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Supporting Information

Palladium catalyzed, heteroatom-guided C-H functionalization in the synthesis of substituted isoquinolines and dihydroisoquinolines

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Experimental:

(i) General Methods:

All commercially available compounds (Acros, Aldrich, Alfa Aesar, Fluka, Merck etc.,) were used without purification. Unless otherwise noted, all reactions were performed in oven-dried glassware. All reactions were run under argon or nitrogen atmosphere. All solvents used in the reactions were purified before use. Tetrahydrofuran, DMF, and toluene were distilled from sodium and benzophenone, whereas dry dichloromethane, dimethylformamide and triethylamine were distilled from CaH₂.¹ Petroleum ether with a boiling range of 40–60 °C was used. Melting points are uncorrected. ¹H, ¹³C and ¹⁹F NMR: Recorded on Bruker Avance III 400 MHz NMR Spectrometer, Bruker Avance III 500 MHz NMR Spectrometer; spectra were recorded at 295 K in CDCl₃ (¹H δ 7.25; ¹³C δ 77.0). HRMS: Bruker Daltonics MicroTOF-Q-II with electron spray ionization (ESI). GC-HRMS: Performed on Agilent 7200 GC-QToF (with Electron Impact (EI), 70eV) with 7890A GC using DB-5 column. IR: Perkin Elmer Spectrum BX FTIR, Shimadzu IRAffinity-1 FTIR and were recorded as thin films between KBr plates.

(ii) General procedures:

(1) 1-(isoquinolin-2(1H)-yl)ethanone (1):²



Sodium borohydride (5.86 g, 155.5 mmol) was gradually added to a mixture of isoquinoline (5 g, 38.75 mmol), acetic anhydride (20 mL, 205.05 mmol) and acetic acid (60 mL), over a period of 1.5 h at 0 $^{\circ}$ C. After the addition was complete, the mixture was warmed to rt for 1 h. The reaction mixture diluted with water (500 mL) and neutralized with sodium carbonate. This was then extracted with EtOAc and the organic extract was dried over anhydrous Na₂SO₄ and

concentrated under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (eluent: Petroleum ether:EtOAc, 4:1). Yield 5.02 g, 75%; Physical appearance: yellow oil; TLC R_f 0.25 (eluent: Petroleum ether:EtOAc, 4:1); ¹H NMR (400 MHz, CDCl₃): δ 7.18-7.11 (m, 2H), 7.07-7.05 (m, 1H), 7.02-6.99 (m, 1H), 6.62 (d, J = 8.0 Hz, 1H), 5.79 (d, J = 8.0 Hz, 1H), 4.91(s, 2H), 2.18 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.46, 130.47, 129.51, 127.68, 127.26, 126.14, 125.96, 124.68, 109.68, 44.35, 21.24; IR (KBr, cm⁻¹): 3044, 2934, 2843, 1654, 1602, 1549, 1483, 1458, 1372, 1241, 1222, 1128, 992, 847, 787, 762, 686, 617, 601, 549.

(2) 1-(1-methylisoquinolin-2(1*H*)-yl)ethanone (5a):³



A solution of methyllithium in THF (3*M*, 5.71 mL, 17.13 mmol) was added dropwise to the solution of isoquinoline (1g, 7.75 mmol) in THF (15 mL) under argon at 0 °C. Temperature was increased to 25 °C over 30 min and then reaction mixture was kept another for 1h at 25 °C. After stirring 1h at 25 °C, reaction mixture was cooled to 0 °C following which, acetyl chloride (0.827 mL, 11.63 mmol) was added dropwise to the reaction mixture. The solution was stirred for a further 30 min at RT and was then diluted with saturated solution of NH₄Cl. The resulting mixture was extracted with ethyl acetate and washed successively with brine. The combined organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel column chromatography (eluent: Petroleum ether:EtOAc, 4:1); Yield: 600mg, 60%; Physical appearance: Yellow oil: TLC R_f 0.27 (4:1 Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.17-7.13 (m, 2H), 7.05-7.01 (m, 2H), 6.53 (d, J = 7.6 Hz, 1H), 5.86 (d, J = 7.6 Hz, 1H), 5.74 (q, J = 6.4 Hz, 1H), 2.17 (s, 3H), 1.23 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.21, 135.00, 129.33, 127.46, 125.88, 124.70, 124.36, 109.69, 49.71, 21.59, 21.10; IR (KBr, cm⁻¹): 3075, 2824, 2844, 1671, 1620, 1509, 1343, 1322, 1277, 1224, 1030, 933, 913, 894, 867, 792, 756, 745, 723.

(3) 1-(1-butylisoquinolin-2(1*H*)-yl)ethanone (5b):³



A solution of *n*-Butyllithium in THF (2 M, 4.65 mL, 9.30 mmol) was added dropwise to the solution of isoquinoline (1g, 7.75 mmol) in THF (10 mL) under argon at -78 °C. Temperature was increased to 25 °C over 30 min and the temperature maintained for another hour, following which the reaction mixture was cooled to 0 °C and acetyl chloride (0.827 mL, 11.63 mmol) was added dropwise. The solution was stirred for a further 30 min at RT and was then diluted with saturated solution of NH₄Cl. This mixture was extracted with ethyl acetate and washed successively with brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel column chromatography (eluent: Petroleum ether:EtOAc, 4:1). Yield: 1.5 g, 84%; Physical appearance: Colourless oil; TLC *R_f* 0.35 (9:1 Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer); δ 7.20-7.12 (m, 2H), 7.07-7.00 (m, 2H), 6.56 (d, *J* = 7.6 Hz, 1H), 5.89 (d, *J* = 7.6 Hz, 1H), 5.64 (t, *J* = 6.8Hz, 1H), 2.16 (s, 3H), 1.60-1.54 (m, 2H), 1.27-1.14 (m, 4H), 0.80 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.47, 133.74, 129.82, 127.42, 127.04, 126.61, 124.92, 124.69, 110.54, 53.45, 34.57, 27.57, 22.60, 21.56, 13.98; IR (KBr, cm⁻¹): 3074, 2822, 2842, 1671, 1620, 1554, 1525, 1344, 1322, 1287, 1234, 1035, 933, 923, 894, 867, 792, 752, 742, 733.

(G) General procedure for the synthesis of 4-arylisoquinolines:

(A) In a pressure tube equipped with a stir bar, *N*-acetyl-1-dihydroisoquinoline (0.57 mmol) was taken in 3 mL of dry toluene. The reaction mixture was degassed for 10 min followed by the addition of $Pd(OAc)_2$ (0.0285 mmol), $Cu(OTf)_2$ (0.57 mmol), Ag_2O (0.57 mmol). The addition of the arylboronic acid (1.14 mmol) was done in portions over a period of 3-5 h. The tube was fitted with Teflon screw cap under an argon flow. The reaction mixture was heated to 100-110 $^{\circ}C$ and allowed to stir for 8-12 h (total time). Upon cooling to room temperature, the reaction

mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography.

(B) In a pressure tube equipped with a stir bar, *N*-acetyl-1-dihydroisoquinoline (0.57 mmol)in 3 mL of dry TFA was taken, followed by the addition of Pd $(TFA)_2 (0.0285 \text{ mmol}), Cu(OTf)_2 (0.57 \text{ mmol}), Ag_2O (0.57 \text{ mmol}), arylboronic acid (1.14 mmol). The tube was fitted with Teflon screw cap under an argon flow. The reaction mixture was heated to 70 °C and allowed to stirr for 8 h (total time). Upon cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was neutralized by NaHCO₃ and the organic layer was extracted with EtOAc, concentrated under reduced pressure and the crude product was purified by silica gel column chromatography.$

(C) General procedure for the synthesis of 1-alkyl-N-acetyl-4-arylisoquinolines:

In a pressure tube equipped with a stir bar, 1-alkyl-*N*-acetyl-1-hydroisoquinoline (0.57 mmol) in 3 mL of dry toluene was taken. The reaction mixture was degassed for 10 min followed by the addition of $Pd(OAc)_2$ (0.0285 mmol), $Cu(OTf)_2$ (0.57 mmol), Ag_2O (0.57 mmol). The addition of the arylboronic acid (2.28 mmol) was done in portions over a period of 3 h. The tube was fitted with Teflon screw cap under an argon flow. The reaction mixture was heated to 110 °C and allowed to stirr for 12-16 h (total time). Upon cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography.

(D) General procedure for the synthesis of 1-alkyl-4-arylisoquinolines:

In a RB flask fitted with a reflux condenser and equipped with a stir-bar, was taken 1-alkyl-*N*-acetyl-4-arylisoquinolines (crude, from above reaction). To this was added 6 M aq. HCl (5 mL) and dioxane (10 mL). The resulting mixture was refluxed for 2 h, during which the reaction was complete. The reaction mixture was cooled, concentrated under reduced pressure and basified using solid Na₂CO₃. After dilution with water and extraction with EtOAc, the combined extracts were concentrated and column chromatographed over silica gel to yield the title compounds.

NMR Experiments:

15 mg of the N-acetyl dihydroisoquinolines was taken in a TFA-d + D₂O mixture (2:1). The data was recorded (500 MHz) before addition of the Palladium catalyst. Upon addition of the catalyst (Pd(TFA)₂ (1 equivalent)), the data was recorded immediately after every 15 minutes. A blank experiment was also run concurrently, without the addition of any palladium catalyst.

4-phenylisoquinoline (2): ^{4,5,6}



Yield: 40%; Physical appearance: Yellow gel; TLC R_f 0.30 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 9.25 (s, 1H), 8.48 (s, 1H), 8.04 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.68-7.60 (m, 2H), 7.54-7.46 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 151.86, 142.60, 136.97, 134.29, 130.67, 130.10, 128.61, 127.94, 127.94, 127.24, 124.83; IR (KBr, cm⁻¹): 2964, 2843, 1575, 1489, 1360, 1344, 1275, 1102, 951, 903, 864, 786, 762, 694. Yield for this compound using Pd(TFA)₂/TFA/Ag₂O/Cu(OTf)₂/70 °C: 52% (single isomer)

4-(4-(tert-butyl) phenyl) isoquinoline (6a):



Yield: 55%; Physical appearance: Yellow gel; TLC R_f 0.32 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 9.22 (s, 1H), 8.48 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.67-7.58 (m, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 1.40 (s, 9H)); ¹³C NMR (100 MHz, CDCl₃): δ 151.73, 150.93, 142.85, 134.32, 133.98, 133.25, 130.42, 129.78,

128.47, 127.85, 127.10, 125.54, 124.98, 34.47, 31.41; IR (KBr, cm⁻¹): 3096, 2959, 2874, 1656, 1617, 1559, 1539, 1457, 1113, 954, 908, 828, 787; GC-HRMS: Calculated for $C_{19}H_{19}N$ [M]⁺ 261.1511, found 261.1505.

Yield for this compound using Pd(TFA)₂/TFA/Ag₂O/Cu(OTf)₂/70 °C: 66% (single isomer)

4-(*p*-tolyl) isoquinoline (6b):⁶



Yield: 51%; Physical appearance: Yellow gel; TLC R_f 0.31 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 9.22 (s, 1H), 8.46 (s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.66-7.58 (m, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 151.80, 142.87, 137.75, 134.31, 134.06, 133.26, 130.42, 129.98, 129.31, 128.46, 127.85, 127.09, 124.87, 21.27; IR (KBr, cm⁻¹): 3026, 2924, 2854, 1541, 1492, 1346, 1253, 1184, 818, 763, 724, 697, 594; GC-HRMS: Calculated for C₁₆H₁₃N [M]⁺ 219.1026, found 219.1020.

Yield for this compound using Pd(TFA)₂/TFA/Ag₂O/Cu(OTf)₂/70 °C: 58% (single isomer)

4-(*m*-tolyl) isoquinoline (6c):



Yield: 58%; Physical appearance: Yellow gel; TLC R_f 0.31 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 9.25 (s, 1H), 8.46 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.70-7.61 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.30-7.26 (m, 3H), 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 151.24, 141.80, 138.37, 136.69, 134.56, 130.94, 130.74, 128.82, 128.51,

128.05, 127.42, 127.18, 125.00, 21.50; IR (KBr, cm⁻¹): 2921, 2854, 1606, 1491, 1463 1358, 1124, 962, 900, 816, 788, 751, 700; GC-HRMS: Calculated for $C_{16}H_{13}N$ [M]⁺ 219.1036, found 219.1030.

Yield for this compound using Pd(TFA)₂/TFA/Ag₂O/Cu(OTf)₂/70 °C: 51% (single isomer)

4-(o-tolyl)isoquinoline (6d):



Yield: 53%; Physical appearance: Yellow gel; TLC R_f 0.30 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 9.26 (s, 1H), 8.39 (s, 1H), 8.04-8.01 (m, 1H), 7.61-7.59 (m, 2H), 7.46-7.44 (m, 1H), 7.39-7.28 (m, 3H), 7.25-7.23 (m, 1H), 2.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 151.93, 142.77, 137.12, 136.35, 134.73, 130.60, 130.53, 130.14, 128.26, 127.86, 127.18, 125.80, 125.00, 20.08; IR (KBr, cm⁻¹): 3051, 3036, 2921, 2854, 1616, 1489, 1460, 1358, 1340, 962, 900, 784, 752, 619, 564; GC-HRMS: Calculated for C₁₆H₁₃N [M]⁺ 219.1030, found 219.1025.

Yield for this compound using Pd(TFA)₂/TFA/Ag₂O/Cu(OTf)₂/70 °C: 58% (single isomer)

4-(4-methoxyphenyl) isoquinoline (6e):⁶



Yield: 59%; Physical appearance: Brown gel; TLC R_f 0.30 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 9.35 (s, 1H), 8.53 (s, 1H), 8.07 (d, J = 7.6 Hz, 2H), 7.95 (d, J = 7.6 Hz, 1H), 7.73-7.64 (m, 2H), 7.425 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 3.88 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 159.73, 140.69, 134.87, 131.38, 131.20, 128.64, 128.32, 127.72,

125.07, 114.22, 55.42; IR (KBr, cm⁻¹): 2934, 2835, 1608, 1516, 1493, 1455, 1341, 1250, 1180, 1030, 883, 826, 787, 755; GC-HRMS: Calculated for $C_{16}H_{13}NO_2$ [M]⁺ 235.1027, found 235.1039.

Yield for this compound using Pd(TFA)₂/TFA/Ag₂O/Cu(OTf)₂/70 °C: 68% (single isomer)

1-methyl-4-phenylisoquinoline (6f):



Yield: 67%; Physical appearance: Colorless gel; TLC R_f 0.28 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.34 (s, 1H), 8.19-8.17 (m, 1H), 7.90-7.88 (m, 1H), 7.65-7.59 (m, 2H), 7.52-7.43 (m, 5H), 3.01 (s, 3H);); ¹³C NMR (100 MHz, CDCl₃): δ 157.95, 141.40, 137.31, 134.37, 131.97, 130.22, 130.07, 128.52, 127.74, 127.14, 126.91, 125.86, 125.51, 22.51; IR (KBr, cm⁻¹): 1564, 1451, 1361, 1071, 1033, 965, 770,731, 701; GC-HRMS: Calculated for C₁₆H₁₃N [M]⁺ 219.1045, found 219.1040.

4-(4-methoxyphenyl)-1-methylisoquinoline (6g):



Yield: 57%; Physical appearance: Yellow gel; TLC R_f 0.26 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s,1H), 8.17 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.64-7.57 (m, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.03 (d, J = 7.6 Hz, 2H), 3.88 (s, 3H), 2.99 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 159.33, 157.59, 141.56, 134.56, 131.61, 131.29, 129.91, 129.61, 127.16, 126.71, 125.83, 125.55, 114.01, 55.38, 22.52; IR (KBr, cm⁻¹): 1568, 1516, 1493, 1455,

1341, 1250, 1180, 1071, 1030, 883, 826, 787, 755, 701; GC-HRMS: Calculated for $C_{17}H_{15}NO$ [M]⁺ 249.1150, found 219.1145.

4-(4-(*tert*-butyl)phenyl)-1-methylisoquinoline (6h):



Yield: 67%; Physical appearance: Colorless gel; TLC R_f 0.28 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.35 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.65-7.58 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 3.00 (s, 3H), 1.39 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 157.62, 150.77, 141.55, 134.44, 134.31, 131.91, 129.88, 128.77, 127.15, 126.81, 125.81, 125.67, 125.45, 34.69, 31.42, 22.51; IR (KBr, cm⁻¹): 1569, 1450, 1391, 1275, 1243, 1071, 1035, 965, 834, 769, 755; GC-HRMS: Calculated for C₂₀H₂₁N [M]⁺ 275.1693, found 275.1689.

1-methyl-4-(p-tolyl)isoquinoline (6i):



Yield: 65%; Physical appearance: Colorless gel; TLC R_f 0.28 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 7.2 Hz, 1H), 7.65-7.58 (m, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 3.00 (s, 3H), 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 157.06, 141.10, 137.59, 134.53, 134.22, 130.07, 129.36, 129.26,

129.07, 127.46, 126.93, 125.87, 125.61, 22.34, 21.26; IR (KBr, cm⁻¹): 1569, 1512, 1450, 1391, 1360, 1275, 1241, 1071, 1035, 965, 815, 755, 615; GC-HRMS: Calculated for $C_{17}H_{15}N$ [M]⁺ 233.1201, found 233.1196.

1-methyl-4-(o-tolyl)isoquinoline (6j):



Yield: 55%; Physical appearance: Yellow gel; TLC R_f 0.28 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.26 (s, 1H), 8.19-8.17 (m, 1H), 7.61-7.56 (m, 2H), 7.46-7.43 (m, 1H), 7.38-7.26 (m, 4H), 3.02 (s, 3H), 2.03 (s, 3H), ¹³C NMR (100 MHz, CDCl₃): δ 157.91, 141.19, 137.27, 136.59, 134.91, 130.74, 130.18, 130.09, 128.16, 127.02, 126.98, 125.89, 125.79, 125.70, 22.34, 2012; IR (KBr, cm⁻¹): 1544, 1512, 1420, 1275, 1241, 1071, 1035, 965, 815, 766; GC-HRMS: Calculated for C₁₇H₁₅N [M]⁺ 233.1197, found 233.1191.

1-butyl-4-phenylisoquinoline (6k):



Yield: 68%; Physical appearance: Yellow gel; TLC R_f 0.40 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.37 (s, 1H), 8.22 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.63-7.57 (m, 2H), 7.52-7.41 (m, 5H), 3.34 (t, J = 8.0 Hz, 2H), 1.92-1.84 (m, 2H), 1.57-1.48 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.85, 141.68, 137.43, 134.69, 131.72,130.23, 129.82, 128.50, 127.70, 126.75, 126.53, 125.60, 125.58, 35.39, 32.03, 23.07,

14.04; IR (KBr, cm⁻¹): 1546, 1523, 1450, 1421, 1369, 1276, 1054, 1034, 970, 846, 771, 701; GC-HRMS: Calculated for C₁₉H₁₉N [M]⁺ 261.1527, found 261.1521.

1-butyl-4-(4-fluorophenyl)isoquinoline (6l):



Yield: 71%; Physical appearance: Colorless gel TLC R_f 0.37 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.33 (s, 1H), 8.23- 8.21 (m, 1H), 7.84-7.81 (m, 1H), 7.65-7.58 (m, 2H), 7.45-7.42 (m, 2H), 7.19 (t, J = 8.4 Hz, 2H), 3.33 (t, J = 8.0 Hz, 2H), 1.92-1.84 (m, 2H), 1.55-1.48 (m, 2H), 0.98 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 162.56 (d, J = 245.5 Hz), 162.06, 141.69, 134.69, 133.36 (d, J = 3.3 Hz), 131.78 (d, J = 8 Hz), 130.70, 129.98, 126.85, 126.53, 125.66, 125.37, 115.63 (d, J = 21.3 Hz), 35.39, 32.01, 23.03, 14.03; ¹⁹F NMR (376 MHz, CDCl₃): δ -114.62; IR (KBr, cm⁻¹): 1568, 1509, 1454, 12251158, 1094, 1154, 973, 834, 804, 751; GC-HRMS: Calculated for C₁₉H₁₈FN [M]⁺ 279.1422, found 279.1416.

1-butyl-4-(*o*-tolyl)isoquinoline (6m):



Yield: 73%; Physical appearance: Colorless gel; TLC R_f 0.41 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.30 (s,1H), 8.23-8.20 (m, 1H), 7.59-7.54 (m, 2H), 7.47-7.43 (m, 1H), 7.38-7.22 (m, 4H), 3.38-3.30 (m, 2H), 2.03 (s, 3H), 1.94-1.86 (m, 2H), 1.59-1.49 (m, 2H),

1.01 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.77, 141.65, 137.33, 136.83, 135.11, 131.25, 130.77, 130.05, 129.76, 128.06, 126.73, 126.40, 125.80, 125.76, 125.57, 35.41, 32.01, 23.11, 20.14, 14.06; IR (KBr, cm⁻¹): 1569, 1447, 1454, 1393, 1230, 1155, 1125, 1053, 970, 849, 767, 738; GC-HRMS: Calculated for C₂₀H₂₁N [M]⁺ 275.1682, found 275.1676.

1-butyl-4-(4-(trifluoromethyl)phenyl)isoquinoline (6n):



Yield: 70%; Physical appearance: Colorless gel; TLC R_f 0.39 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.36 (s, 1H), 8.25-8.22 (m, 1H), 7.82-7.79 (m, 1H), 7.76 (d, J = 8.0 Hz, 2H); 7.67-7.59 (m, 4H), 3.34 (t, J = 8.0 Hz, 2H); 1.92-1.84 (m, 2H), 1.58-1.49 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 162.74, 141.66, 141.27, 134.28, 130.55, 130.36, 130.24, 129.79, 127.07, 126.53, 125.76, 125.50 (q, J = 3.7 Hz), 125.10, 35.42, 31.96, 23.04, 14.06; ¹⁹F NMR (376 MHz, CDCl₃): δ -62.50; IR (KBr, cm⁻¹): 1568, 1519, 1489, 1325, 1233, 1068, 1019, 971, 840, 772; GC-HRMS: Calculated for C₂₀H₁₈F₃N [M]⁺ 329.1388, found 329.1382.

1-butyl-4-(3-(trifluoromethyl)phenyl)isoquinoline (60):



Yield: 78%; Physical appearance: Colorless gel; TLC R_f 0.36 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.36 (s, 1H), 8.25-8.23 (m, 1H), 7.79-7.74(m, 2H), 7.71 (d, J = 7.2

Hz, 1H), 7.68-7.60 (m, 4H), 3.34 (t, J = 8.0 Hz, 2H); 1.92-1.84 (m, 2H), 1.57-1.48 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 162.71, 141.73, 138.32, 134.38, 133.50, 130.30, 129.08,127.07, 126.91 (q, J = 3.7 Hz), 126.53, 125.78, 125.03, 124.56 (q, J = 3.7 Hz), 35.41, 31.99, 23.04, 14.02; ¹⁹F NMR (376 MHz, CDCl₃): δ -62.52; IR (KBr, cm⁻¹): 1519, 1489, 1325, 1233, 1068, 1019, 971, 840, 772, 775; GC-HRMS: Calculated for C₂₀H₁₈F₃N [M]⁺ 329.1400, found 329.1395.

3-phenylisoquinoline (6u):^{5,6}



Yield: 20%; Spectral data in agreement with literature values.⁵

3, 4-diphenylisoquinoline (6t):



Yield: 35%; Physical appearance: Pale yellow gel; TLC R_f 0.32 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 9.5 (s, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.72-7.66 (m, 3H), 7.39-7.36 (m, 5H), 7.23-7.22 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 149.66, 131.04, 130.36, 128.59, 128.31, 128.25, 128.09, 128.05, 126.03; IR (KBr, cm⁻¹): 2963, 2843, 1624, 1590 1575, 1489, 1360, 1344, 1275, 1102, 951, 903, 864, 786, 762, 694. GC-HRMS: Calculated for C₂₁H₁₅N [M]⁺ 281.1170, found 281.1165.

1-(1-methyl-4-phenylisoquinolin-2(1*H*)-yl)ethanone (7a):



Yield: 67%; Physical appearance: Pale yellow solid, M.p. 41-43 °C; TLC R_f 0.31 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.37-7.28 (m, 5H), 7.13 (d, J = 6.80 Hz, 1H), 7.09-7.06 (m, 2H), 6.99 (d, J = 7.60 Hz, 1H), 6.51 (s, 1H), 5.73 (q, J = 6.80 Hz, 1H), 2.17 (s, 3H), 1.27 (d, J = 6.80 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.36, 137.26, 135.72, 130.23, 129.19, 128.70, 127.83, 127.66, 127.47, 127.31, 126.11, 124.34, 123.65, 122.92, 49.90, 21.27, 21.12; IR (KBr, cm⁻¹): 3059, 2974, 2925, 1669, 1624, 1564, 1451, 1361, 1071, 1033, 965, 770,731, 701; GC-HRMS: Calculated for C₁₈H₁₇NO [M]⁺ 263.1296, found 263.1301.





Yield: 57%; Physical appearance: Yellow oil; TLC R_f 0.31 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.36 (d, J = 8.8 Hz, 2H), 7.25-7.17 (m, 3H), 7.06 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.80 Hz, 2H), 6.58 (s, 1H), 5.83 (q, J = 6.8 Hz, 1H), 3.88 (s, 3H), 2.27 (s, 3H), 1.33 (d, J = 6.80 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.28, 159.22, 135.72, 130.32, 129.52, 127.75, 127.27, 126.06, 124.21, 123.27, 122.43, 114.10, 55.37, 49.83, 21.68, 21.06; IR (KBr, cm⁻¹): 3058, 2974, 2934, 2835, 1672, 1608, 1568, 1516, 1493, 1455, 1341, 1250, 1180, 1071, 1030, 883, 826, 787, 755, 701; GC-HRMS: Calculated for C₁₉H₁₉NO₂ [M]⁺ 293.1417, found 293.1412.

1-(4-(4-(tert-butyl) phenyl)-1-methylisoquinolin-2(1*H*)-yl) ethanone (7c):



Yield: 67 %; Physical appearance: Yellow oil; TLC R_f 0.33 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.45 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.22-7.11 (m, 4H), 6.58 (s, 1H), 5.8 (q, J = 6.40 Hz, 1H), 2.24 (s, 1H), 1.37 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 168.32, 150.71, 135.75, 134.23, 130.33, 128.79, 127.75, 127.27, 126.07, 125.59, 124.32, 123.51, 122.71, 49.88, 34.65, 31.40, 21.68, 21.07; IR (KBr, cm⁻¹): 2964, 2926,1671, 1624, 1569, 1450, 1391, 1275, 1243, 1071, 1035, 965, 834, 769, 755; GC-HRMS: Calculated for C₂₂H₂₅NO [M]⁺ 319.1935, found 319.1930.

1-(1-methyl-4-(*p*-tolyl) isoquinolin-2(1*H*)-yl) ethanone (7d):



Yield: 65%; Physical appearance: Yellow solid; M.p. 42-45 °C; TLC R_f 0.33 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.31 (d, J = 8.00 Hz, 2H), 7.25-7.20 (m, 3H), 7.16 (d, J = 7.2 Hz, 2H), 7.08 (d, J = 7.6 Hz, 1H), 6.75 (s, 1H), 5.81 (q, J = 6.4 Hz, 1H), 2.41 (s, 3H), 2.24 (s, 3H), 1.35 (d, J = 6.40 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.36, 137.46, 135.73, 134.26, 130.36, 129.38, 129.08, 127.67, 127.48, 126.06, 124.25, 122.67, 49.89, 21.67, 21.24, 21.10; IR (KBr, cm⁻¹): 2974, 2924, 2862, 1669, 1624, 1569, 1512, 1450, 1391, 1360, 1275, 1241, 1071, 1035, 965, 815, 755, 615; GC-HRMS: Calculated for C₁₉H₁₉NO [M]⁺ 277.1457, found 277.1452.

1-(1-methyl-4-(*o*-tolyl) isoquinolin-2(1*H*)-yl) ethanone (7e):



Yield: 55%; Physical appearance: Yellow gel; TLC R_f 0.32 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.36-7.26 (m, 3H), 7.19-7.14 (m, 3H), 7.12-7.07 (m, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.52 (s, H), 5.84 (q, J = 6.4 Hz, 1H), 2.20 (s, 3H), 2.17 (s, 3H), 1.38 (d, J = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.28, 138.07, 135.72, 134.73, 130.42, 130.21, 128.13, 127.73, 127.51, 126.23, 125.97, 123.70, 123.02, 49.38, 21.68, 21.01, 20.24; IR (KBr, cm⁻¹): 2938, 2924, 2848, 2124, 2105, 2094,1672,1640, 1624, 1544, 1512, 1420, 1275, 1241, 1071, 1035, 965, 815, 766; GC-HRMS: Calculated for C₁₉H₁₉NO [M]⁺ 277.1470, found 277.1465.

1-(1-butyl-4-phenylisoquinolin-2(1*H*)-yl)ethanone (7f):



Yield: 68%; Physical appearance: Yellow oil; TLC R_f 0.36 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.47-7.39 (m, 5H), 7.23-7.21 (m, 1H), 7.19-7.15 (m, 2H), 7.09 (d, J = 7.4 Hz, 1H), 6.64 (s, 1H), 5.72 (q, J = 6.8 Hz, 1H), 2.26 (s, 3H), 1.17-1.64 (m, 2H), 1.30-1.28 (m, 4H), 0.90-0.86 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.65, 137.29, 134.63, 130.72, 129.11, 128.72, 127.69, 127.50, 127.29, 126.84, 124.54, 124.29, 123.32, 122.60, 53.69, 34.77, 27.79, 22.66, 21.68, 14.04; IR (KBr, cm⁻¹): 3059, 2942, 2930, 2860, 1670, 1624,

1546, 1523, 1450, 1421, 1369, 1276, 1054, 1034, 970, 846, 771, 701; GC-HRMS: Calculated for $C_{21}H_{23}NO[M]^+$ 305.1780, found 305.1778.

1-(1-butyl-4-(4-fluorophenyl) isoquinolin-2(1*H*)-yl)ethanone (7g):



Yield: 71%; Physical appearance: Yellow gel; TLC R_f 0.36 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.39-7.35 (m, 2H), 7.19-7.13 (m, 2H), 7.11-7.07 (m, 2H), 7.02(d, J = 7.60 Hz, 1H), 6.86-6.92 (m, 1H), 6.79-6.76 (m, 1H), 6.59 (s, 1H), 5.69 (t, J = 6.40 Hz, 1H), 2.26 (s, 3H), 1.70-1.66 (m, 2H), 1.32-1.24 (m, 4H), 0.89-0.83(m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.85, 163.29 (d, J = 245.3 Hz), 134.52, 133.17 (d, J = 3.3 Hz), 130.79 (d, J = 8 Hz), 130.59, 127.63, 127.34, 126.89, 124.1, 123.75, 123.26, 116.24, (d, J = 8.8 Hz), 115.75, 115.54, 53,57, 34.77, 27.77, 22.63, 21.60, 14.01; ¹⁹F NMR (376 MHz, CDCl₃): δ - 114.39; IR (KBr, cm⁻¹): 3070, 2960, 2930, 1668, 1621, 1568, 1509, 1454, 12251158, 1094, 1154, 973, 834, 804, 751; GC-HRMS: Calculated for C₂₁H₂₂FNO [M]⁺ 323.1686, found 323.1681.

1-(1-butyl-4-(o-tolyl) isoquinolin-2(1H)-yl) ethanone (7h):



Yield: 73%; Physical appearance: Reddish brown gel; TLC R_f 0.36 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.33-7.24 (m, 3H), 7.22-7.08 (m, 4H), 6.67 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 5.74 (t, J = 7.2 Hz, 1H), 2.22 (s, 3H), 2.16 (s, 3H),

1.74 (broad, 2H), 1.13 (broad, 4H), 0.85 (broad, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.60, 138.07, 136.56, 133.55, 130.94, 130.45, 130.25, 128.12, 127.33, 126.73, 126.25, 124.09, 123.60, 53.65, 34.48, 27.75, 22.66, 21.69, 20.35, 13.97; IR (KBr, cm⁻¹): 3066, 3019, 2930, 2859, 1670, 1626, 1569, 1447, 1454, 1393, 1230, 1155, 1125, 1053, 970, 849, 767, 738; GC-HRMS: Calculated for C₂₂H₂₅NO [M]⁺ 319.1936, found 319.1931.

1-(1-butyl-4-(4-(trifluoromethyl) phenyl) isoquinolin-2(1*H*)-yl) ethanone (7i):



Yield: 70%; Physical appearance: Yellow oil; TLC R_f 0.36 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.60 (d, J = 8.40 Hz, 2H), 7.45 (d, J = 8.40 Hz, 2H), 7.23-7.21 (m, 1H), 7.20-7.16 (m, 2H), 7.01 (d, J = 7.6 Hz, 1H), 6.60 (s, 1H), 5.70 (t, J = 6.8 Hz, 1H), 2.19 (s, 3H), 1.65-1.56 (m, 2H), 1.23-1.17 (m, 4H), 0.78 (broad, 3H); ¹³C NMR (100 MHz, CDCL₃): δ 168.61, 134.51, 130.07, 129.38, 127.81, 127.06, 127.02, 125.70 (d, J = 3.7 Hz), 124.19, 123.90, 53.73, 34.81, 26.58, 22.60, 21.64, 13.98; ¹⁹F NMR (376 MHz, CDCl₃): δ -62.50; IR (KBr, cm⁻¹): 3072, 2959, 2932, 1672, 1623, 1568, 1519, 1489, 1325, 1233, 1068, 1019, 971, 840, 772, 7755; GC-HRMS: Calculated for C₂₂H₂₂F₃NO [M]⁺ 373.1653, found 373.1657.

1-(1-butyl-4-(2-(trifluoromethyl) phenyl) isoquinolin-2(1H)-yl) ethanone (7j):



Yield: 78%; Physical appearance: Yellow oil; TLC R_f 0.36 (4:1, Petroleum ether:EtOAc); ¹H NMR (400 MHz, CDCl₃) (major rotamer): δ 7.70-7.50 (m, 5H), 7.18 (t, J = 7.4 Hz, 2H), 6.99 (d, J = 7.4 Hz, 1H), 6.66 (s, 1H), 5.72 (t, J = 7.20 Hz, 1H), 2.27 (s, 3H), 1.72-1.67 (m, 2H), 1.33-1.28 (m, 4H), 0.85 (broad, 3H), ¹³C NMR (100 MHz, CDCl₃): δ 168.62, 138.21, 134.49, 132.52, 131.37, 131.05, 130.66, 129.91, 127.46, 127.03, 125.79 (q, J = 3.7 Hz,), 124.41 (q, J = 3.7 Hz), 124.16, 123.81, 123.06, 53.72, 34.83, 27.75, 22.61, 21.65, 13.99; ¹⁹F NMR (376 MHz, CDCl₃): δ -62.52; IR (KBr, cm⁻¹): 2958, 2931, 1669, 1626, 1566, 1447, 1452, 1393, 1324, 1167, 1125, 1026, 825, 764, 704; GC-HRMS: Calculated for C₂₂H₂₂F₃NO [M]⁺ 373.1631, found 373.1626.

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 CF_3 .ŃAc 7j 'n-Bu (mixture of rotamers

L



Deuteration experiments:

(i) At Zero time, without Pd catalyst



(ii) 15 min, after addition of Pd(TFA)₂



(iii) 35 min, after addition of $Pd(TFA)_2$







тm

(iv) Experiment without palladium catalyst, at 1 hour:





(v) Deuterated aromatized isoquinoline(H:D 21:4)

X-ray structures of C-4 arylated substrates:

