)N\(_2\)NaO\(_4\) [M+Na\(^+\)]: 435.2260; Found: 435.2261.

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\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.55 (d, \(J = 7.3\) Hz, 2H), 7.37 (t, \(J = 7.6\) Hz, 2H), 7.29–7.26 (m, 2H), 7.19 (br s, 1H), 7.17 (s, 1H), 4.66–4.59 (m, 1H), 3.65–3.60 (m, 2H), 3.52–3.45 (m, 1H), 3.10 (t, \(J = 6.8\) Hz, 6H), 1.40 (d, \(J = 6.9\) Hz, 2H), 1.19 (d, \(J = 6.7\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.51, 162.21, 141.31, 140.83, 134.95, 127.88, 126.21, 125.38, 123.95, 117.89, 48.84, 45.61, 39.60, 29.04, 19.93, 19.17; HRMS Calcd for C\(_{20}\)H\(_{26}\)N\(_2\)NaO\(_2\)S [M+Na\(^+\)]: 381.1613; Found: 381.1626.

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\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.51 (d, \(J = 8.5\) Hz, 2H), 7.43–7.39 (m, 3H), 7.35 (d, \(J = 2.1\) Hz, 1H), 7.10 (br s, 1H), 6.92 (d, \(J = 8.5\) Hz, 1H), 4.72–4.65 (m, 1H), 3.88 (s, 3H), 3.58–3.53 (m, 2H), 3.51–3.45 (m, 1H), 2.93 (t, \(J = 6.9\) Hz, 2H), 1.40 (d, \(J = 6.8\) Hz, 6H), 1.17 (d, \(J = 6.7\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.38, 162.13, 156.51, 138.76, 131.57, 130.88, 128.37, 127.51, 126.69, 125.47, 119.94, 109.85, 54.63, 48.65, 45.62, 38.61, 29.29, 19.96, 19.16; HRMS Calcd for C\(_{23}\)H\(_{30}\)BrN\(_2\)O\(_3\) [M+H\(^+\)]: 461.1440; Found: 461.1444.

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\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.58–7.56 (m, 2H), 7.47 (d, \(J = 1.7\) Hz, 1H), 7.44–7.38 (m, 4H), 7.36–7.33 (m, 1H), 7.06 (br s, 1H), 4.74–4.67 (m, 1H), 3.65–3.59 (m, 2H), 3.52–3.45 (m, 1H), 3.06 (t, \(J = 7.1\) Hz, 2H), 1.40 (d, \(J = 6.8\) Hz, 6H), 1.17 (d, \(J = 6.7\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.38, 161.92, 139.34, 138.97, 135.57, 132.38, 129.06, 128.80, 127.98, 126.75, 126.41, 126.21, 125.89, 48.70, 45.70, 38.01, 32.46, 28.46, 19.95, 19.16; HRMS Calcd for C\(_{22}\)H\(_{27}\)ClN\(_2\)NaO\(_2\) [M+Na\(^+\)]: 409.1659; Found: 409.1672.

S4
1H NMR (400 MHz, CDCl₃) δ 7.59 (dd, J = 12.6, 7.9 Hz, 3H), 7.47–7.41 (m, 3H), 7.37–7.31 (m, 2H), 7.06 (br s, 1H), 4.75–4.69 (m, 1H), 3.64–3.59 (m, 2H), 3.52–3.45 (m, 1H), 3.07 (t, J = 7.1 Hz, 2H), 1.41 (d, J = 6.8 Hz, 6H), 1.17 (d, J = 6.6 Hz, 6H); 13C NMR (101 MHz, CDCl₃) δ 162.38, 161.91, 140.01, 138.95, 137.30, 132.38, 128.79, 127.99, 126.80, 126.18, 126.16, 122.70, 48.70, 45.70, 34.88, 19.95, 19.16; HRMS Calcd for C₂₂H₂₇BrN₂O₂ [M+Na⁺]: 453.1154; Found: 453.1136.

1H NMR (400 MHz, CDCl₃) δ 7.50 (s, 1H), 7.44–7.36 (m, 5H), 7.23 (s, 1H), 7.10 (br s, 1H), 4.73–4.67 (m, 1H), 3.57–3.54 (m, 2H), 3.52–3.46 (m, 1H), 3.00 (t, J = 7.1 Hz, 2H), 1.40 (d, J = 6.8 Hz, 6H), 1.17 (d, J = 6.7 Hz, 6H); 13C NMR (101 MHz, CDCl₃) δ 206.15, 162.33, 161.78, 138.48, 137.22, 134.15, 132.57, 132.51, 130.45, 128.51, 127.25, 127.05, 48.69, 45.72, 37.84, 31.77, 30.06, 19.93, 19.14; HRMS Calcd for C₂₂H₂₇Cl₂N₂O₂ [M+H⁺]: 421.1450; Found: 421.1457.

1H NMR (400 MHz, CDCl₃) δ 7.55 (d, J = 7.5 Hz, 2H), 7.46–7.40 (m, 4H), 7.29 (t, J = 7.3 Hz, 1H), 7.12 (br s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.71–4.65 (m, 1H), 3.88 (s, 3H), 3.59–3.54 (m, 2H), 3.51–3.44 (m, 1H), 2.94 (t, J = 6.8 Hz, 2H), 1.40 (d, J = 6.7 Hz, 6H), 1.16 (d, J = 6.6 Hz, 6H); 13C NMR (101 MHz, CDCl₃) δ 162.40, 162.19, 156.24, 139.82, 132.87, 128.54, 127.82, 126.49, 125.91, 125.81, 125.60, 109.77, 54.59, 48.64, 45.58, 38.72, 29.30, 19.94, 19.15; HRMS Calcd for C₂₃H₃₀N₂O₃Na₂ [M+Na⁺]: 405.2154; Found: 405.2152.

5. Pd-catalyzed ortho alkynylation of presubstituted β-arylethamide

![Chemical structure](image_url)
A mixture of presubstituted β-arylethamide 4 (0.2 mmol, 1.0 eq), bromoalkyne (0.4 mmol, 2.0 eq), Pd(OAc)$_2$ (4.5 mg, 10 mol%), CsOAc (0.4 mmol, 2.0 eq), and 1 mL toluene in a 15 mL glass vial was heated at 120 °C with vigorous stirring for 48 hours. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (Ethyl acetate/Petroleum ether = 1:50 to 1:15) to give product 2.

**1H NMR (400 MHz, CDCl$_3$)** δ 7.61–7.59 (m, 2H), 7.42 (t, $J = 7.4$ Hz, 2H), 7.35 (t, $J = 7.3$ Hz, 1H), 7.07 (d, $J = 1.2$ Hz, 1H), 6.96 (d, $J = 1.2$ Hz, 1H), 6.88 (br s, 1H), 4.70–4.63 (m, 1H), 3.92 (s, 3H), 3.69–3.64 (m, 2H), 3.50–3.44 (m, 1H), 3.12 (t, $J = 6.9$ Hz, 2H), 1.40 (d, $J = 6.8$ Hz, 6H), 1.16–1.14 (m, 27H); **13C NMR (101 MHz, CDCl$_3$)** δ 163.36, 163.03, 161.82, 142.83, 142.42, 140.75, 128.88, 127.87, 127.35, 120.79, 111.83, 108.19, 101.09, 100.60, 56.15, 49.67, 46.59, 39.41, 34.55, 20.91, 20.15, 18.85, 11.52; HRMS Calcd for C$_{34}$H$_{50}$N$_2$NaO$_3$Si: 585.3488; Found: 585.3473.

**1H NMR (400 MHz, CDCl$_3$)** δ 7.52 (dd, $J = 8.0$, 1.4 Hz, 2H), 7.39–7.32 (m, 3H), 6.97 (br s, 1H), 6.73 (s, 1H), 4.70–4.64 (m, 1H), 3.86 (s, 3H), 3.71–3.66 (m, 2H), 3.50–3.42 (m, 3H), 1.40 (d, $J = 6.8$ Hz, 6H), 1.17–1.15 (m, 27H), 0.96 (d, $J = 2.8$ Hz, 21H); **13C NMR (101 MHz, CDCl$_3$)** δ 162.97, 162.85, 160.59, 146.79, 145.47, 140.98, 129.39, 128.04, 127.68, 114.91, 112.63, 110.61, 103.89, 100.60, 100.57, 97.27, 56.08, 49.47, 46.55, 39.37, 33.04, 21.02, 20.21, 18.87, 18.72, 11.52, 11.38; HRMS Calcd for C$_{45}$H$_{70}$N$_2$NaO$_3$Si$_2$: 765.4823; Found: 765.4816.

**1H NMR (400 MHz, CDCl$_3$)** δ 7.61–7.59 (m, 2H), 7.43–7.40 (m, 2H), 7.35–7.30 (m, 3H), 6.89 (br...
s, 1H), 4.71–4.64 (m, 1H), 3.69–3.65 (m, 2H), 3.51–3.44 (m, 1H), 3.16–3.12 (m, 2H), 2.54 (s, 3H), 1.40 (d,\( J = 6.8 \) Hz, 6H), 1.16–1.14 (m, 27H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.35, 163.00, 141.93, 141.35, 140.93, 140.55, 128.86, 127.66, 127.30, 126.65, 125.71, 122.20, 103.79, 100.33, 49.66, 46.61, 39.50, 34.81, 21.67, 20.93, 20.15, 18.87, 11.48; HRMS Calcd for C\(_{34}\)H\(_{51}\)N\(_2\)O\(_2\)Si [M+\( \text{H}^+\)]: 547.3720; Found: 547.3723.

1\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.52–7.50 (m, 2H), 7.38–7.30 (m, 3H), 7.11 (s, 1H), 7.02 (br s, 1H), 4.75–4.69 (m, 1H), 3.71–3.69 (m, 2H), 3.50–3.44 (m, 3H), 2.50 (s, 3H), 1.40 (d,\( J = 6.8 \) Hz, 6H), 1.17–1.15 (m, 27H), 0.97 (d,\( J = 3.3 \) Hz, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.91, 161.73, 143.98, 142.79, 140.33, 139.75, 128.43, 128.28, 126.98, 126.49, 121.93, 118.94, 102.94, 102.39, 99.31, 97.57, 48.41, 45.57, 38.46, 32.19, 20.81, 20.04, 19.20, 17.89, 17.71, 10.46, 10.35; HRMS Calcd for C\(_{45}\)H\(_{70}\)N\(_2\)NaO\(_6\)Si\(_2\) [M+\( \text{Na}^+\)]: 749.4874; Found: 749.4880.

1\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.89 (dd,\( J = 7.8, 1.1 \) Hz, 1H), 7.56–7.52 (m, 1H), 7.48 (dd,\( J = 7.7, 1.2 \) Hz, 1H), 7.43–7.39 (m, 1H), 6.90 (br s, 1H), 6.71 (s, 1H), 5.98 (s, 2H), 4.74–4.67 (m, 1H), 3.75 (s, 3H), 3.64–3.59 (m, 2H), 3.51–3.45 (m, 1H), 3.01 (t,\( J = 6.8 \) Hz, 2H), 1.41 (d,\( J = 6.8 \) Hz, 6H), 1.18–1.14 (m, 27H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.30, 162.30, 161.99, 148.46, 142.51, 135.05, 132.99, 130.99, 130.30, 129.73, 129.27, 127.07, 122.01, 121.84, 103.70, 100.84, 99.13, 97.90, 51.30, 48.66, 45.62, 38.60, 32.81, 19.94, 19.18, 17.84, 10.43; HRMS Calcd for C\(_{36}\)H\(_{50}\)N\(_2\)NaO\(_8\)Si\(_2\) [M+\( \text{Na}^+\)]: 657.3336; Found: 657.3349.

1\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.04 (d,\( J = 7.0 \) Hz, 1H), 7.56–7.52 (m, 1H), 7.40 (dd,\( J = 15.6, 7.7 \) Hz, 2H), 6.94 (br s, 1H), 5.99 (s, 2H), 4.77–4.71 (m, 1H), 3.72 (s, 3H), 3.65–3.60 (m, 2H), 3.51–
3.44 (m, 1H), 3.36–3.29 (m, 2H), 1.40 (d, \( J = 6.8 \) Hz, 6H), 1.19 (d, \( J = 6.6 \) Hz, 6H), 1.14 (d, \( J = 2.7 \) Hz, 21H), 0.88 (s, 21H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 165.82, 161.97, 161.79, 148.38, 142.53, 136.47, 134.92, 131.09, 130.82, 129.72, 129.20, 127.29, 125.41, 115.58, 103.98, 102.20, 101.09, 98.96, 97.59, 96.31, 51.15, 48.50, 45.57, 38.53, 31.39, 20.02, 19.21, 17.85, 17.63, 17.62, 10.42, 10.24; HRMS Calcd for C\(_{47}\)H\(_{71}\)N\(_2\)O\(_6\)Si\(_2\) [M+H\(^+\)]: 815.4851; Found: 815.4862.

\[ \text{MeO} \]
\[ \text{N(Pr)}\]_\(_2\)  
\[ \text{2d}_{\text{mono}} \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.54–7.52 (m, 2H), 7.39 (t, \( J = 7.3 \) Hz, 2H), 7.33 (dd, \( J = 8.4, 6.1 \) Hz, 1H), 6.95 (s, 1H), 6.91 (br s, 1H), 4.76–4.70 (m, 1H), 3.99 (s, 3H), 3.64–3.59 (m, 5H), 3.52–3.45 (m, 1H), 3.03 (t, \( J = 6.9 \) Hz, 2H), 1.40 (d, \( J = 6.8 \) Hz, 6H), 1.16 (d, \( J = 2.5 \) Hz, 27H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 162.24, 161.87, 154.68, 148.38, 136.67, 136.14, 135.57, 128.30, 127.30, 126.59, 125.76, 116.88, 99.81, 99.24, 60.18, 59.98, 48.64, 45.68, 38.49, 33.12, 19.95, 19.17, 17.86, 10.52; HRMS Calcd for C\(_{35}\)H\(_{52}\)N\(_2\)NaO\(_4\)Si [M+Na\(^+\)]: 615.3594; Found: 615.3595.

\[ \text{MeO} \]
\[ \text{N(Pr)}\]_\(_2\)  
\[ \text{2d}_{\text{mono}} \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38–7.31 (m, 5H), 7.01 (br s, 1H), 4.81–4.74 (m, 1H), 3.97 (s, 3H), 3.67–3.62 (m, 2H), 3.54 (s, 3H), 3.52–3.45 (m, 1H), 3.37 (t, \( J = 7.4 \) Hz, 2H), 1.40 (d, \( J = 1.9 \) Hz, 6H), 1.19–1.15 (m, 27H), 0.91 (s, 21H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 161.89, 161.67, 154.50, 148.48, 139.76, 139.02, 135.51, 128.99, 126.91, 126.53, 118.91, 117.74, 102.31, 99.45, 99.36, 97.64, 60.19, 59.99, 48.41, 45.62, 38.43, 31.74, 20.06, 19.20, 17.87, 17.66, 10.50, 10.24; HRMS Calcd for C\(_{46}\)H\(_{72}\)N\(_2\)NaO\(_4\)Si [M+Na\(^+\)]: 795.4928; Found: 795.4913.

\[ \text{MeO} \]
\[ \text{N(Pr)}\]_\(_2\)  
\[ \text{2d}_{\text{mono}} \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.72–7.69 (m, 2H), 7.38–7.28 (m, 3H), 7.10 (br s, 1H), 4.74–4.67 (m, 1H), 3.68–3.64 (m, 2H), 3.54–3.47 (m, 1H), 3.24 (t, \( J = 6.7 \) Hz, 2H), 1.42 (d, \( J = 6.8 \) Hz, 6H), 1.22 (d, \( J = 6.7 \) Hz, 6H), 1.07 (d, \( J = 2.6 \) Hz, 21H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 162.43, 161.94, 145.49, 142.65, 134.60, 127.29, 127.23, 126.53, 119.63, 118.52, 99.96, 95.78,
48.74, 45.67, 38.76, 28.59, 20.01, 19.18, 17.78, 10.43; HRMS Calcd for C$_{31}$H$_{46}$N$_2$NaO$_2$Si [M+Na$^+$]: 561.2947; Found: 561.2946.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.75–7.72 (m, 2H), 7.35–7.29 (m, 3H), 6.93 (br s, 1H), 4.72–4.66 (m, 1H), 3.67–3.62 (m, 2H), 3.54–3.47 (m, 1H), 3.20 (t, $J$ = 6.6 Hz, 2H), 1.42 (d, $J$ = 6.8 Hz, 6H), 1.23 (d, $J$ = 6.7 Hz, 6H), 1.03–1.02 (m, 42H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.55, 161.98, 145.91, 144.82, 133.16, 128.68, 126.81, 120.32, 116.21, 99.47, 98.08, 96.65, 95.51, 48.83, 45.70, 38.56, 28.55, 20.02, 19.20, 17.74, 17.70, 10.40, 10.38; HRMS Calcd for C$_{42}$H$_{66}$N$_2$NaO$_2$Si$_2$ [M+Na$^+$]: 741.4281; Found: 741.4288.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48–7.46 (m, 2H), 7.37–7.35 (m, 2H), 7.26 (br s, 1H), 7.15 (d, $J$ = 8.5 Hz, 1H), 6.90 (d, $J$ = 8.5 Hz, 1H), 4.81–4.74 (m, 1H), 3.88 (s, 3H), 3.58–3.53 (m, 2H), 3.52–3.45 (m, 1H), 3.24 (t, $J$ = 6.6 Hz, 2H), 1.41 (d, $J$ = 6.8 Hz, 6H), 1.19 (d, $J$ = 6.7 Hz, 6H), 0.99 (d, $J$ = 3.3 Hz, 21H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.23, 156.01, 138.95, 135.78, 130.35, 130.05, 129.58, 127.49, 122.35, 120.22, 109.76, 102.73, 54.85, 48.45, 45.59, 38.69, 30.08, 26.73, 20.04, 19.16, 17.67, 10.35; HRMS Calcd for C$_{34}$H$_{49}$BrN$_2$NaO$_2$Si [M+Na$^+$]: 663.2594; Found: 663.2588.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J$ = 6.7 Hz, 2H), 7.38–7.32 (m, 4H), 7.15 (d, $J$ = 8.3 Hz, 1H), 7.01 (br s, 1H), 4.81–4.74 (m, 1H), 3.69–3.64 (m, 2H), 3.53–3.46 (m, 1H), 3.38 (t, $J$ = 7.1 Hz, 2H), 1.42 (d, $J$ = 6.8 Hz, 6H), 1.20 (d, $J$ = 6.7 Hz, 6H), 0.97 (d, $J$ = 4.0 Hz, 21H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.18, 161.82, 143.56, 139.24, 138.17, 132.72, 128.42, 127.99, 127.09, 126.63, 123.10, 102.45, 99.44, 48.54, 45.67, 37.65, 31.14, 20.03, 19.18, 17.82, 17.66, 10.30; HRMS Calcd for C$_{33}$H$_{46}$ClN$_2$NaO$_2$Si [M+Na$^+$]: 589.2993; Found: 589.3000.
6. Pd-catalyzed ortho-iodination of presubstituted β-arylethamide

A mixture of presubstituted β-arylethamide 1 (0.2 mmol, 1.0 eq), iodine (0.6 mmol, 3.0 eq), Pd(OAc)$_2$ (4.5 mg, 10 mol%), PhI(OAc)$_2$ (0.4 mmol, 2.0 eq), NaHCO$_3$ (0.2 mmol, 1.0 eq), and 1 mL DCE in a 15 mL glass vial was heated at 100 °C with vigorous stirring for 36 hours. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (Ethyl acetate/Petroleum ether = 1:12) to give product 3.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 (t, $J = 6.1$ Hz, 4H), 7.28 (d, $J = 2.1$ Hz, 2H), 7.17 (br s, 1H), 6.65 (s, 1H), 4.95–4.88 (m, 1H), 3.63–3.49 (m, 5H), 1.44 (d, $J = 6.8$ Hz, 6H), 1.23 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 163.05, 162.78, 158.10, 149.33, 145.58, 144.43, 129.19, 128.19, 128.01, 110.65, 94.25, 91.57, 56.90, 49.59, 47.46, 46.82, 37.78, 21.09, 20.21; HRMS Calcd for C$_{23}$H$_{29}$IN$_2$NaO$_3$ [M+Na$^+$]: 531.1121; Found: 531.1116.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59–7.57 (m, 2H), 7.43–7.40 (m, 2H), 7.37–7.33 (m, 2H), 7.27 (s, 1H), 7.04 (br s, 1H), 4.80–4.74 (m, 1H), 3.63–3.58 (m, 2H), 3.53–3.46 (m, 1H), 3.13 (t, $J = 7.3$ Hz, 2H), 2.55 (s, 3H), 1.41 (d, $J = 6.8$ Hz, 6H), 1.18 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.30, 161.83, 142.11, 141.26, 140.21, 139.04, 127.96, 126.76, 126.22, 126.04, 125.14, 105.62, 48.67, 45.75, 40.41, 38.30, 29.20, 19.99, 19.18; HRMS Calcd for C$_{23}$H$_{29}$IN$_2$NaO$_2$ [M+Na$^+$]: 515.1171; Found: 515.1165.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91 (dd, $J = 7.8$, 1.0 Hz, 1H), 7.57–7.53 (m, 1H), 7.47–7.41 (m, 2H), 7.03 (br s, 1H), 6.78 (s, 1H), 5.98 (s, 2H), 4.80–4.73 (m, 1H), 3.75 (d, $J = 5.6$ Hz, 3H), 3.57–3.46 (m, 3H), 2.97 (t, $J = 7.2$ Hz, 2H), 1.42 (d, $J = 6.8$ Hz, 6H), 1.19 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.17, 163.30, 162.90, 149.28, 142.16, 135.68, 134.00, 132.08, 131.31, 130.60, 130.35, 128.18, 123.53, 122.89, 100.79, 52.32, 49.69, 46.72, 39.52, 38.42, 20.98, 20.19; HRMS Calcd for C$_{25}$H$_{30}$IN$_2$NaO$_6$ [M+Na$^+$]: 603.0968; Found: 603.0980.
1H NMR (400 MHz, CDCl$_3$) δ 7.46–7.39 (m, 3H), 7.19–7.17 (m, 2H), 7.03 (br s, 1H), 6.92 (s, 1H), 4.82–4.75 (m, 1H), 3.90 (s, 3H), 3.59–3.52 (m, 3H), 3.50 (s, 3H), 1.42 (d, $J$ = 6.8 Hz, 6H), 1.24 (d, $J$ = 6.7 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 163.47, 162.98, 153.04, 145.61, 142.17, 142.02, 137.38, 129.75, 128.05, 127.69, 113.43, 95.71, 60.84, 56.14, 49.73, 46.73, 41.52, 39.32, 21.03, 20.18; HRMS Calcd for C$_{24}$H$_{31}$IN$_2$NaO$_4$ [M+Na$^+$]: 561.1226; Found: 561.1236.

7. Pd-catalyzed ortho-acetoxylation of presubstituted β-arylethamide

A mixture of presubstituted β-arylethamide 1 (0.2 mmol, 1.0 eq), Pd(OAc)$_2$ (4.5 mg, 10 mol%), Phl(OAc)$_2$ (0.6 mmol, 3.0 eq), HOAc (0.4 mmol, 2 eq) and 1 mL toluene in a 15 mL glass vial was heated at 60 °C with vigorous stirring for 36 hours. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (Ethyl acetate/Petroleum ether = 1:8 to 1:3) to give product 4.

1H NMR (400 MHz, CDCl$_3$) δ 7.57–7.55 (m, 2H), 7.42 (t, $J$ = 7.5 Hz, 2H), 7.34 (t, $J$ = 7.3 Hz, 1H), 7.05 (dd, $J$ = 7.1, 1.8 Hz, 2H), 6.97 (br s, 1H), 4.67–4.60 (m, 1H), 3.88 (s, 3H), 3.56–3.46 (m, 3H), 2.83 (t, $J$ = 7.2 Hz, 2H), 2.39 (s, 3H), 1.41 (d, $J$ = 6.8 Hz, 6H), 1.16 (d, $J$ = 6.7 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.46, 162.49, 162.09, 150.52, 139.83, 139.22, 137.05, 131.16, 127.88, 126.63, 126.38, 119.94, 108.96, 55.18, 48.74, 45.62, 38.42, 29.12, 19.93, 19.72, 19.17; HRMS Calcd for C$_{25}$H$_{32}$N$_2$NaO$_5$ [M+Na$^+$]: 463.2209; Found: 463.2204.

1H NMR (400 MHz, CDCl$_3$) δ 7.57–7.55 (m, 2H), 7.43–7.39 (m, 2H), 7.34–7.31 (m, 3H), 7.01 (br s, 1H), 4.66–4.59 (m, 1H), 3.57–3.44 (m, 2H), 3.47 (dd, $J$ = 13.6, 6.8 Hz, 1H), 2.80 (t, $J$ = 7.3 Hz, 2H), 2.41 (s, 3H), 2.22 (s, 3H), 1.41 (d, $J$ = 6.8 Hz, 6H), 1.16 (d, $J$ = 6.7 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.57, 162.50, 162.15, 146.72, 139.83, 139.22, 137.05, 131.16, 127.88, 126.63, 126.38, 119.94, 108.96, 55.18, 48.74, 45.62, 38.42, 29.12, 19.93, 19.72, 19.17; HRMS Calcd for C$_{25}$H$_{32}$N$_2$NaO$_5$ [M+Na$^+$]: 447.2260; Found: 447.2264.
1H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 7.8 Hz, 1H), 7.57–7.53 (m, 1H), 7.47–7.40 (m, 2H), 7.00 (br s, 1H), 6.73 (s, 1H), 5.95 (d, J = 4.0 Hz, 2H), 4.71–4.65 (m, 1H), 3.74 (s, 3H), 3.50–3.45 (m, 3H), 2.77 (t, J = 7.2 Hz, 2H), 2.39 (s, 3H), 1.41 (d, J = 6.8 Hz, 6H), 1.18 (d, J = 6.7 Hz, 6H);

13C NMR (101 MHz, CDCl₃) δ 167.41, 162.42, 162.02, 144.14, 137.83, 134.89, 130.96, 130.32, 129.83, 129.33, 127.01, 124.12, 122.23, 119.94, 101.22, 51.24, 48.71, 45.66, 38.77, 28.82, 19.95, 19.63, 19.19; HRMS Calcd for C₂₇H₃₃N₂O₈ [M+H⁺]: 513.2237; Found: 513.2262.

8. Pd-catalyzed intramolecular amination of presubstituted β-arylethamide

A mixture of presubstituted β-arylethamide 1c (0.2 mmol, 1.0 eq), Pd(OAc)₂ (4.5 mg, 10 mol%), PhI(OAc)₂ (0.8 mmol, 4.0 eq), HOAc (0.4 mmol, 2 eq) and 1 mL toluene in a 15 mL glass vial was heated at 90 °C with vigorous stirring for 36 hours. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (Ethyl acetate/Petroleum ether = 1:5) to give product 5.

1H NMR (400 MHz, CDCl₃) δ 7.88 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.43–7.36 (m, 2H), 6.72 (d, J = 9.4 Hz, 1H), 5.97 (s, 1H), 5.85 (s, 1H), 5.35 (t, J = 4.8 Hz, 0.23H), 4.10–3.94 (m, 2.65H), 3.76 (d, J = 4.1 Hz, 3H), 3.57–3.48 (m, 1.23H), 3.14 (t, J = 8.0 Hz, 1.22H), 2.23–2.19 (m, 0.28H), 2.04–1.98 (m, 0.5H), 1.51 (d, J = 6.8 Hz, 3H), 1.45 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.6 Hz, 6H); 13C NMR (101 MHz, CDCl₃) δ 168.49, 168.45, 164.08, 163.59, 163.12, 160.99, 145.95, 145.23, 136.52, 136.49, 135.19, 133.89, 131.90, 131.85, 131.19, 131.10, 130.94, 130.76, 130.23, 128.75, 127.79, 122.71, 122.66, 119.80, 119.14, 118.45, 118.02, 101.25, 100.85, 52.31, 52.22, 51.07, 50.76, 49.91, 49.53, 46.10, 46.04, 36.04, 32.04, 31.07, 29.91, 29.74, 29.83, 29.74, 29.66, 29.62, 29.46, 29.38, 29.06, 27.43, 27.35, 25.68, 22.82, 21.09, 20.26, 19.90; HRMS Calcd for C₂₅H₂₈N₂NaO₆ [M+Na⁺]: 475.1845; Found: 475.1840.
9. Pd-catalyzed ortho-alkynylation of 3b

A mixture of presubstituted β-arylethamide 3b (0.2 mmol, 1.0 eq), bromoalkyne (0.4 mmol, 2.0 eq), Pd(OAc)$_2$ (6.6 mg, 15 mol%), KOAc (0.8 mmol, 4.0 eq), AgOAc (0.8 mmol, 4.0 eq), and 1 mL toluene in a 15 mL glass vial was heated at 140 °C with vigorous stirring for 72 hours. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (Ethyl acetate/Petroleum ether = 1:20) to give product 7.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 (d, $J = 6.8$ Hz, 2H), 7.37–7.28 (m, 3H), 7.10 (s, 1H), 6.98 (br s, 1H), 4.81–4.75 (m, 1H), 3.56–3.48 (m, 3H), 3.07 (s, 1H), 2.31 (s, 3H), 2.18 (d, $J = 6.8$ Hz, 2H), 1.22 (d, $J = 6.7$ Hz, 6H), 0.97 (d, $J = 3.0$ Hz, 21H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.66, 163.35, 162.90, 147.60, 143.42, 140.54, 133.64, 131.38, 130.72, 129.51, 127.96, 127.35, 121.26, 103.74, 98.70, 49.57, 46.64, 39.05, 29.36, 21.03, 20.71, 20.19, 18.68, 16.89, 11.33; HRMS Calcd for C$_{36}$H$_{52}$N$_2$NaO$_4$Si [M+Na$^+$]: 627.3594; Found: 627.3597.

10. References
11. The structure determination of 2b, 2e, 4b according to HMBC spectrum
12. $^1$H and $^{13}$C NMR spectra

![NMR spectra image]

$^1$H NMR spectrum (top) and $^{13}$C NMR spectrum (bottom) for compound 1a.