

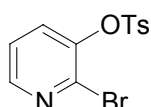
Regioselective Functionalization of Trisubstituted Pyridines Using a Bromine-Magnesium Exchange

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Supporting Information

General All reactions were carried out under argon atmosphere in dried glassware. Elemental analyses were carried out on a Heraeus CHN-Rapid-Elementanalyzer in the microanalytical laboratories of the Department Chemie, Ludwig-Maximilians-Universität Munich. All starting materials were purchased from commercial sources and used without further purification. Toluene was predried over KOH and continuously refluxed and freshly distilled from sodium. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Preparative chromatography was performed on silica gel 60 (0.063-0.200 mm) from Merck. Yields referred to isolated yields of compounds estimated to be > 95% pure as determined by ¹H-NMR, capillary GC and combustion analysis (new compounds).



1

Toluene-4-sulfonic acid 2-bromo-pyridin-3-yl ester (1): A solution of 2-bromo-3-hydroxypyridine (3.48 g, 20 mmol), TsCl (4.19 g, 22 mmol), NEt₃ (2.42 g, 24 mmol) and DMAP (10 mol %) in CH₂Cl₂ (60 mL) was stirred at room temperature for 5 h. The reaction mixture was subsequently washed with water, 1 N hydrochloric acid, and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (eluent: pentane:ether = 3:1) to provide **1** (5.58 g, 85 %) as a solid; m.p.: 64.5-65.0 °C.

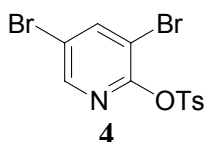
¹H NMR (CDCl₃, 300 MHz): 8.19 (dd, *J*₁ = 4.9 Hz, *J*₂ = 1.8 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.65 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.8 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.19-7.24 (m, 1 H), 2.37 (s, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 147.7, 146.3, 144.3, 136.5, 132.0, 131.8, 129.9, 128.6, 123.5, 21.7;

IR (KBr): 1597, 1570, 1556, 1496, 1373, 1411, 1203, 859 cm^{-1} ;

MS (EI, 70 ev): 329 (^{81}Br , 6 %), 327 (^{79}Br , 6 %), 155 (94 %), 91 (100 %);

HRMS (EI): calcd. for $\text{C}_{12}\text{H}_{10}\text{BrNO}_3\text{S}$: 326.9525, found: 326.9574.



3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (4): A solution of 3,5-dibromo-2-hydroxypyridine (5.06 g, 20 mmol), TsCl (4.19 g, 22 mmol), NEt_3 (2.42 g, 24 mmol) and DMAP (10 mol %) in CH_2Cl_2 (60 mL) was stirred at 0 $^\circ\text{C}$ overnight. The reaction mixture was subsequently washed with water, 1 N hydrochloric acid, and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (eluent: pentane:ether = 3:1) to provide **4** (6.51 g, 80 %) as a solid; m. p.: 97.4-97.9 $^\circ\text{C}$.

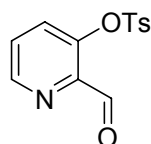
^1H NMR (CDCl_3 , 300 MHz): 8.22 (d, $J = 2.2$ Hz, 1 H), 8.06 (d, $J = 2.2$ Hz, 1 H), 7.94 (d, $J = 8.4$ Hz, 2 H), 7.35 (d, $J = 8.4$ Hz, 2 H), 2.44 (s, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 153.2, 147.2, 145.7, 145.2, 133.7, 129.7, 128.8, 117.9, 112.0, 21.7;

IR (KBr): 1598, 1557, 1418, 1375, 770 cm^{-1} ;

MS (EI, 70 ev): 343 ($\text{M}^+ - \text{C}_5\text{H}_4$ ($^{81}\text{Br}^{79}\text{Br}$), 40 %), , 155 (50 %), 91 (100 %);

Anal. Calcd for $\text{C}_{12}\text{H}_9\text{Br}_2\text{NO}_3\text{S}$: C, 35.41; H, 2.23; N, 3.44; Found: C, 35.28; H, 2.01; N, 3.39.



Toluene-4-sulfonic acid 2-formyl-pyridin-3-yl ester (3a). A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of toluene-4-sulfonic acid 2-bromo-pyridin-3-yl ester (**1**) (164 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 $^\circ\text{C}$, and the resulting mixture was stirred at this temperature for 7 h to complete the bromine-magnesium exchange (checked by GC analysis of hydrolyzed reaction aliquots). DMF (1.0 mmol in 0.5 mL of

THF) was added and the reaction mixture was warmed to 25 °C. After 1 h the reaction mixture was quenched with saturated aqueous NH₄Cl. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:1) yielded the product **3a** (122 mg, 88 %) as a solid; m.p.: 104.5-105.0 °C.

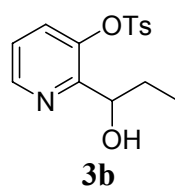
¹H NMR (CDCl₃, 300 MHz): 9.89 (s, 1 H), 8.67 (dd, *J*₁ = 4.4 Hz, *J*₂ = 1.3 Hz, 1 H), 7.68-7.75 (m, 1 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.52 (dd, *J*₁ = 8.4 Hz, *J*₂ = 4.4 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 2.41 (s, 3 H);

¹³C NMR (CDCl₃, 75 MHz): 187.9, 148.5, 146.8, 146.5, 144.8, 132.5, 131.2, 130.0, 128.5, 128.4, 21.7;

IR (KBr): 1718, 1596, 1578, 1352, 1164, 889 cm⁻¹;

MS (EI, 70 ev): 248 (M⁺-CHO, 0.04 %), 155 (51 %), 139 (13 %), 122 (57 %), 91 (100 %);

Anal. Calcd for C₁₃H₁₁NO₄S: C, 56.31; H, 4.00; N, 5.05; Found: C, 56.34; H, 4.06; N, 5.03.



Toluene-4-sulfonic acid 2-(1-hydroxy-propyl)-pyridin-3-yl ester (3b) A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of toluene-4-sulfonic acid 2-bromo-pyridin-3-yl ester (**1**) (164 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 7 h to complete the bromine-magnesium exchange (checked by GC analysis of hydrolyzed reaction aliquots). Propionaldehyde (0.60 mmol in 0.5 mL of THF) was added and the reaction mixture was warmed to 25 °C. After 1 h the reaction mixture was quenched with saturated aqueous NH₄Cl. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:2) yielded the product **3b** (130 mg, 85 %) as an oil.

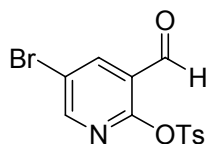
¹H NMR (CDCl₃, 300 MHz): 8.38 (d, *J* = 4.9 Hz, 1 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.15-7.20 (m, 1 H), 4.46-4.50 (m, 1 H), 3.86 (bs, 1 H), 2.39 (s, 3 H), 1.41-1.68 (m, 2 H), 0.75 (t, *J* = 7.5 Hz, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 155.1, 146.3, 146.2, 143.3, 132.4, 130.2, 130.1, 128.1, 123.2, 69.3, 29.9, 21.7, 9.4;

IR (film): 3345, 2927, 1598, 1418, 1377 cm^{-1} ;

MS (EI, 70 eV): 306 ($\text{M}^+ - \text{H}$, 0.08 %), 290 (7 %), 278 (100 %), 263 (9 %), 155 (92 %), 124 (53 %), 91 (99 %);

HRMS (EI): calcd. for $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{S}$ ($\text{M}^+ - \text{H}$): 306.0800, found: 306.0807 ($\text{M}^+ - \text{H}$).



6a

Toluene-4-sulfonic acid 5-bromo-3-formylpyridin-2-yl ester (6a) A dry and argon-flushed 10 ml flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**) (204 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at $-30\text{ }^\circ\text{C}$, and the resulting mixture was stirred at this temperature for 2 h to complete the bromine-magnesium exchange (checked by GC analysis of hydrolyzed reaction aliquots). DMF (1.0 mmol in 0.5 mL of THF) was added and the reaction mixture was warmed to $25\text{ }^\circ\text{C}$. After 1 h the reaction mixture was quenched with saturated aqueous NH_4Cl . The aqueous phase was extracted with diethyl ether ($3 \times 20\text{ mL}$). The combined organic fractions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 3:1) yielded the product **6a** (158 mg, 88 %) as a solid; m.p.: $86.7\text{--}87.3\text{ }^\circ\text{C}$.

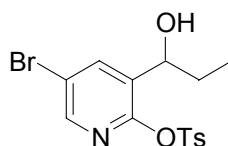
^1H NMR (CDCl_3 , 300 MHz): 10.18 (s, 1 H), 8.46 (d, $J = 2.7\text{ Hz}$, 1 H), 8.32 (d, $J = 2.7\text{ Hz}$, 1 H), 7.91 (d, $J = 8.4\text{ Hz}$, 1 H), 7.37 (d, $J = 8.4\text{ Hz}$, 1 H), 2.45 (s, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 185.9, 156.3, 153.6, 146.2, 140.8, 133.0, 129.9, 128.8, 123.4, 119.1, 21.8;

IR (KBr): 1697, 1596, 1578, 1430, 1178, 724 cm^{-1} ;

MS (EI, 70 eV): 293 (M^+ (^{81}Br)- C_5H_4 , 0.5 %), 291 (M^+ (^{79}Br)- C_5H_4 , 0.5 %), 265 (51 %), 263 (52 %), 155 (41 %), 91 (100 %);

Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{BrNO}_4\text{S}$: C, 43.84; H, 2.83; N, 3.93; Found: C, 43.76; H, 2.76; N, 3.87.



6b

Toluene-4-sulfonic acid 5-bromo-3-(1-hydroxy-propyl)-pyridin-2-yl ester (6b): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**) (204 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 2 h to complete the bromine-magnesium exchange (checked by GC analysis of hydrolyzed reaction aliquots). Propionaldehyde (0.60 mmol in 0.5 mL of THF) was added and the reaction mixture was warmed to 25 °C and quenched with saturated aqueous NH₄Cl. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:2) yielded the product **6b** (168 mg, 87 %) as a solid; m.p.: 110.3-111.0 °C.

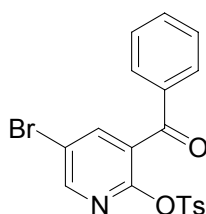
¹H NMR (CDCl₃, 300 MHz): 8.12 (d, *J* = 2.7 Hz, 1 H), 8.02 (d, *J* = 2.7 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 4.87-4.91 (m, 1 H), 2.44 (s, 3 H), 2.26 (bs, 1 H), 1.64-1.82 (m, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H);

¹³C NMR (CDCl₃, 75 MHz): 152.8, 147.2, 145.5, 140.3, 133.9, 133.5, 129.7, 128.7, 118.9, 68.9, 30.3, 21.7, 9.8;

IR (KBr): 3566, 3053, 1595, 1558, 1372, 1207, 669 cm⁻¹;

MS (EI, 70 ev): 386 (M⁺, 0.01 %), 358 (Br⁸¹, 6 %), 356 (Br⁷⁹, 6 %), 294 (Br⁸¹, 87 %), 292 (Br⁷⁹, 87 %), 155 (89 %), 91 (100 %);

HRMS (EI): calcd. for C₁₅H₁₅BrNO₄S (M⁺-H): 383.9905, found: 383.9868 (M⁺-H).



6c

Toluene-4-sulfonic acid 3-benzoyl-5-bromo-pyridin-2-yl ester (6c): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**) (204 mg, 0.5 mmol) in dry

THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 2 h to complete the bromine-magnesium exchange (checked by GC of hydrolyzed reaction aliquots). THF (1.0 mL) and the solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) were added at this temperature and stirred for 15 min. Benzoyl chloride (0.75 mmol in 0.5 mL of THF) was added and the reaction mixture was stirred at -30 °C for 1 h, then warmed to rt and stirred for 1 h before it was quenched with aq. ammonia (2 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:1) yielded the product **6c** (192 mg, 89 %) as a solid; m.p.: 102.5-103.1 °C.

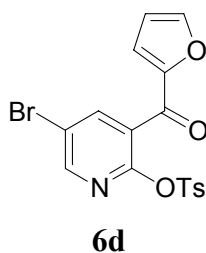
¹H NMR (CDCl₃, 300 MHz): 8.43 (d, *J* = 2.7 Hz, 1 H), 7.94 (d, *J* = 2.7 Hz, 1 H), 7.54-7.71 (m, 5 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 2.35 (s, 3 H);

¹³C NMR (CDCl₃, 75 MHz): 190.5, 152.4, 150.5, 145.4, 142.2, 135.6, 134.0, 133.1, 129.7, 129.4, 128.5, 128.3, 127.5, 117.9, 21.5;

IR (KBr): 1659, 1598, 1572, 1382, 1173, 689 cm⁻¹;

MS (EI, 70 eV): 369 (M⁺ (⁸¹Br)-C₅H₄, 13 %), 367 (M⁺ (⁷⁹Br)-C₅H₄, 13 %), 340 (14 %), 288(31 %), 155 (22%), 91 (100 %);

Anal. Calcd for C₁₉H₁₄BrNO₄S: C, 52.79; H, 3.26; N, 3.24; Found: C, 52.61; H, 2.90; N, 3.17.



Toluene-4-sulfonic acid 5-bromo-3-(furan-2-carbonyl)-pyridin-2-yl ester (6d): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**) (204 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 2 h to complete the bromine-magnesium exchange (checked by GC of hydrolyzed reaction aliquots). THF (1.0 mL) and the solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) were added at this temperature and stirred for 15 min. 2-Furoyl chloride (0.75 mmol in 0.5 mL of THF) was added and the reaction mixture was stirred at -30 °C for 1 h, then warmed to rt and stirred for 1 h before it

was quenched with aq. ammonia (2 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:1) yielded the product **6d** (176 mg, 83 %) as a solid; m.p.: 133.0-134.0 °C.

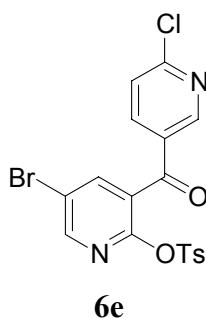
¹H NMR (CDCl₃, 300 MHz): 8.42 (d, *J* = 2.2 Hz, 1 H), 8.01 (d, *J* = 2.2 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.65-7.66 (m, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 4.0 Hz, 1 H), 6.58 (dd, *J*₁ = 4.0 Hz, *J*₂ = 1.8 Hz, 1 H), 2.40 (s, 3 H);

¹³C NMR (CDCl₃, 75 MHz): 177.1, 152.6, 151.3, 150.8, 148.2, 145.6, 142.2, 133.5, 129.6, 128.6, 126.7, 121.4, 117.8, 112.9, 21.7;

IR (KBr): 1659, 1564, 1584, 1375, 1176, 752 cm⁻¹;

MS (EI, 70 eV): 359 (M⁺ (⁸¹Br)-C₅H₄, 3 %), 357 (M⁺ (⁷⁹Br)-C₅H₄, 3 %), 331 (M⁺ (⁸¹Br)-C₇H₈, 43 %), 329 (M⁺ (⁷⁹Br)-C₇H₈, 43 %), 274 (5 %), 155 (17 %), 91 (100 %);

Anal. Calcd for C₁₇H₁₂BrNO₅S: C, 48.36; H, 2.86; N, 3.32; Found: C, 48.14; H, 2.86; N, 3.26.



Toluene-4-sulfonic acid 5-bromo-3-(6-chloro-pyridine-3-carbonyl)-pyridin-2-yl ester (6e): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**) (407 mg, 1.0 mmol) in dry THF (3.0 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 1.10 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 2 h to complete the bromine-magnesium exchange (checked by GC of hydrolyzed reaction aliquots). THF (2.0 mL) and the solution of CuCN·2LiCl (1.10 mmol, 1.10 mL, 1.0 M in THF) were added at this temperature and stirred for 15 min. 6-Chloronicotinoyl chloride (1.50 mmol in 1.0 mL of THF) was added and the reaction mixture was stirred at -30 °C for 1 h, then warmed to rt and stirred for 1 h before it was quenched with aq. ammonia (2 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic fractions were washed with brine (20 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography yielded the product **6e** (351 mg, 75 %) as a solid; m.p.: 171.7-172.2 °C.

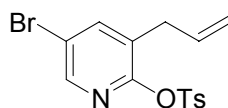
^1H NMR (CDCl_3 , 300 MHz): 8.61 (d, $J = 2.2$ Hz, 1 H), 8.50 (d, $J = 2.2$ Hz, 1 H), 8.07 (d, $J = 2.7$ Hz, 1 H), 7.95 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz, 1 H), 7.67 (d, $J = 8.4$ Hz, 2 H), 7.38 (d, $J = 8.4$ Hz, 1 H), 7.27 (d, $J = 8.4$ Hz, 2 H), 2.42 (s, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 188.5, 156.2, 152.5, 152.0, 151.0, 146.0, 142.9, 139.1, 132.9, 130.5, 129.7, 128.4, 126.1, 124.4, 118.5, 21.7;

IR (KBr): 1680, 1582, 1560, 1421, 1377, 1175 cm^{-1} ;

MS (EI, 70 eV): 406 (M^+ ($^{81}\text{Br}^{37}\text{Cl}$)- C_5H_4 , 3 %), 404 (M^+ ($^{79}\text{Br}^{37}\text{Cl}$ and $^{81}\text{Br}^{35}\text{Cl}$)- C_5H_4 , 4 %), 402 (M^+ ($^{79}\text{Br}^{35}\text{Cl}$)- C_5H_4 , 1 %), 376 (12 %), 323 (30 %), 155 (29 %), 91 (100 %);

Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{BrClN}_2\text{O}_4\text{S}$: C, 46.22; H, 2.59; N, 5.99; Found: C, 45.93; H, 2.30; N, 5.85.



6f

Toluene-4-sulfonic acid 3-allyl-5-bromo-pyridin-2-yl ester (6f): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**) (204 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 2 h to complete the bromine-magnesium exchange (checked by GC analysis of hydrolyzed reaction aliquots). Allyl bromide (0.60 mmol in 0.5 mL of THF) and CuCN·2LiCl (2 mol %, 10 μL , 1.0 M in THF) were added and the reaction mixture was warmed to 25 °C. After 1 h the reaction mixture was quenched with saturated aqueous NH_4Cl . The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 5:1) yielded the product **6f** (171 mg, 93 %) as an oil.

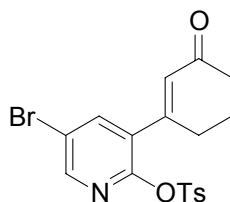
^1H NMR (CDCl_3 , 300 MHz): 8.11 (d, $J = 2.7$ Hz, 1 H), 7.92 (d, $J = 8.4$ Hz, 2 H), 7.69 (d, $J = 2.7$ Hz, 1 H), 7.33 (d, $J = 8.4$ Hz, 2 H), 5.78-5.91 (m, 1 H), 5.07-5.20 (m, 2 H), 3.38 (d, $J = 6.6$ Hz, 2 H), 2.43 (s, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 154.4, 146.4, 145.3, 142.4, 134.1, 133.4, 129.6, 129.2, 128.6, 118.4, 118.3, 33.5, 21.7;

IR (film): 1640, 1596, 1557, 1426, 1376, 1176, 1090, 833 cm^{-1} ;

MS (EI, 70 ev): 368 (M^+ , 0.1 %), 305 (M^+ (^{81}Br)- C_5H_4 , 30 %), 303 (M^+ (^{79}Br)- C_5H_4 , 30 %), 288 (50 %), 155 (11 %), 91 (100 %);

HRMS (EI): calcd. for $\text{C}_{15}\text{H}_{15}\text{BrNO}_3\text{S}$ ($M^+ + \text{H}$): 367.9956, found: 367.9991.



6g

Toluene-4-sulfonic acid 5-bromo-3-(3-oxo-cyclohex-1-enyl)-pyridin-2-yl ester (6g): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**) (204 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 2 h to complete the bromine-magnesium exchange (checked by GC of hydrolyzed reaction aliquots). THF (1.0 mL) and the solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) were added at this temperature and stirred for 15 min. 3-Iodo-cyclohex-2-enone (0.60 mmol in 1.0 mL of THF) was added and the reaction mixture was stirred at -30 °C for 3 h, then warmed to rt and stirred for 1 h before it was quenched with aq. ammonia (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:1) yielded the product **6g** (177 mg, 84 %) as a solid; m.p.: 108.5-109.3 °C.

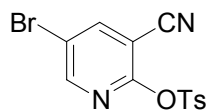
^1H NMR (CDCl_3 , 300 MHz): 8.24 (d, $J = 2.2$ Hz, 1 H), 7.84 (d, $J = 8.4$ Hz, 2 H), 7.73 (d, $J = 2.2$ Hz, 1 H), 7.31 (d, $J = 8.4$ Hz, 2 H), 6.01 (t, $J = 1.3$ Hz, 1 H), 2.64 (t, $J = 6.0$ Hz, 2 H), 2.41 (t, $J = 6.6$ Hz, 2 H), 2.41 (s, 3 H), 2.00-2.10 (m, 2 H);

^{13}C NMR (CDCl_3 , 75 MHz): 198.3, 154.8, 152.2, 148.7, 145.7, 140.9, 133.7, 130.4, 129.7, 129.5, 128.6, 118.2, 37.1, 29.2, 22.9, 21.6;

IR (KBr): 1671, 1596, 1419, 1375, 1172 cm^{-1} ;

MS (EI, 70 ev): 359 (M^+ (^{81}Br)- C_5H_4 , 2 %), 357 (M^+ (^{79}Br)- C_5H_6 , 2 %), 331 (M^+ (^{81}Br)- C_7H_8 , 7 %), 329 (M^+ (^{81}Br)- C_7H_8 , 7 %), 266 (21 %), 155 (17 %), 91 (100 %);

Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{BrNO}_4\text{S}$: C, 51.19; H, 3.82; N, 3.32; Found: C, 51.22; H, 3.92; N, 3.22.



6h

Toluene-4-sulfonic acid 5-bromo-3-cyano-pyridin-2-yl ester (6h): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**) (204 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 2 h to complete the bromine-magnesium exchange (checked by GC of hydrolyzed reaction aliquots). TsCN (0.60 mmol in 1.0 mL of THF) was added and the reaction mixture was warmed to 25 °C and quenched with saturated aqueous NH₄Cl. The aqueous phase was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic fractions were washed with brine (20 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:1) yielded the product **6h** (125 mg, 71 %) as a solid; m.p.: 105.0-105.6 °C.

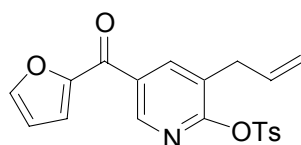
¹H NMR (CDCl₃, 300 MHz): 8.50 (d, *J* = 2.4 Hz, 1 H), 8.10 (d, *J* = 2.4 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 2.45 (s, 3 H);

¹³C NMR (CDCl₃, 75 MHz): 156.0, 152.8, 146.4, 145.4, 132.8, 129.9, 128.9, 117.3, 112.0, 103.1, 21.8;

IR (KBr): 2243, 1595, 1550, 1429, 1386, 1192, 823 cm⁻¹;

MS (EI, 70 ev): 290 (M⁺ (⁸¹Br)-C₅H₄, 10 %), 288 (M⁺ (⁷⁹Br)-C₅H₄, 10 %), 155 (52 %), 91 (100 %);

Anal. Calcd for C₁₃H₉BrN₂O₃S: C, 44.21; H, 2.57; N, 7.93; Found: C, 44.26; H, 2.56; N, 7.88.



8a

Toluene-4-sulfonic acid 3-allyl-5-(furan-2-carbonyl)-pyridin-2-yl ester (8a): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3-allyl-5-bromo-2-pyridyl 4-methylbenzenesulfonate (184 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at -30 °C, and the resulting mixture was stirred at this temperature for 7 h to complete the bromine-magnesium exchange (checked by GC of hydrolyzed reaction aliquots). THF (1.0 mL) and the solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) were added at this temperature

and stirred for 15 min. 2-Furoyl chloride (0.75 mmol in 0.5 mL of THF) was added and the reaction mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 1 h, then warmed to rt and stirred for 1 h before quenched with aq. ammonia (2 mL). The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 2:1) yielded the product **8a** (144 mg, 75 %) as an oil.

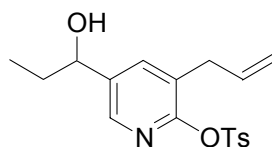
^1H NMR (CDCl_3 , 300 MHz): 8.71 (d, $J = 2.2$ Hz, 1 H), 8.14 (d, $J = 2.2$ Hz, 1 H), 7.96 (d, $J = 8.4$ Hz, 2 H), 7.66 (d, $J = 1.8$ Hz, 1 H), 7.33 (d, $J = 8.4$ Hz, 2 H), 7.26 (d, $J = 3.5$ Hz, 1 H), 6.58 (dd, $J_1 = 3.5$ Hz, $J_2 = 1.8$ Hz, 1 H), 5.81-5.94 (m, 1 H), 5.04-5.15 (m, 2 H), 3.42 (d, $J = 6.6$ Hz, 2 H), 2.41 (s, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 178.9, 157.8, 151.8, 147.5, 146.8, 145.4, 140.8, 134.0, 133.5, 131.4, 129.5, 128.7, 126.5, 120.7, 118.1, 112.6, 33.5, 21.6;

IR (film): 1647, 1596, 1566, 1377, 1189, 816 cm^{-1} ;

MS (EI, 70 eV): 383 (M^+ , 0.01 %), 319 (80 %), 304 (93 %), 290 (9 %), 155 (9 %), 91 (100 %);

HRMS (EI): calcd. for $\text{C}_{20}\text{H}_{18}\text{NO}_5\text{S}$ ($\text{M}^+\text{+H}$): 384.0906, found: 384.0908.



8b

Toluene-4-sulfonic acid 3-allyl-5-(1-hydroxy-propyl)-pyridin-2-yl ester (8b): A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 3-allyl-5-bromo-2-pyridyl 4-methylbenzenesulfonate (184 mg, 0.5 mmol) in dry THF (1.5 mL). *i*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at $-30\text{ }^{\circ}\text{C}$, and the resulting mixture was stirred at this temperature for 7 h to complete the bromine-magnesium exchange (checked by GC of hydrolyzed reaction aliquots). Propionaldehyde (0.60 mmol in 0.5 mL of THF) was added and the reaction mixture was warmed to $25\text{ }^{\circ}\text{C}$ and quenched with saturated aqueous NH_4Cl . The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:1) yielded the product **8b** (139 mg, 80 %) as an oil.

^1H NMR (CDCl_3 , 300 MHz): 7.99 (d, $J = 2.2$ Hz, 1 H), 7.92 (d, $J = 8.4$ Hz, 2 H), 7.57 (d, $J = 2.2$ Hz, 1 H), 7.32 (d, $J = 8.4$ Hz, 2 H), 5.78-5.94 (m, 1 H), 5.02-5.13 (m, 2 H), 4.50-4.61 (m,

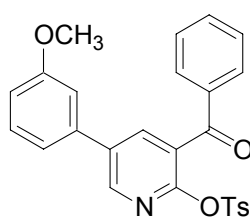
1 H), 3.38 (d, $J = 6.6$ Hz, 2 H), 2.42 (s, 3 H), 2.25 (bs, 1 H), 1.61-1.79 (m, 2 H), 0.87 (t, $J = 7.3$ Hz, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 154.9, 145.0, 143.5, 139.0, 137.9, 134.4, 134.2, 129.5, 128.6, 126.7, 117.6, 72.8, 33.8, 31.8, 21.6, 9.8;

IR (film): 3411, 1714, 1640, 1597, 1584, 1416, 1307 cm^{-1} ;

MS (EI, 70 eV): 347 (M^+ , 0.01 %), 330 (0.1 %), 283 (49 %), 268 (39 %), 254 (100 %), 155 (15 %), 91 (82 %);

HRMS (EI): calcd. for $\text{C}_{18}\text{H}_{22}\text{NO}_4\text{S}$ ($\text{M}^+\text{+H}$): 348.1270, found: 348.1259.



10

Toluene-4-sulfonic acid 3-benzoyl-5-(3-methoxyphenyl)pyridin-2-yl ester (10): A mixture of toluene-4-sulfonic acid 3-benzoyl-5-bromo-pyridin-2-yl ester (**6c**): (216 mg, 0.5 mmol), 3-methoxybenzeneboronic acid (152 mg, 1.0 mmol), TBAB (16 mg, 10 mol %), $\text{Pd}(\text{dba})_2$ (14 mg, 5 mol %), tri (2-furyl) phosphine (12 mg, 10 mol %) in THF (2.0 mL) and water (0.5 mL) was refluxed for 12 h under nitrogen. Water (5.0 mL) was added and the aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:1) yielded the product **10** (206 mg, 90 %) as a solid; m. p.: 144.0-144.5 $^\circ\text{C}$.

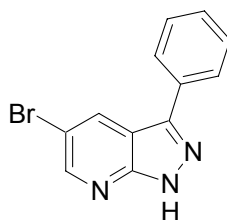
^1H NMR (CDCl_3 , 300 MHz): 8.57 (d, $J = 2.7$ Hz, 1 H), 7.97 (d, $J = 2.7$ Hz, 1 H), 7.71 (d, $J = 7.1$ Hz, 2 H), 7.65 (d, $J = 8.4$ Hz, 2 H), 7.55 (t, $J = 7.5$ Hz, 1 H), 7.40 (t, $J = 7.5$ Hz, 2 H), 7.31 (t, $J = 8.0$ Hz, 1 H), 7.17 (d, $J = 8.4$ Hz, 2 H), 7.05 (d, $J = 8.0$ Hz, 1 H), 7.0 (t, $J = 2.2$ Hz, 1 H), 6.89 (dd, $J_1 = 8.0$ Hz, $J_2 = 2.6$ Hz, 1 H), 3.77 (s, 3 H), 2.34 (s, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 192.3, 160.2, 153.1, 148.0, 145.3, 138.6, 137.1, 136.3, 135.6, 133.8, 133.7, 130.4, 129.9, 129.5, 128.6, 128.5, 126.2, 119.5, 114.1, 112.9, 55.4, 21.7;

IR (KBr): 1668, 1596, 1379, 1428, 1180, 864 cm^{-1} ;

HRMS calcd for $\text{C}_{26}\text{H}_{21}\text{NNaO}_5\text{S}$ ($\text{M}^+\text{+Na}$): 482.1038, found: 482.1029;

Anal. calcd for $\text{C}_{26}\text{H}_{21}\text{NO}_5\text{S}$: C, 67.96; H, 4.61; N, 3.05; Found: C, 67.86; H, 4.49; N, 2.95.



11

5-Bromo-3-phenyl-1H-pyrazolo[3,4-b]pyridine (11): The mixture of toluene-4-sulfonic acid 3-benzoyl-5-bromo-pyridin-2-yl ester (**6c**) (108 mg, 0.25 mmol) and hydrazine hydrate (0.1 mL) in toluene (1.0 mL) was stirred at 80 °C for 4 h. Water (5.0 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 3:1) yielded the product **11** (60 mg, 88 %) as a solid; m.p.: 205.5-206.0 °C.

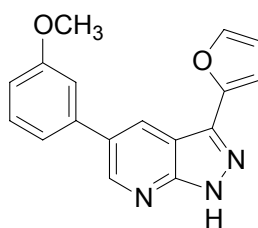
¹H NMR (DMSO-d₆, 300 MHz): 8.78 (d, *J* = 1.8 Hz, 1 H), 8.62 (d, *J* = 1.8 Hz, 1 H), 8.01 (d, *J* = 7.5 Hz, 2 H), 7.38-7.54 (m, 3 H);

¹³C NMR (DMSO-d₆, 75 MHz): 151.4, 149.5, 142.6, 132.7, 132.5, 129.3, 128.6, 126.9, 113.8, 112.5;

IR (KBr): 3430, 3195, 1596, 1481, 1371, 1256, 926, 758 cm⁻¹;

MS (EI, 70 ev): 275 (M⁺ (⁸¹Br), 100%), 273 (M⁺ (⁷⁹Br), 100 %), 246 (7 %), 193 (7 %), 164 (6 %);

HRMS (EI): calcd. for C₁₂H₈BrN₃: 272.9902, found: 272.9903.



12

3-Furan-2-yl-5-(3-methoxy-phenyl)-1H-pyrazolo[3,4-b]pyridine (12): A mixture of toluene-4-sulfonic acid 5-bromo-3-(furan-2-carbonyl)-pyridin-2-yl ester (**6d**): (211 mg, 0.5 mmol), 3-methoxybenzeneboronic acid (152 mg, 1.0 mmol), TBAB (16 mg, 10 mol %), Pd(dba)₂ (14 mg, 5 mol %), tri (2-furyl) phosphine (12 mg, 10 mol %) in THF (2.0 mL) and water (0.5 mL) was refluxed for 12 h under nitrogen. Hydrazine hydrate (0.5 mL) was added after the reaction mixture was cooled to room temperature and then it was refluxed for 6 h. Water (5.0 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 20

mL). The combined organic fractions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography yielded (eluent: pentane:ether = 2:1) the product **12** (112 mg, 77 %) as a solid; m.p.: 198.0-198.5 °C.

^1H NMR (DMSO-d_6 , 300 MHz): 8.89 (d, $J = 1.3$ Hz, 1 H), 8.65 (d, $J = 1.3$ Hz, 1 H), 7.87 (s, 1 H), 7.30-7.46 (m, 3 H), 7.21 (d, $J = 3.1$ Hz, 1 H), 6.98 (d, $J = 7.9$ Hz, 1 H), 6.70 (s, 1H), 3.86 (s, 3 H);

^{13}C NMR (CDCl_3 , 75 MHz): 160.2, 152.2, 149.2, 148.2, 143.5, 139.6, 136.2, 130.5, 130.4, 127.9, 120.0, 113.5, 113.2, 112.1, 111.8, 108.1, 55.6;

IR (KBr): 3430, 3132, 1602, 1509, 1490, 1476, 1260, 1219 cm^{-1} ;

MS (EI, 70 eV): 291 (M^+ , 100 %), 262 (7 %), 248 (11 %), 219 (7%), 145 (12 %);

HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_2$: 291,1008, found: 291,1005.

