Supporting Information for the Letter Entitled

**“Synthesis of 5-Bromopyridyl-2-Magnesium Chloride and Its
Application in the Synthesis of Functionalized Pyridines”**

Jinhua J. Song,* Nathan K. Yee, Zhulin Tan, Jinghua Xu, Suresh R. Kapadia
and Chris H. Senanayake

*Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900
Old Ridgebury Road/P.O. Box 368, Ridgefield, Connecticut 06877*

Synthesis of 5-bromo-2-iodopyridine (1):

1

2,5-dibromo-pyridine (100 g, 0.42 mol) was suspended in acetonitrile (500 mL) at rt. Then the NaI (94 g, 0.63 mol) and AcCl (45 mL, 0.63 mol) were added. The reaction was refluxed for 3 h and was quenched with K₂CO₃ aq solution to pH=8. Ethyl acetate (1.5 L) was added to extract the organic materials. The organic layer was washed with NaHSO₃ (saturated aqueous solution) and brine and dried over MgSO₄. Concentration gave a residue which was subjected to the same conditions pushed the reaction to completion. The reaction was worked up in the same manner as described above and compound **1** was obtained as light brown crystals (102 g, 85%) after removal of the volatiles.

¹H NMR (CDCl₃, 400 MHz) δ 8.44 (s, 1H), 7.60 (d, *J*= 8.26 Hz, 1H), 7.44 (d, *J*= 8.25 Hz, 1H).

Synthesis of 5-bromo-2-iodo-3-picoline (6): **6**

The mixture of 2,5-dibromo-3-picoline **4** (10 g, 40 mmol), sodium iodide (14 g, 160 mmol) and acetyl chloride (4.2 mL, 60 mmol) in acetonitrile (60 mL) was refluxed for 16 h. It was carefully quenched with water and treated with NaHCO₃ saturated aqueous solution until pH = 8. Product was extracted with ethyl acetate (100 mL x 2). The combined organic layer was dried over sodium sulfate and concentrated. Residue was subjected to above reaction condition again and worked up as above. Organic extract was washed with sodium bisulfite saturated aqueous solution (100 mL), dried over sodium sulfate and concentrated. The residue was purified on silica gel column and eluted with 20% ethyl acetate/hexanes to give pure product **6** as light yellow oil, which solidified gradually (7.5 g, 63%).

¹H NMR (CDCl₃, 400 MHz) δ 8.26 (s, 1H), 7.58 (s, 1H), 2.38 (s, 3H).

Labeling experiment:

To a solution of 5-bromo-2-iodopyridine **1** (1 g, 3.5 mmol) in THF (7 mL) at 0 °C was added isopropyl magnesium chloride (2 M/THF, 1.85 mL, 3.7 mmol) dropwise. After the mixture was stirred at 0 °C for 45 min, MeOH-d₄ (0.6 mL) was added slowly. The reaction mixture was stirred at room temperature for 15 min. The reaction mixture

was then quenched with 10 mL NH_4Cl (saturated aq solution). Methylene chloride (20 mL) was added to dilute the organic phase and then layers were separated. The aqueous layer was extracted with methylene chloride (10 mL). The combined organic layer was dried over MgSO_4 and concentrated to an oil. ^1H NMR of this crude product showed >95% D incorporation at the position para to bromine. The crude product was further purified by chromatography to give 3-bromo-6-deuteropyridine (533 mg, 95%).

^1H NMR (CDCl_3 , 400 MHz) δ 8.70 (d, J = 2.28 Hz, 1H), 7.83 (dd, J = 2.28, 8.08 Hz, 1H), 7.21 (d, J = 8.32 Hz, 1H).

Experimental procedures for synthesis of compounds 3a to 3h:

In a 22 L 3-neck round-bottom flask equipped with mechanical stirrer, 1 kg (3.52 mol) of 5-bromo-2-iodopyridine (**1**) was dissolved in 5 L of THF. The solution was cooled to –15 to –10 °C. Then 1.9 L (3.8 mol, 1.08 eq) of 2 M *i*-PrMgCl in THF was added at the rate to keep the internal temperature below 0 °C (1 h). The reaction mixture became a brown suspension. After the reaction mixture was stirred between –15 to 0 °C for 1 h, 400 mL (5.16 mol, 1.5 eq) of anhydrous DMF was added at the rate to keep the internal temperature below 0 °C. After stirring at these temperatures for 30 min, the cooling bath was removed and allowed to warm to room temperature over 1 h. The reaction mixture was then cooled to 0 °C and 4 L of 2 N HCl aqueous solution was added at the rate to keep the internal temperature below 25 °C. The mixture was stirred for 30 min. The pH

was adjusted to pH 6-7 by adding about 150 mL of 2 N NaOH aqueous solution. The layers were separated and the THF layer was concentrated to give the dark brown wet solids, the aqueous layer was extracted with 3 L of CH₂Cl₂. The CH₂Cl₂ layer was used to dissolve the residue obtained from the THF layer, the resulting solution was washed with water (2 L x 2). The combined organic layer was dried by stirring with MgSO₄ (400 g) for 30 min, and filtered. Evaporation of solvents gave 589 g (90% yield) of the desired aldehyde (**3a**) as brownish-yellow solids.

¹H NMR (CDCl₃, 400 MHz) δ 10.05 (s, 1H), 8.86 (d, J = 2.27 Hz, 1H), 8.03 (dd, J = 2.27, 8.34 Hz, 1H), 7.86 (d, J = 8.34 Hz, 1H).

3b

To a solution of 5-bromo-2-iodopyridine **1** (1 g, 3.5 mmol) in THF (7 mL) at 0 °C was added isopropyl magnesium chloride (2 M/THF, 1.85 mL, 3.7 mmol) dropwise. After the mixture was stirred at 0 °C for 45 min, *N*-methoxy-*N*-methyl benzamide (0.64 mL, 4.22 mmol) was added slowly. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with 10 mL of NH₄Cl (saturated aq solution). Ethyl acetate (20 mL) was added to dilute the organic phase and layers were separated. The organic layer was concentrated under house vacuum and the residue was purified by flash column chromatography (50% EtOAc/hexanes) to yield desired compound **3b** (0.69 g, 75%).

^1H NMR (CDCl_3 , 400 MHz) δ 8.78 (d, J = 1.76 Hz, 1H), 8.04 (m, 3H), 7.96 (d, J = 8.32 Hz, 1H), 7.61 (m, 1H), 7.49 (t, J = 7.84 Hz, 2H).

3c

To a solution of 5-bromo-2-iodopyridine **1** (1.0 g, 3.5 mmol) in THF (8 mL) at 0 °C was added isopropyl magnesium chloride (2 M/THF, 2.1 mL, 4.2 mmol) dropwise. After the mixture was stirred at 0 °C for 1 h, *N*-methoxy-*N*-methyl trifluoroacetamide (0.82 g, 5.28 mmol) was added slowly. The reaction mixture was then stirred at room temperature for 15 h. The reaction mixture was quenched with NH_4Cl (15 mL saturated aq solution). CH_2Cl_2 (20 mL) was added to dilute the organic phase and layers were separated. The organic layer was concentrated under house vacuum and the residue was purified by flash column chromatography (20% EtOAc/hexanes) to yield compound **3c** (0.527 g, 55%).

^1H NMR (CDCl_3 , 400 MHz) δ 8.65 (d, J = 2.16 Hz, 1H), 8.01 (dd, J = 2.16, 8.40 Hz, 1H), 7.69 (d, J = 8.40 Hz, 1H), 5.10 (s, 2H).

^{13}C NMR (CDCl_3 , 100 MHz) δ 151.2, 148.7, 140.7, 140.1, 126.1, 123.7, 122.7.

3d

To a solution of 5-bromo-2-iodopyridine **1** (1.1 g, 3.8 mmol) in THF (5 mL) at -10 °C was added isopropyl magnesium chloride (2 M/THF, 2.0 mL, 4.0 mmol) dropwise to keep the internal temperature below 0 °C. After the mixture was stirred between -15 to 0 °C for 1 h, butraldehyde (0.5 mL, 5.5 mmol) was added slowly and the internal temperature was kept below -5 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C and quenched and neutralized with HCl (1 M/water) to pH 6-7. Toluene (20 mL) was added to dilute the organic phase and layers were separated. The organic layer was concentrated under house vacuum and the residue was purified by flash column chromatography (CH₂Cl₂/MeOH: 98/2, v/v) to yield compound **3d** (0.62 g, 69%).

¹H NMR (CDCl₃, 400 MHz) δ 8.60 (d, *J*= 2.20 Hz, 1H), 7.80 (dd, *J*= 8.32, 2.28 Hz, 1H), 7.19 (d, *J*= 8.30 Hz, 1H), 4.71 (m, 1H), 3.61 (d, *J*=5.64 Hz, 1H), 1.81-1.62 (m, 2H), 1.42 (m, 2H), 0.94 (t, *J*=7.36 Hz, 3H).

¹³C NMR (CDCl₃, 100 MHz) δ 171.2, 159.3, 149.1, 131.5, 128.8, 82.5, 50.4, 28.4, 23.8.

3e

To a solution of 5-bromo-2-iodopyridine **1** (1.0 g, 3.5 mmol) in CH₂Cl₂ (8 mL) at 0 °C was added isopropyl magnesium chloride (2 M/THF, 2.1 mL, 4.2 mmol) dropwise. After the mixture was stirred at 0 °C for 45 min, the reaction mixture was cooled to -78 °C. A solution of TsCN (1 g, 5.3 mmol) in CH₂Cl₂ (2 mL) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with

HCl (2 M in water) to pH 7. Water (10 mL) and CH₂Cl₂ (75 mL) were added to dilute the mixture and layers were separated. The aqueous layer was extracted with CH₂Cl₂ (25 mL x 3). The combined organic layer was dried over Na₂SO₄/MgSO₄ and filtered. After removing the volatiles, the residue was purified by trituration with hexanes (30 mL) to yield compound **3e** as a solid (0.53 g, 82%).

¹H NMR (CDCl₃, 400 MHz) δ 8.79 (d, *J* = 2.28 Hz, 1H), 7.99 (dd, *J* = 2.24, 8.32 Hz, 1H), 7.59 (d, *J* = 8.32 Hz, 1H).

3f

To a solution of 5-bromo-2-iodopyridine **1** (1.0 g, 3.5 mmol) in CH₂Cl₂ (7 mL) at 0 °C was added isopropyl magnesium chloride (2 M/THF, 2.1 mL, 4.2 mmol) dropwise. The mixture was stirred at 0 °C for 45 min to form the Grignard solution. In a separate flask, to a solution of dipiperidinomethane (0.96 g, 5.28 mmol) in CH₂Cl₂ (9 mL) at 22 °C was added dropwise the freshly distilled trifluoroacetic anhydride (0.7 mL, 4.93 mmol), keeping the T below 25 °C. The mixture was stirred at rt for 30 min to form the iminium salt solution and cooled to 0 °C. The Grignard solution was cannulated into the salt solution. The reaction was quenched with NH₄Cl (15 mL, saturated aq) and layers were separated. The organic layer was concentrated to a residue which was purified by column chromatography (EtOAc) to give **3f** as an oil (0.74 g, 82%).

¹H NMR (CDCl₃, 400 MHz) δ 8.60 (d, *J* = 2.28 Hz, 1H), 7.76 (dd, *J* = 2.52, 8.32 Hz, 1H), 7.35 (d, *J* = 8.32 Hz, 1H), 3.56 (s, 2H), 2.41 (s, 4H), 1.56 (m, 4H), 1.45 (m, 2H).

3g

To a solution of 5-bromo-2-iodopyridine **1** (1.0 g, 3.5 mmol) in THF (5 mL) at -10 °C was added isopropyl magnesium chloride (2 M/THF, 1.9 mL, 3.8 mmol) dropwise to keep the internal temperature below 0 °C. After the mixture was stirred between -15 to 0 °C for 1 h, phenyl disulfide (1.15 g, 5.3 mmol) was added slowly and the internal temperature was kept below -5 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C and quenched with HCl (1 M/water) to pH 6-7. Toluene (20 mL) was added to dilute the organic phase and layers were separated. The organic layer was concentrated under house vacuum and the residue was purified by flash column chromatography (CH₂Cl₂/hexanes: 1/3, v/v) to yield compound **3g** (0.79 g, 84%).

¹H NMR (CDCl₃, 400 MHz) δ 8.46 (dd, *J* = 0.63, 2.42 Hz, 1H), 7.57 (m, 3H), 7.44 (m, 3H), 6.78 (dd, *J* = 0.70, 8.60 Hz, 1H).

3h

To a solution of 5-bromo-2-iodopyridine **1** (1.0 g, 3.5 mmol) in THF (5 mL) at -10 °C was added isopropyl magnesium chloride (2 M/THF, 1.8 mL, 3.6 mmol) dropwise to keep the internal temperature below 0 °C. After the mixture was stirred between -15 to 0

°C for 1 h, chlorotrimethylsilane (0.66 mL, 5.3 mmol) was added slowly and the internal temperature was kept below -5 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then cooled to 0 °C and quenched with HCl (1 M/water) to pH 6-7. CH₂Cl₂ (20 mL) was added to dilute the organic phase and then layers were separated. The organic layer was concentrated under house vacuum and the residue was purified by flash column chromatography (CH₂Cl₂/hexanes: 1/4, v/v) to yield compound **3h** (0.685 g, 84%). ¹H NMR (CDCl₃, 400 MHz) δ 8.83 (dd, *J* = 0.76, 2.32 Hz, 1H), 7.72 (dd, *J* = 2.33, 8.08 Hz, 1H), 7.39 (dd, *J* = 0.80, 8.06 Hz, 1H), 0.30 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz) δ 169.4, 153.0, 139.4, 131.5, 122.7, 0.0.

Synthesis of compound 5 via Grignard intermediate:

5

To a solution of 5-bromo-2-iodo-3-picoline **6** (0.30 g, 1 mmol) in CH₂Cl₂ (8 mL) at 0 °C was added isopropyl magnesium chloride (2 M/THF, 0.52 mL, 1.05 mmol) dropwise. The mixture was stirred at 0 °C for 1.5 h and then was cooled down to -20 °C. Phenyl isocyanate (0.23 g, 1.3 mmol) was added slowly. The reaction mixture was warmed up to 0 °C in about 0.5 h and stirred at 0 °C for 1h. Then, the mixture was stirred at room temperature for 14 h. Reaction was quenched with water and neutralized with 2 M HCl aqueous solution to pH 7. The organic solvent and water were evaporated under

vacuum. Dimethyl fumarate, an internal reference compound was used for NMR assay.

Assay yield: 86%.

^1H NMR (CDCl_3 , 400 MHz) δ 10.02 (s, 1H), 8.51 (d, $J = 2.16$ Hz, 1H), 7.82 (d, $J = 2.16$ Hz, 1H), 7.74 (d, $J = 7.56$ Hz, 2H), 7.38 (t, $J = 7.80$ Hz, 2H), 7.14 (t, $J = 7.32$ Hz, 1H), 2.81 (s, 3H).

400 MHz, CDCl₃

400 MZ, CDCl₃

400 Mz, CDCl₃

400 Mz, CDCl₃

400 Mz, CDCl₃

400 Mz, CDCl₃

400 Mz, CDCl₃

400 Mz, CDCl₃

400 MHz, CDCl₃

400 Mz, CDCl₃

400 Mz, CDCl₃

400 Mz, CDCl₃