Nickel-catalyzed reductive alkylation of halogenated pyridines with secondary alkyl bromides

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I. Experimental Section

General Methods: All reactions were carried out under an atmosphere of nitrogen unless otherwise indicated. All NMR spectra were recorded on Bruker Avance 500 MHz spectrometer at STP unless otherwise indicated. ^1H NMR and ^{13}C NMR chemical shifts are reported in δ units, parts per million (ppm) relative to the chemical shift of residual solvent. Reference peaks for chloroform in ^1H NMR and ^{13}C NMR spectra were set at 7.26 ppm and 77.0 ppm, respectively. High-resolution mass spectra (HRMS) were obtained using a Agilent 7890-5975. Melting point was recorded on a micro melting point apparatus (X-4, YUHUA Co., Ltd, Gongyi, China). Column chromatography was performed using silica gel 300-400 mesh (purchased from Qingdao-Haiyang Co. China) as the solid support.

Chemicals: The following anhydrous solvents were purchased from Acros: THF (99.5%, stabilized), DMF (N,N- dimethylformamide, 99.8%), DMA (N,N-dimethylacetamide, 99.5%, extra pure). NiBr_2 (Alfa Aesar), Ni(COD)_2 (Strem). Zinc powder (Aladdin) was activated before use. Unless otherwise noted, all other reagents and starting materials were purchased from commercial sources and used without further purification. 4-bromo-1-tosylpiperidine and 2-bromo-2,3-dihydro-1H-indene were synthesized according to the literature procedures.

General Procedure for alkylation of halogenated pyridines with

secondary alkyl bromides: To a flame-dried Schlenk tube equipped with a magnetic stir bar was loaded alkyl bromide (0.15 mmol, 100 mol%, solid), halogenated pyridine (0.30 mmol, 300 mol%, solid), ligand (0.015 mmol, 10 mol%), zinc powder (0.45 mmol, 300 mol%). The tube was capped with a rubber septum and moved to a dry glove box, at which NiBr₂ (0.015 mmol, 10 mol%), MgCl₂ (0.15 mmol, 100 mol%) and Bu₄NBr (0.075 mmol, 50 mol%) were added. Then the tube was moved out of the glove box. Alkyl bromide (0.15 mmol, 100 mol%, liquid), halogenated pyridine (0.30 mmol, 300 mol%, liquid), pyridine (0.15 mmol, 100 mol%) and DMA (1.0 mL) were added *via* syringe. After the reaction mixture was allowed to stir overnight under N₂ atmosphere at 30 °C, it was directly loaded onto a silica column without work-up. The residue in the reaction vessel was rinsed with small amount of DCM or eluent. Flash column chromatography provided the product as solid or oil.

II .Spectral Data of New Compounds

5-methyl-2-(1-tosylpiperidin-4-yl)pyridine (Table 2, entry 3), a white power solid. mp 184-186 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.32 (m, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.41 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 3.91 (d, *J* = 11.6 Hz, 2H), 2.58 (tt, *J* = 12.1 Hz, 3.6 Hz, 1H), 2.44 (s, 3H), 2.37 (td, *J* = 12.0 Hz, 2.5 Hz, 2H), 2.28 (s,

3H), 2.02 -1.93 (m, 2H), 1.92-1.81 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 160.6, 149.6, 143.4, 137.1, 133.3, 130.9, 129.6, 127.7, 120.1, 46.5, 43.1, 31.2, 21.5, 18.0. IR (KBr, cm^{-1}) ν 2993, 2920, 2838, 1596, 1459, 1331, 1243, 1161, 723.

HRMS (ESI): m/z (M^+) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: 330.1402, found 330.1406.

4-methyl-2-(1-tosylpiperidin-4-yl)pyridine (Table 2, entry 4), a white power solid. mp 142-144 °C. ^1H NMR (500 MHz, CDCl_3): δ 8.34 (d, $J = 5.0$ Hz, 1H), 7.66 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 6.96-6.89 (m, 2H), 3.91 (d, $J = 5.0$ Hz, 2H), 2.57 (tt, $J = 12.0$ Hz, 3.7 Hz, 1H), 2.44 (s, 3H), 2.36 (td, $J = 12.0$ Hz, 2.5 Hz, 2H), 2.31 (s, 3H), 2.01-1.95 (m, 2H), 1.93 -1.82 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 163.2, 148.8, 147.5, 143.3, 133.1, 129.4, 127.5, 122.5, 121.4, 46.3, 43.2, 31.0, 21.4, 20.9. IR (KBr, cm^{-1}) ν 2981, 2919, 2840, 1603, 1444, 1330, 1247, 1164, 726. HRMS (ESI): m/z (M^+) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: 330.1405. Found 330.1402.

2-(2,3-dihydro-1H-inden-2-yl)pyridine (Table 2, entry 5 and entry 6), a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 8.62-8.54 (m, 1H), 7.61 (td, $J = 7.7$ Hz, 1.9 Hz, 1H), 7.28-7.21 (m, 3H), 7.20-7.16 (m, 2H), 7.15-7.11 (m, 1H), 3.93-3.84 (m, 1H), 3.39 (dd, $J = 15.4$ Hz, 8.4 Hz, 2H), 3.28 (dd, $J = 15.5$ Hz, 8.8 Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 164.4, 149.2, 142.8, 136.4, 126.5, 124.4, 121.5, 121.4, 47.4, 39.7. IR (KBr, cm^{-1}) ν 3019, 2934, 2844, 1590, 1472, 1432, 743. HRMS (ESI): m/z (M^+) calcd for $\text{C}_{14}\text{H}_{13}\text{N}$:

195.1048. Found 195.1045.

3-(2,3-dihydro-1H-inden-2-yl)pyridine(Table 2, entry 7), a yellow oil.

^1H NMR (500 MHz, CDCl_3): δ 8.63 (s, 1H), 8.52(d, $J = 3.0$ Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.34-7.22 (m, 5H), 3.82-3.70 (m, 1H), 3.44 (dd, $J = 15.4$ Hz, 8.2 Hz, 2H), 3.12 (dd, $J = 15.5$ Hz, 8.8 Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 149.0, 147.7, 142.3, 140.7, 134.2, 126.7, 124.4, 123.4, 42.7, 40.6. IR (KBr, cm^{-1}) ν 3022, 2932, 2845, 1574, 1479, 1423, 744. HRMS (ESI): m/z (M^+) calcd for $\text{C}_{14}\text{H}_{13}\text{N}$: 195.1048. Found 195.1045.

4-(2,3-dihydro-1H-inden-2-yl)-2-methylpyridine (Table 2, entry 8), a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 8.39 (d, $J = 5.0$ Hz, 1H), 7.28-7.23 (m, 2H), 7.22-7.17 (m, 2H), 7.07 (s, 1H), 7.00 (d, $J = 5.0$ Hz, 1H), 3.70-3.55 (m, 1H), 3.36 (dd, $J = 15.4$ Hz, 8.3 Hz, 2H), 3.06 (dd, $J = 15.5$ Hz, 8.5 Hz, 2H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 158.5, 154.7, 149.2, 142.3, 126.7, 124.4, 122.0, 119.5, 44.5, 40.2, 24.5. IR (KBr, cm^{-1}) ν 3019, 2934, 2845, 1603, 1482, 1446, 746. HRMS (ESI): m/z (M^+) calcd for $\text{C}_{15}\text{H}_{15}\text{N}$: 209.1204. Found 209.1206.

2-(2,3-dihydro-1H-inden-2-yl)-4-methylpyridine (Table 2, entry 9), a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 8.42 (d, $J = 5.0$ Hz, 1H), 7.28-7.22 (m, 2H), 7.20-7.14 (m, 2H), 7.06 (s, 1H), 6.96 (d, $J = 5.0$ Hz, 1H), 3.92-3.77 (m, 1H), 3.76 (dd, $J = 15.4$ Hz, 8.4 Hz, 2H), 3.27 (dd, $J = 15.6$ Hz, 9.0 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 164.0, 148.8,

147.3, 142.6, 126.2, 124.2, 122.3, 122.2, 47.1, 39.5, 20.9. IR (KBr, cm^{-1}) ν 3018, 2926, 2848, 1603, 1481, 743. HRMS (ESI): m/z (M^+) calcd for $\text{C}_{15}\text{H}_{15}\text{N}$: 209.1204. Found 209.1206.

2-(2,3-dihydro-1H-inden-2-yl)-5-methylpyridine (Table 2, entry 10), a yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 8.39 (d, $J = 2.0$ Hz, 1H), 7.42 (dd, $J = 8.0$ Hz, 2.0 Hz, 1H), 7.28-7.21 (m, 2H), 7.20-7.15 (m, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 3.92-3.78 (m, 1H), 3.37 (dd, $J = 15.4$ Hz, 8.4 Hz, 2H), 3.24 (dd, $J = 15.5$ Hz, 8.8 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 161.5, 149.6, 142.9, 137.1, 130.6, 126.5, 124.4, 121.0, 47.0, 39.8, 18.1. IR (KBr, cm^{-1}) ν 3020, 2934, 2845, 1600, 1483, 1459, 743. HRMS (ESI): m/z (M^+) calcd for $\text{C}_{15}\text{H}_{15}\text{N}$: 209.1204. Found 209.1206.

2-(2,3-dihydro-1H-inden-2-yl)-5-methoxypyridine (Table 2, entry 11), a white solid. mp 65-67 °C. ^1H NMR (500 MHz, CDCl_3): δ 8.27 (dd, $J = 2.5$ Hz, 1.0 Hz, 1H), 7.25-7.22 (m, 2H), 7.20-7.12 (m, 4H), 3.85 (s, 3H), 3.88-3.80 (m, 1H), 3.35 (dd, $J = 15.3$ Hz, 8.3 Hz, 2H), 3.22 (dd, $J = 15.5$ Hz, 8.8 Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 156.4, 154.0, 142.8, 136.4, 126.4, 124.3, 121.5, 121.3, 55.6, 46.5, 39.8. IR (KBr, cm^{-1}) ν 3011, 2926, 2849, 1492, 1456, 1265, 1030, 744. HRMS (ESI): m/z (M^+) calcd for $\text{C}_{15}\text{H}_{15}\text{NO}$: 225.1154. Found 225.1155.

2-(2,3-dihydro-1H-inden-2-yl)-6-methylpyridine (Table 2, entry 12), a yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 7.48 (t, $J = 7.7$ Hz, 1H),

7.26-7.22 (m, 2H), 7.20-7.15 (m, 2H), 7.00 (dd, $J = 12.6$ Hz, 7.8 Hz, 2H), 3.92-3.79 (m, 1H), 3.38 (dd, $J = 15.5$ Hz, 8.4 Hz, 2H), 3.24 (dd, $J = 15.6$ Hz, 8.5 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 164.0, 157.7, 142.9, 136.7, 126.4, 124.4, 120.8, 118.0, 47.5, 39.9, 24.6.

2-(2,3-dihydro-1H-inden-2-yl)-5-(trifluoromethyl)pyridine (Table 2, entry 13), a yellow solid. mp 74-76 °C. ^1H NMR (500 MHz, CDCl_3): δ 8.87-8.81 (m, 1H), 7.84 (dd, $J = 8.2$ Hz, 2.1 Hz, 1H), 7.35 (d, $J = 8.2$ Hz, 1H), 7.30-7.23 (m, 2H), 7.22-7.17 (m, 2H), 3.99-3.91 (m, 1H), 3.41 (dd, $J = 15.7$ Hz, 8.4 Hz, 2H), 3.29 (dd, $J = 15.6$ Hz, 8.5 Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 168.5, 146.2 (q, $J = 3.8$ Hz), 142.2, 133.5 (q, $J = 3.4$ Hz), 126.7, 124.4, 124.4 (q, $J = 32.5$ Hz), 123.8 (q, $J = 270.1$ Hz, CF_3), 121.3, 47.3, 39.6. IR (KBr, cm^{-1}) ν 3024, 2922, 2847, 1605, 1484, 1458, 1329, 747. HRMS (ESI): m/z (M^+) calcd for $\text{C}_{15}\text{H}_{12}\text{F}_3\text{N}$: 263.0922. Found 263.0924.

2-(2-((tert-butyldimethylsilyl)oxy)cyclopentyl)pyridine(Table 2, entry 14), a yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 8.56 (dd, $J = 4.8$ Hz, 0.8 Hz, 1H), 7.55 (td, $J = 7.7$ Hz, 1.9 Hz, 1H), 7.14 (d, $J = 7.8$ Hz, 1H), 7.11-7.06 (m, 1H), 4.31 (q, $J = 7.4$ Hz, 1H), 3.06-2.95 (m, 3H), 2.12-1.93 (m, 2H), 1.89-1.75 (m, 1H), 1.71-1.60 (m, 1H), 0.75 (s, 9H), -0.20 (s, 3H), -0.29 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 163.2, 149.4, 135.8, 123.9, 121.2, 80.6, 56.3, 35.1, 30.2, 25.7, 21.9, 18.0, -5.10, -5.20. IR (KBr, cm^{-1}) ν 3006, 2928, 2856, 1590, 1472, 1113, 836, 775. GC-MS (EI): m/z (M^+)

calcd for $C_{16}H_{27}NOSi$: 277.2. Found 277.2.

3-(pyridin-2-yl)butyl benzoate (Table 2, entry 15), a white solid. mp 120-122 °C. 1H NMR (500 MHz, $CDCl_3$): δ 8.58-8.54 (m, 1H), 8.01-7.95 (m, 2H), 7.59 (td, $J = 7.7$ Hz, 1.8 Hz, 1H), 7.57-7.52 (m, 1H), 7.46-7.39 (m, 2H), 7.16 (d, $J = 7.8$ Hz, 1H), 7.13-7.08 (m, 1H), 4.35-4.27 (m, 1H), 4.26-4.20 (m, 1H), 3.18-3.07 (m, 1H), 2.35-2.25 (m, 1H), 2.14-2.09 (m, 1H), 1.36 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 165.1, 149.4, 136.5, 132.8, 130.3, 129.5, 128.3, 121.9, 121.4, 63.4, 38.9, 35.4, 21.1. IR (KBr, cm^{-1}) ν 3006, 2963, 2925, 1717, 1590, 1474, 1276, 1114, 712. HRMS (ESI): m/z (M^+) calcd for $C_{16}H_{17}NO_2$: 255.1259. Found 225.1261.

3-(pyridin-2-yl)butyl 4-methoxybenzoate (Table 2, entry 16), a white solid. mp 156-158 °C. 1H NMR (500 MHz, $CDCl_3$): δ 8.58-8.51 (m, 1H), 7.98-7.88 (m, 2H), 7.58 (td, $J = 7.7$ Hz, 1.9 Hz, 1H), 7.15 (d, $J = 7.8$ Hz, 1H), 7.13-7.07 (m, 1H), 6.93-6.86 (m, 2H), 4.30-4.23 (m, 1H), 4.22-4.16 (m, 1H), 3.85 (s, 3H), 3.19-3.03 (m, 1H), 2.33-2.20 (m, 1H), 2.13-2.01 (m, 1H), 1.36 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 165.2, 163.2, 149.4, 136.4, 131.5, 122.8, 121.9, 121.3, 113.5, 63.1, 55.4, 38.9, 35.5, 21.1. IR (KBr, cm^{-1}) ν 3006, 2962, 2928, 2843, 1710, 1606, 1511, 1277, 1257, 1168, 771. HRMS (ESI): m/z (M^+) calcd for $C_{16}H_{17}NO_2$: 285.1365. Found 285.1368.

III. ^1H NMR and ^{13}C NMR spectra

(Table 2, entry 3)

(Table 2, entry 5 and entry 6)

(Table 2, entry 7)

(Table 2, entry 8)

(Table 2, entry 9)

(Table 2, entry 10)

(Table 2, entry 11)

(Table 2, entry 12)

(Table 2, entry 13)

(Table 2, entry 14)