Synthesis

1.1 Synthesis of 3-acetamidopyridine, 1

3-Acetamidopyridine was prepared by the previously reported method.[1] 3-Aminopyridine (1.882 g, 20.0 mmol) was dissolved in a mixture of pyridine (10 mL) and acetic anhydride (10 mL) and the resulting solution was kept at room temperature for 24 h. Water (10 mL) was added and the solution was evaporated in vacuo to dryness. The precipitates thus obtained were washed thoroughly with diethyl ether and recrystalized from methanol. Mp. 133-134 ^{o}C. IR (KBr pellet, cm^{-1}) 3244m [υ(NH)], 1687vs [υ(C=O)], 1554vs [υ(amide II)].

1.2 Synthesis of A1

3-Acetamidopyridine (0.027 g, 0.20 mmol) was dissolved in chloroform (15 mL). To this solution was added 1,4-diiodotetrafluorobenzene (0.040 g, 0.10 mmol) in dichloromethane (10 mL). The resulting solution was brought to a boil and then left to stand at ambient temperature. The colorless crystals suitable for X-ray analysis were afforded in 4 days. Mp. 122-124 ^{o}C. IR (KBr pellet, cm^{-1}) 3287m [υ(NH)], 1679s [υ(C=O)], 1554m [υ(amide II)], 1460vs , 942s [υ(1,4-diiodotetraflorobenzene)].

2.1 Synthesis of 4-(acetamidomethyl)pyridine, 2

4-(Acetamidomethyl)pyridine was prepared by employing a modification of the previously reported procedure.[2] Acetic anhydride (10 mL) was added very slowly into 4-(aminomethyl)pyridine (5.0 mL, 50.0 mmol) with continous stirring and the resulting solution was refluxed for one hour. Excess of acetic anhydride and acetic acid produced during the reaction were evaporated and product thus obtained was recrystalized from diethyl ether. Mp 88-89 ^{o}C. IR (KBr pellet, cm^{-1}) 3265m [υ(NH)], 1643vs [υ(C=O)], 1556vs [υ(amide II)].

2.2 Synthesis of A2

A solution of 4-(Acetamidomethyl)pyridine (0.030 g, 0.20 mmol) and 1,4-diiodotetrafluorobenzene (0.040 g, 0.10 mmol) in dichloromethane (15 mL) was boiled and allowed to stand at ambient temperature. The colorless crystals suitable foe X-ray analysis were afforded in 6 days. Mp. 112-113 ^{o}C. IR (KBr pellet, cm^{-1}) 3292m [υ(NH)], 1652vs [υ(C=O)], 1541m [υ(amide II)], 1462s, 944m [υ(1,4-diiodotetraflorobenzene)].

4.1 Synthesis of 2-(4-pyridyl)-benzimidazole, 4 [3]

A mixture of 1,2-phenylenediamine (4.519 g, 41.80 mmol) and 4-pyridinecarboxaldehyde (4.48 g, 41.8 mmol, 4.00 ml) in ethanol (800 ml) was stirred for two hours at room temperature. Iodobenzene diacetate (18.86 g, 58.50 mmol) was added to the reaction mixture and the resulting dark brown solution was stirred for an additional hour at room temperature. The solvent was then removed via rotary evaporation and the residue dissolved in ethyl acetate. The organic layer was washed with 5% aqueous $NaHCO_3$ and brine solutions. The ethyl acetate was removed via rotary evaporation and the resulting solid purified via column chromatography (2:1 ethyl acetate:hexanes) to

afford pure 2-(4-pyridyl)-benzimidazole. Yield: 6.36 g , 78%, m.p. 216-219^{o}C, ^{1}H NMR: δ_H(400 MHz; DMSO-d_6) 8.884 (2H, d), 8.344 (2H, d), 7.725 (2H, m), 7.343 (2H, m)

4.2 Synthesis of A4

2-(4-Pyridyl)-benzimidazole (8.4 mg, 0.043 mmol) was dissolved in methanol and added to a solution of 1,4-diiodotetrafluorobenzene (17.3 mg, 0.0430 mmol) in CH_2Cl_2 (2.0 ml). The resulting solution was allowed to evaporate slowly to give colorless rods suitable for X-ray diffraction. m.p. 162-164^{o}C

5.1 Synthesis of 1-(3-methoxypyrid-5-yl)-2-(3-pyrid-5-yl)ethyne, 5

3-Bromopyridine (396mg, 2.51 mmol), 3-methoxy-5-ethynylpyridine (400mg, 3.01 mmol), copper iodide (16mg, 0.084 mmol), triphenylphosphine (60mg, 0.226 mmol), bis(triphenylphosphine)palladium(II) dichloride (60mg, 0.086 mmol) were added to a round bottom flask. Tetrahydrofuran (20 mL) and triethylamine (20 mL) were added and dinitrogen bubbled through the resultant mixture for 10 minutes. A condenser was attached and the mixture heated at 70 ËšC under a dinitrogen atmosphere. The reaction was monitored by TLC and allowed to cool to room temperature upon completion (48 hours). The solution was then diluted with 50 mL of ethyl acetate, washed with water (3 x 100 mL) then washed with saturated aqueous sodium chloride (1 x 100 mL). The organic layer was separated and dried over magnesium sulfate. The solvent was removed on a rotary evaporator and the residue chromatographed on silica with a hexanes/ethyl acetate mixture (10:1) as the eluant. The product was further purified by recrystallization in hexanes/ethyl acetate (1:1) and isolated as a white solid (525 mg, 83%). M.p: 100-102 ºC; 1H NMR (^{1}H; 400 MHz, $CDCl_3$): 8.780(d, J = 1.2Hz, 1H), 8.60 (dd, J = 4.8Hz, J = 1.6Hz, 1H), 8.40 (d, J = 1.2Hz, 1H), 8.31 (d, J = 8.31Hz, 1H), 7.84 (dt, J = 7.6Hz, 1.8Hz, 1H), 7.34 7.32 (m, 1H), 3.90 (s, 3H).

5.2 Synthesis of A5

1-(3-Methoxypyrid-5-yl)-2-(3-pyrid-5-yl)ethyne (10.0mg, 0.04 mmol) and 1,4-diiodotetrafluorobenzene (18.0mg, 0.04 mmol) were added to a beaker and dissolved in a mixture of dichloromethane and toluene (5:5 mL). Upon slow evaporation of the solvent over 2 days, colorless rod-shaped crystals formed. m.p. 92-94 °C; IR (KBr pellet) υ 3039, 1590, 1460, 1422, 1233, 1161, 943, 803, 758, 701 cm^{-1}.

6.1 Synthesis of 5-methoxy-3,3'-bipyridine, 6

3-Pyridylboronic acid was prepared as previously reported.[4] A solution of 3-bromopyridine (100 mmol, 9.65 ml) and triisopropylborate (120 mmol, 27.7 ml) in dry THF (150 ml) was cooled to –80 C using a dry ice/ acetone bath. Butyl lithium (1.6 M in hexanes, 120 mmol, 75.0 ml) was added dropwise to the stirred THF solution over 60 minutes and the resulting yellow solution was allowed to react for 60 min. The cold bath was removed and the solution allowed to warm to –20 C, where a 2 N HCl solution (100 ml) was added. When the solution reached room temperature, the acidic aqueous layer was separated, and its pH adjusted to 7 using 5 N NaOH. NaCl (25.0 g) was added to the

solution and the aqueous layer was then extracted with THF (3 x 125 ml portions). The THF was removed in vacuo and the resulting solid dissolved in a 4:4:1 methanol:acetone:water solution. The solution was concentrated under reduced pressure and then placed in an ice bath to aid precipitation. The product was collected via vacuum filtration. Yield: 11.17 g (91 %); ^{1}H NMR: δ_H(400 MHz; Methanol-d_4) 7.675 (1H, t), 8.395 (1H, d), 8.500 (1H, d), 8.592 (1H, s); IR: 1369 cm^{-1} (B-O). Note: a suitable NMR spectra was not obtained using DMSO or $CDCl_3$.

3-Pyridylboronic acid and 5-methoxy-3-bromopyridine were combined, the solvent was removed from the reaction flask via rotary evaporation and the resulting solid dissolved in ethyl acetate and water. The aqueous layer was separated, and the ethyl acetate was removed on the rotavap. The resulting solid was purified via column chromatography (ethyl acetate: hexanes 1:1) to yield pure 5-methoxy-3,3'-bipyridine. Yield: 0.970 g (64%), m.p. 35-38^{o}C, ^{1}H NMR: δ_H(400 MHz; DMSO-d_6) 8.990 (1H, d), 8.643 (1H, dd), 8.551 (1H, d), 8.355 (1H, d), 8.191 (1H, dt), 7.737 (1H, t), 7.536 (1H, dd)

6.2 Synthesis of A6

A solution of 5-methoxy-3,3'-bipyridine (8 mg, 0.043 mmol) in ethanol (1 ml) was added to a solution of 1,4-diiodotetrafluorobenzene (17.3 mg, 0.043 mmol) in CH_2Cl_2 (2 ml). Slow evaporation of the solvent precipitated colorless needles of **A6** suitable for X-ray diffraction. m.p. 87-90^{o}C.

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X-ray data were collected on a Bruker SMART 1000 four-circle CCD diffractometer at 173 K (**3**, **4**, **6**, and **7**), or a SMART APEX CCD diffractometer at 100 K (**1**, **2**, and **5**) using, in either case, a fine-focus molybdenum Kα tube. Data were collected using SMART (**3**, **4**, **6**, and **7**) [(a)] or APEX2 (**1**, **2**, and **5**) [(b)] software. Initial cell constants were found by small widely separated "matrix" runs. Generally, an entire hemisphere of reciprocal space was collected regardless of Laué symmetry. Scan speed and scan width were chosen based on scattering power and peak rocking curves.

Unit cell constants and orientation matrix were improved by least-squares refinement of reflections thresholded from the entire dataset. Integration was performed with SAINT,[(c)] using this improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied. Laué symmetry, space group, and unit cell contents were found with XPREP.

Data were reduced with SHELXTL.[(d)] The structures were solved in all cases by direct methods without incident. Only one sample (**4**) contained solvent, and none of the molecules in any of the samples displayed disorder. Except where indicated, hydrogen atoms were assigned to idealized positions and were allowed to ride. Heavy atoms were refined with anisotropic thermal parameters. Absorption correction was carried out on all datasets.

1 A small degree of merohedral twinning (emulating *mmm* Laué symmetry, β= 90.860°) was treated with the SHELXL BASF command. Coordinates for the amide protons H13 and H23 were allowed to refine.

2 The halobenzene sits on an inversion center, and the amide sits on a general position, for a 1:2 halobenzene : amide ratio. All hydrogen atoms, including the amide proton H17, were placed in idealized positions and were allowed to ride.

3 There are two independent halobenzenes, each sitting on inversion centers, and a heterocycle, on a general position, giving overall 1:1 ratio of molecules.

4 A molecule of methanol solvent was located in the difference Fourier map; refinement of this molecule was uneventful. Hydrogen bond coordinates of the alcohol proton H1S and the imidazole proton H11 were allowed to refine.

5 The asymmetric unit contains two independent halobenzenes and two heterocycles. All hydrogen atoms were placed in idealized positions and were allowed to ride.

6 The unit cell contains the following species: (a) two independent halobenzenes, each sitting on an inversion center, (b) two independent halobenzenes, each sitting on a general position, and (c) two independent heterocycles, each sitting on a general position. Overall stoichiometry is therefore 3:2 halobenzene : heterocycle. All hydrogen atoms were placed in idealized positions and were allowed to ride.

7 The unit cell contains the following species: (a) a dicarboxylic acid, sitting on a crystallographic 2-fold rotation axis, (b) a halobenzene, sitting on a general position, and (c) a heterocycle, sitting on a general position. Overall stoichiometry was therefore 1:1:2 diacid : halobenzene : heterocycle. All hydrogen atoms, including the carboxylic acid proton H21 and amide proton H32, were placed in idealized positions and were allowed to ride.

(a) SMART v5.060, © 1997 - 1999, Bruker Analytical X-ray Systems, Madison, WI.
(b) APEX2 v2.2.0 © 2005 - 2007, Bruker AXS, Madison, WI.

(c) SAINT v7.46a, © 1997 - 2007, Bruker AXS, Madison, WI.

(d) SHELXTL v6.10, © 2001 , Bruker AXS, Madison, WI.