Supporting Information

A practical Buchwald-Hartwig Amination of 2-Bromopyridines with Volatile Amines

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A 250-mL, round-bottomed flask fitted with a magnetic stir-bar was charged with Pd(OAc)_2 (164 mg, 0.730 mmol, 0.05 equiv.), dppp (602 mg, 1.46 mmol, 0.10 equiv.), and sodium *tert*-butoxide (3.09 g, 32.1 mmol, 2.2 equiv.). After purging with nitrogen for 5 minutes, toluene was added (100 mL) while being stirred. Next, the *tert*-butyl 4-(6-bromopyridin-2-yl)piperazine-1-carboxylate (**1**, 15.0 g, 10.0 mmol, 1 equiv.), *N*-methyl(phenyl)methanamine (2.3 mL, 17.5 mmol, 1.20 equiv.), and toluene (distilled, 50 mL) is added. The dark red mixture was refluxed for 1 h. After cooling to room temperature, the mixture was transferred to a separatory funnel. The reaction flask was rinsed with diethyl ether (2×50 mL), brine (100 mL), water (20 mL), and again with diethyl ether (50 mL). All of the rinses were also transferred to the separatory funnel and the layers were then mixed and separated. The aqueous layer was extracted with diethyl ether (50 mL), and the combined organic layers were dried over MgSO_4 . The mixture was filtered and the MgSO_4 was washed with 50 mL diethyl ether. Concentration *in vacuo* gave a crude brown oil which was further purified using flash chromatography eluting with a mixture of 4:1 EtOAc/Pent. to give the desired coupling product **2** as a white solid 5.44 g (90.7%). mp = 115.4 °C; $^1\text{H-NMR}$ (CDCl_3) δ ppm 7.33-7.21 (m, 6H), 5.92 (dd, $J_1 = 8.0$ Hz, $J_2 = 10.0$ Hz, 2H), 4.75 (s, 2H), 3.48-3.43 (m, 8H), 2.99 (s, 3H), 1.46 (s, 9H). $^{13}\text{C-NMR}$ (CDCl_3) δ ppm 158.4, 158.3, 155.1, 139.7, 139.6, 139.4, 139.3, 128.7, 128.6, 127.4, 127.3, 126.9, 95.2, 94.5, 79.9, 79.8, 76.9, 53.3, 45.4, 36.2, 28.7. IR (cm^{-1}) 1685, 1579, 1411, 1241, 1162, 1119, 705, 675. $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_2$, calcd, C, 69.08; H, 7.91; N, 14.65; O, 8.37, found, C, 69.00; H, 7.97; N, 14.60.

Entry 2, **4-(6-Cyclopropylamino-pyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester**, 55% grey flaky crystals. To an Ace-ThredTM sealed tube was added **1b** (1.0 g, 2.92 mmol) in toluene (10 mL), followed by cyclopropylamine (0.84 g, 14.61 mmol), Pd(OAc)_2 (33 mg, 0.15 mmol), dppp (0.12 g, 0.29 mmol), NaOt-Bu (0.56 g, 5.84 mmol). The tube was then sealed and heated in electronically controlled pipe heater, which was operated behind heavy shielding, at 80 °C overnight (14 h) with mechanical shaking. After cooling to room temperature, the resulting black suspension was submitted to column chromatography directly eluting with 2:1 hexanes/EtOAc to give the desired amination product as grey flaky crystals after recrystallization from ethanol (0.515 g, 55.4%). mp = 95.3 °C; $^1\text{H-NMR}$ (CDCl_3) δ ppm 7.34 (dd, $J_1 = 7.3$ Hz, $J_2 = 8.2$ Hz, 1H), 6.38 (d, $J = 7.1$ Hz, 1H), 6.18 (d, $J = 8.2$ Hz, 1H), 4.30 (d, $J = 7.6$ Hz, 1H), 4.20 (m, 2H), 3.82 (m, 1H), 2.82 (m, 2H), 2.58 (m, 1H), 1.84 (m, 2H), 1.65 (m, 2H), 1.46 (s, 9H), 1.21

(d, $J = 6.4$ Hz, 1H); MS(APCI), M/z 319.22 ($M+1$). $C_{17}H_{26}N_4O_2$, calcd, C, 64.12; H, 8.23; N, 17.60; found, C, 64.05; H, 8.53; N, 17.55.

Entry 1, **4-(6-Methylamino-pyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester**, 77% yield as a viscous oil. 1H -NMR ($CDCl_3$) δ ppm 7.28 (dd, $J_1 = 8.0$ Hz, $J_2 = 7.8$ Hz, 1H), 5.92 (d, $J = 8.0$ Hz, 1H), 5.77 (d, $J = 8.0$ Hz, 1H), 4.52 (bs, 1H), 3.49 (m, 8H), 2.85 (s, 3H), 1.47 (s, 9H); MS(APCI), M/z 293.2 ($M+1$).

Entry 3, **4-(6-Dimethylamino-pyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester**, 76% as a colorless oil. 1H -NMR($CDCl_3$) δ (ppm): 7.28 (dd, $J_1 = 8.0$ Hz, $J_2 = 7.8$ Hz, 1H), 5.92 (dd, $J_1 = 8.0$ Hz, $J_2 = 10.0$ Hz, 2H), 3.08 (6H, s), 3.48-3.43 (m, 8H), 1.46 (s, 9H); MS(APCI), M/z 307.2 ($M+1$).

Entry 4, **6-Isopropylamino-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester**, 93% yield as shiny crimson crystals. To an Ace-ThredTM sealed tube was added **1b** (2.0 g, 5.86 mmol) in toluene (10 mL), followed by isopropylamine (1.73 g, 29.3 mmol), $Pd(OAc)_2$ (66 mg, 0.29 mmol), dppp (120 mg, 0.29 mmol), $NaOt-Bu$ (1.13 g, 11.72 mmol). The tube was then sealed and heated in electronically controlled pipe heater, which was operated behind heavy shielding, at 80 °C overnight (14 h) with mechanical shaking. After cooling to room temperature, the resulting black suspension was submitted to column chromatography directly eluting with 2:1 hexanes/EtOAc to give the desired amination product as grey flaky crystals (1.73 g, 93%). mp = 115.5 °C; 1H -NMR($CDCl_3$) δ (ppm): 7.34 (dd, $J_1 = 7.3$ Hz, $J_2 = 8.2$ Hz, 1H), 6.38 (d, $J = 7.1$ Hz, 1H), 6.18 (d, $J = 8.2$ Hz, 1H), 4.30 (d, $J = 7.6$ Hz, 1H), 4.20 (m, 2H), 3.82 (m, 1H), 2.82 (m, 2H), 2.58 (m, 1H), 1.84 (m, 2H), 1.65 (m, 2H), 1.46 (s, 9H), 1.21 (d, $J = 6.4$ Hz, 1H); MS(APCI), M/z 320.3 ($M+1$).

Entry 5, **6-Dimethylamino-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester**, 98% yield as beige crystals. mp = 73.7 °C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 7.37 (dd, $J_1 = 7.2$ Hz, $J_2 = 7.2$ Hz, 1H), 6.38 (d, $J = 7.4$ Hz, 1H), 6.33 (d, $J = 8.4$ Hz, 1H), 4.20 (bs, 2H), 3.06 (s, 3H), 2.80 (m, 2H), 2.65 (m, 1H), 1.90-1.70 (m, 4H), 1.47 (s, 9H); MS(APCI), M/z 306.2 (M+1).

Entry 6, **6-Ethylamino-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester**, 70% yield as a viscous oil. $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 7.30 (dd, $J_1 = 7.2$ Hz, $J_2 = 7.4$ Hz, 1H), 6.42 (d, $J = 7.4$ Hz, 1H), 6.22 (d, $J = 8.3$ Hz, 1H), 4.22 (bs, 2H), 3.25 (m, 2H), 3.35 (m, 2H), 2.80 (m, 2H), 2.65 (m, 1H), 1.90-1.70 (m, 4H), 1.47 (s, 9H), 1.26 (t, $J = 7.2$ Hz, 3H); MS(APCI), M/z 306.3 (M+1).

Entry 7, **6-Propylamino-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester**, 73% yield as a viscous oil. $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 7.30 (dd, $J_1 = 7.2$ Hz, $J_2 = 7.4$ Hz, 1H), 6.42 (d, $J = 7.4$ Hz, 1H), 6.22 (d, $J = 8.3$ Hz, 1H), 4.22 (bs, 2H), 3.25 (m, 2H), 3.35 (m, 2H), 2.80 (m, 2H), 2.65 (m, 1H), 1.90-1.70 (m, 4H), 1.47 (s, 9H), 1.26 (t, $J = 7.2$ Hz, 3H); MS(APCI), M/z 306.3 (M+1).

Entry 8, **2-Ethylamino-6-piperidinylpyridine**, 94% yield as a viscous oil. $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm 7.27 (1 H, t, $J = 16.0$ Hz), 5.96 (1 H, d, $J = 8.2$ Hz), 5.72 (1 H, d, $J = 7.8$ Hz), 4.19 (1 H, s), 3.47 (4 H, m), 3.26 (2 H, dt, $J = 12.6, 7.2$ Hz), 1.62 (6 H, m), 1.25 (3 H, m). MS(APCI), 206.2 (M+1).

Entry 9, **(6-Methoxy-pyridin-2-yl)-dimethyl-amine**, colorless oil, 95% yield. $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm 7.38 (1H, t, $J = 8.0$ Hz), 6.02 (2H, dd, $J = 15.7, 7.9$ Hz), 3.89 (3H, s), 3.07 (6H, s). MS(AP+) = 153.1, (M+1).

Entry 10, **(6-Ethoxy-pyridin-2-yl)-dimethyl-amine**, 28% yield as a viscous oil. ^1H -NMR (CDCl_3) δ ppm 7.35(1 H, t, $J=8.0$ Hz), 5.99 (2H, dd, $J=15.7, 7.9$ Hz), 4.33 (2H, q, $J=7.0$ Hz), 3.08 (6H, s), 1.40 (3H, t, $J=7.0$ Hz); MS(APCI), 166.1 ($\text{M}+1$).

GAINS_SAMPLE_REFERENCE: XB-H Coupling
GAINS_USER_ID: 1102
GAINS_INSTRUMENT: freeman
GAINS_EXPERIMENT_TIME: 01/30/2007 13:13:49
GAINS_END_TIME: 01/30/2007 13:15:15

XB-H Coupling
SMA NMR B28/1039S - Freeman

Automation directory: /export/home/auto/20070130

Pulse Sequence: szpu1
Solvent: cdcl3
Temp: 25.0 C / 298.1 K
Sample #1, user Jack li
File: 0101
INOVA-400 "freeman"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 5.130 sec
Width 6387.7 Hz
16 repetitions
OBSERVE H1, 399.768825 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 50 sec

56

Acquisition Time (sec)	1.3566	Date	Mar 9 2007	Date Stamp	Mar 9 2007
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Frequency (MHz)	100.53	Nucleus	¹³ C	Number of Transients	512
Points Count	32768	Pulse Sequence	s2pul	Receiver Gain	50.00
Spectrum Offset (Hz)	10052.2295	Sweep Width (Hz)	24154.59	Temperature (degree C)	25.000
Original Points Count 32768					
Solvent CHLOROFORM-d					

VerticalScaleFactor = 1

Date: Fri Mar 09 12:35:15 2007 (GMT*070309WANG)

Scans: 32

FTIR - ATR Technology THERMO NICOLET- Avatar 370

Resolution: 4.000

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 GAINS_USER_ID: yue01
 GAINS_INSTRUMENT: freeman
 GAINS_EXPERIMENT_TIME: 05/01/2006 16:09:25
 GAINS_END_TIME: 05/01/2006 16:11:35

recrystallized
 recrystallized
 SMA NMR B28/1039s --#Freeman

Automation directory: /export/home/auto/20060501

Pulse Sequence: s2pu1
 Solvent: cdcl3
 Temp: 25.0 C / 298.1 K
 Sample #31, user WEN-SONG YUE
 File: 3101 "freeman"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 5.123 sec
 Width 6336.4 Hz
 16 repetitions
 OBSERVE H1, 399.7688825 MHz
 DATA PROCESSING
 FT size 65536
 Total time 1 min, 38 sec

GAINS_SAMPLE_REFERENCE: recrystallized
GAINS_USER_ID: yue01
GAINS_INSTRUMENT: Freeman
GAINS_EXPERIMENT_TIME: 05/01/2006 16:09:25
GAINS_END_TIME: 05/01/2006 16:11:35

recrystallized
recrystallized
SMA NMR B2B/1039S -#Freeman

Automation directory: /export/home/auto/20060501

Pulse Sequence: s2pul

Solvent: cdcl3
Temp: 25.0 C / 298.1 K
Sample #31, user WEN-SONG YUE
File: 3101 "freeman"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 5.123 sec
Width 6396.4 Hz
16 repetitions
OBSERVE H1, 399.768825 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 38 sec

510

GAINS_SAMPLE_REFERENCE: X26-dimethyl
 GAINS_USER_ID: 1102
 GAINS_INSTRUMENT: freeman
 GAINS_EXPERIMENT_TIME: 06/12/2006 14:39:33
 GAINS_END_TIME: 06/12/2006 14:42:32

X26-dimethyl
 SMA NMR B28/1039S - Freeman

Automation directory: /export/home/auto/20060612

Pulse Sequence: s2pu1

Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
 Sample #38, user Jack Li
 File: 3801
 INOVA-400 "freeman"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 5.130 sec
 Width 6387.7 Hz
 16 repetitions
 OBSERVE H1, 399.7688825 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FI size 65536
 Total time 1 min, 50 sec

511

GAINS_SAMPLE_REFERENCE: The real isopropyl
 GAINS_USER_ID: 1102
 GAINS_INSTRUMENT: freeman
 GAINS_EXPERIMENT_TIME: 05/08/2006 13:58:28
 GAINS_END_TIME: 05/08/2006 14:00:39

The real isopropyl
 SMA NMR B28/1039S - Freeman

Automation directory: /export/home/auto/20060508

Pulse Sequence: s2pul

Solvent: cdc13
 Temp. 25.0 C / 298.1 K
 Sample #31, user Jack Li
 File: 3101
 INOVA-400 "freeman"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 5.123 sec
 Width 6396.4 Hz
 16 repetitions
 OBSERVE H1, 399.7688825 MHz
 DATA PROCESSING
 FT size 65536
 Total time 1 min, 38 sec

GAINS_SAMPLE_REFERENCE: Xdimethyl
 GAINS_USER_ID: 1102
 GAINS_INSTRUMENT: freeman
 GAINS_EXPERIMENT_TIME: 05/08/2006 14:05:03
 GAINS_END_TIME: 05/08/2006 14:07:14

Xdimethyl
 SMA NMR B28/1039S - Freeman

Automation directory: /export/home/auto/20060508

Pulse Sequence: s2pul

Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
 Sample #32, user Jack Lj
 File: 3201
 INOVA-400 "freeman"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 5.123 sec
 Width 6396.4 Hz
 16 repetitions
 OBSERVE H1, 399.7688825 MHz
 DATA PROCESSING
 FT size 65536
 Total time 1 min, 38 sec

70% yield

GAINS_SAMPLE_REFERENCE: ethyl
GAINS_USER_ID: yue01
GAINS_INSTRUMENT: freeman
GAINS_EXPERIMENT_TIME: 05/31/2006 15:58:16
GAINS_END_TIME: 05/31/2006 16:01:21

ethyl
ethyl

SMA NMR B2B/1039S - Freeman

Automation directory: /export/home/auto/2006053.

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #36, user VEN-SONG YUE
File: 3601
INOVA-400 "freeman"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 5.130 sec
Width 6387.7 Hz
16 repetitions
OBSERVE H1, 399.7688825 MHz
DATA PROCESSING
FT size 65336
Total time 1 min, 38 sec

514

GAINS_SAMPLE_REFERENCE: 56
GAINS_USER_ID: yue01
GAINS_INSTRUMENT: freeman
GAINS_EXPERIMENT_TIME: 05/30/2006 13:14:15
GAINS_END_TIME: 05/30/2006 13:17:56

56

SMA NMR B28/1039S - Freeman

Automation directory: /export/home/auto/20060530

Pulse Sequence: s2pul1

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #23, user WEN-SONG YUE
File: 2301
INOVA-400 "freeman"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 5.130 sec
Width 6387.7 Hz
16 repetitions
OBSERVE H1, 399.7688825 MHz
DATA PROCESSING
F1 size 65536
Total time 1 min, 38 sec

515

GAINS_SAMPLE_REFERENCE: 511550x018
 GAINS_USER_ID: zzwangl
 GAINS_INSTRUMENT: freeman
 GAINS_EXPERIMENT_TIME: 05/30/2006 11:32:21
 GAINS_END_TIME: 05/30/2006 11:34:24

511550x018
 SMA NMR B28/1039S Freeman

Automation directory: /export/home/auto/20060530

Pulse Sequence: s2pul

Solvent: cdc13
 Temp. 25.0 C / 298.1 K
 Sample #16, user zhi wang
 File: 1601
 INOVA-400 "freeman"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 5.130 sec
 Width 6387.7 Hz
 16 repetitions
 OBSERVE H1, 399.768825 MHz
 DATA PROCESSING
 FI size 65536
 Total time 1 min, 38 sec

516

GAINS_SAMPLE_REFERENCE: 00110358-0059-001
 GAINS_USER_ID: zzwang1
 GAINS_INSTRUMENT: freeman
 GAINS_EXPERIMENT_TIME: 02/01/2007 14:41:39
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00110358-0059-001
 SMA NMR B28/1039S - Freeman

Automation directory: /export/home/auto/20070201

Pulse Sequence: s2pul

Solvent: cdcl3
 Temp: 25.0 C / 298.1 K
 Sample #5, user zhi wang
 File: 0501 "freeman"
 INOVA-400

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 5.130 sec
 Width 6387.7 Hz
 16 repetitions
 OBSERVE HL, 399.7688825 MHz
 DATA PROCESSING
 FT size 65536
 Total time 1 min, 50 sec

517

GAINS_SAMPLE_REFERENCE: 00110358-0059-001
 GAINS_USER_ID: zzwang1
 GAINS_INSTRUMENT: freeman
 GAINS_EXPERIMENT_TIME: 02/01/2007 14:41:39
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00110358-0059-001
 SMA NMR 828/1039S - Freeman

Automation directory: /export/home/auto/20070201

Pulse Sequence: s2pul

Solvent: cdcl3
 Temp: 25.0 C / 298.1 K
 Sample #5, user zhi wang
 File: 0501 "freeman"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 5.130 sec
 Width 6367.7 Hz
 16 repetitions
 OBSERVE H1, 399.7688825 MHz
 DATA PROCESSING
 FT size 65536
 Total time 1 min, 50 sec