Supporting Information

Microwave-Promoted Suzuki Reactions of Aryl Chlorides in Aqueous Media

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Materials and Instruments:

The catalyst POPd2 was purchased from Combiphos Catalysts, Inc. TBAI and Cs_2CO_3 were purchased from Aldrich. All reagents and solvents were purchased and used without further purification. Personal ChemistryTM Creator and Smith stations were used for microwave reactions. Routine LC-MS was run in house with an integrated LC-MS system with a Shimadzu LC instrument and Micromass DMZ MS instrument. The high-resolution mass spectra (HRMS) were done at Harvard MS Facility at the Department of Chemical & Chemical Biology of Harvard University. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Mercury 300 spectrometer in CDCl_3 solution. Chemical shifts are given in parts per million (*ppm*) downfield from tetramethylsilane (TMS) as an internal reference, and coupling constants (*J*-values) are in hertz (Hz). Selected data are reported in the following manner: chemical shift; multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad); coupling constants and assignment. The product isolation was performed on prep-TLC plates (Whatman®) using hexane and ethyl acetate as the mobile phase. All reactions were monitored by reverse phase HPLC and LC/MS on a Shimadzu LC system.

General procedure for microwave-promoted reactions

A solution of the aryl chlorides and the boronic acids were prepared at 0.25 M in DMF. A solution of the Pd catalysts was prepared at

0.075 M in DMF. A solution of TBAI was prepared at 0.20 M in DMF. A solution of Cs_2CO_3 was prepared at 2.0 M in H_2O . To a reaction vessel was added 400 μL (100 μmole , 1 equiv) of aryl chloride, 40 μL (3 μmole , 3 mol%) of catalysts, 600 μL (150 μmole , 1.5 equiv) of aryl boronic acid, 200 μL (400 μmole , 4 equiv) of Cs_2CO_3 and 60 μL (12 μmole , 12 mol%) of TBAI. The reaction mixture was heated by microwave irradiation at 150 $^\circ\text{C}$ in high absorbance for 15 min. The resulting solution was cooled to rt and then diluted with 2.0 mL of ethyl acetate and 1.0 mL of water. The aqueous phase was extracted with 2 x 1.0 mL of ethyl acetate. The combined organic layer was washed with NH_4Cl (aq) (2 x 1.0 mL) and finally concentrated *in vacuo*. The crude product was then purified by preparative TLC using hexane and ethyl acetate (20 to 1 by volume) as the mobile phase to provide the cross coupled product.

General procedure for conventionally heated reactions

A solution of the aryl chlorides and the boronic acids were prepared at 0.25 M in DMF. A solution of Pd catalysts was prepared at 0.075 M in DMF. A solution of TBAI was prepared at 0.20 M in DMF. A solution of Cs_2CO_3 was prepared at 2.0 M in H_2O . To a reaction vessel was added 400 μL (100 μmole , 1 equiv) of aryl chloride, 40 μL (3 μmole , 3 mol%) of POPd2, 600 μL (150 μmole , 1.5 equiv) of aryl boronic acid, 200 μL (400 μmole , 4 equiv) of Cs_2CO_3 and 60 μL (12 μmole , 12 mol%) of TBAI. The reaction was sealed and heated at 150 $^\circ\text{C}$ for 2 h. The resulting solution was cooled to rt and then diluted with 2.0 mL of ethyl acetate

and 1.0 mL of water. The aqueous phase was extracted with 2 x 1.0 mL of ethyl acetate. The combined organic layer was then washed with NH₄Cl (aq) (2 x 1.0 mL) and finally concentrated *in vacuo*. The crude product was then purified by preparative TLC using hexane and ethyl acetate as the mobile phase to provide the cross coupled product.

Compound characterization and quantification

In general, compounds were characterized by NMR (¹H and ¹³C) and HRMS. Biphenyl compounds with low boiling point were confirmed by LC/MS in comparison with commercially available authentic samples. Product yields were determined by either isolation or UV quantification relative to authentic samples.

a. UV quantification for known compounds

Commercially available biphenyl compounds were purchased as standards. For each compound, a series of stock solution in DMSO with concentration at 0.25 mg/mL, 0.50 mg/mL, 0.75 mg/mL, 1.00 mg/mL, 1.25 mg/mL and 1.5 mg/mL were prepared. After obtaining HPLC-UV for the series, a graph was plotted using the concentration value (mg/mL) on the X-axis and UV peak area (mv) on the Y-axis to provide a standard concentration curve. Desired biphenyl products were quantified by comparing experimental UV absorption data to the standard curve.

b. Isolated compounds

5-Phenylindole (entry 1 in Table 3). This compound was obtained from 5-indolyl boronic acid and chlorobenzene by the general procedures described (Yield 61%). ¹H NMR (300MHz, CDCl₃): 6.63 (m, 1H), 7.24 (m, 1H), 7.33 (m, 1H), 7.46 (m, 4H), 7.67 (dd, *J* = 1.2, 7.2Hz, 2H), 7.88 (s, 1H), 8.16 (b, 1H); ¹³C NMR (75 MHz, CDCl₃): 103.2, 111.5, 119.5, 122.2, 125.1, 126.6, 127.6, 128.6, 128.9, 133.7, 135.5, 142.8. HRMS-EI calcd. for C₁₄H₁₁N (M⁺ +H), 193.0891; found 193.0888.

5-(4-Methoxyphenyl)indole (entry 2 in Table 3). This compound was obtained from 5-indolyl boronic acid and 4-chloroanisole by the general procedure for microwave irradiation (Yield 72%). ¹H NMR (300MHz, CDCl₃): 3.86(s, 3H), 6.60 (m, 1H), 7.0 (m, 2H), 7.26 (m, 1H), 7.43 (s, 2H), 7.58 (dd, *J* = 1.2, 8.4Hz, 2H), 7.81 (s, 1H), 8.16 (b, 1H); ¹³C NMR (75 MHz, CDCl₃): 55.6, 103.2, 111.4, 114.3, 118.9, 121.9, 125.0, 128.6, 133.3, 135.2, 135.4, 158.7. HRMS-EI calcd. for C₁₅H₁₃NO (M⁺ +H), 223.0997, found 223.1002.

5-(4-Fluorophenyl)indole (entry 3 in Table 3). This compound was obtained from 5-indolyl boronic acid and 1-chloro-4-fluorobenzene by the general procedure for microwave irradiation (Yield 76%). ¹H NMR (300MHz, CDCl₃): 6.60 (m, 1H), 7.12 (m, 2H), 7.24 (m, 1H), 7.28(m, 1H), 7.44 (m, 1H), 7.58 (m, 2H), 7.80 (m, 1H), 8.18 (b, 1H); ¹³C NMR (75 MHz, CDCl₃): 103.2, 111.5, 115.5, 115.8, 119.4, 122.0, 125.2, 128.6, 128.9, 129.0, 132.7, 135.4, 163.8. HRMS-EI calcd. for C₁₄H₁₀FN (M⁺ +H), 211.0797, found 211.0806.

5-(4-Methylphenyl)indole (entry 4 in Table 3). This compound was obtained from 5-indolyl boronic acid and 1-chloro-4-methylbenzene by the general procedure for microwave irradiation (Yield 71%). ¹H NMR (300MHz, CDCl₃): 2.31 (s, 3H), 6.59 (m, 1H), 7.17 (m, 1H), 7.26 (m, 4H), 7.43 (d, *J* = 8.1Hz, 2H), 7.58 (m, 1H), 8.2 (b, 1H); ¹³C NMR (75 MHz, CDCl₃): 20.9, 103.0, 110.6, 121.4, 124.0, 124.8, 125.8, 126.9, 130.4, 130.6, 134.1, 135.0, 136.0. HRMS-EI calcd. for C₁₅H₁₃N (M⁺ +H), 207.1048, found 207.1045.

5-(2-Methylphenyl)indole (entry 5 in Table 3). This compound was obtained from 5-indolyl boronic acid and 1-chloro-2-methylbenzene by the general procedure for microwave irradiation (Yield 68%). ¹H NMR (300MHz, CDCl₃): 2.25 (s, 3H), 6.59 (m, 1H), 7.17 (m, 1H), 7.27 (m, 5H), 7.43 (m, 1H), 7.58 (m, 1H), 8.2 (b, 1H); ¹³C NMR (75 MHz, CDCl₃): 20.9, 100.3, 103.0, 110.6, 121.3, 124.0, 124.8, 125.8, 126.9, 128.0, 130.4, 130.6, 136.0, 143.3. HRMS-EI calcd. for C₁₅H₁₃N (M⁺ +H), 207.1045, found 207.1052.

5-(4-Trifluoromethylphenyl)indole (entry 6 in Table 3). This compound was obtained from 5-indolyl boronic acid and 1-chloro-4-trifluoromethylbenzene by the general procedure for microwave irradiation (Yield 64%). ¹H NMR (300MHz, CDCl₃): 6.64 (m, 1H), 7.28 (m, 1H), 7.47 (m, 2H), 7.72 (m, 4H), 7.88 (m, 1H), 8.23 (b, 1H); ¹³C NMR (75 MHz, CDCl₃): 103.4, 111.7, 119.8, 122.0, 125.4, 125.7, 125.8, 125.9, 127.7, 132.1, 135.9, 146.3. HRMS-EI calcd. for C₁₅H₁₀F₃N (M⁺ +H), 261.0765, found 261.0769.

5-(4-Cyanophenyl)indole (entry 7 in Table 3). This compound was obtained from 5-indolyl boronic acid and 4-chloro-

benzenenitrile by the general procedure for microwave irradiation (Yield 75%). ¹H NMR (300 MHz, CDCl₃): 6.61 (m, 1H), 7.27 (m, 1H), 7.42 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.71 (m, 4H), 7.863 (m, 1H), 8.26 (b, 1H); ¹³C NMR (75 MHz, CDCl₃): 103.5, 109.9, 111.9, 119.6, 119.9, 121.8, 125.6, 128.0, 128.7, 131.5, 132.7, 136.2, 147.3. HRMS-EI calcd. for C₁₅H₁₀N₂ (M⁺ +H), 218.0844, found 218.0847.

5-phenyl-1 indole
Pulse Sequence: zgpg30

S-phenyl indole-C13
Pulse Sequence: zgpg30

S10

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Ambient temperature
 Mercury-398 "mercury"
 PULSE SEQUENCE
 Relax. delay 1.149 sec
 Pulse 1: 9.000 sec
 Width 18761.7 Hz
 360 repetitions
 DECOUPLE C13, 75.454385 MHz
 DECOUPLE H1, 399.678735 MHz
 Power 1.00
 Continuously on
 VOLTAGE modulated
 DATA PROCESSING
 Line broadening 1.2 Hz
 F2 size 32768
 Total time 18 min, 3 sec

S12

S13

```

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sample    Jul 8      dfrq 480.12s
solvent    COCl2     dn    H1
file      20040708  exp    50
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aquisition
=====
c1/c2     400.323    dm    mm
in        1.913      dm    C
at        23936      dm    200
mp        8008.0      wtfile
pb        202.000     p1
b1        10         p2
ss        4          p3
=====
t1/t2     56        warr
pw        13.5      wexp
di        2.000     wbp
tor       0         wnt
ct        64
=====
clock     y
gain      not used
=====
ll        n
in        n
sp        y
=====
sp        -214.7
wp        4395.6
vs        137
sc        0
=====
hzmax     2500
ls        342.51
rfl       1011.7
rfp       0
tn        0
=====
me cdc gh 3.000

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S14

S15

Suzuki-2-Me

exptl stdsh

SAMPLE DEC. & VT
 Date Jul 5 2004 dfrq 400.133
 Solvent dms-d₆ HI
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 Prgm /standards/2004-07-05/2004-07-05-01
 nmh
 ds
 ACQUISITION
 tfrq 400.133 dmf PROCESSING
 in HI
 p1 1.1888 vt16
 wv 23136 proc
 bw 8008.0 fn not used
 Td not used
 bs 16 werr
 ss 4 weap
 cpar 500
 g1 13.5 wdr
 nt 1.000 wnt
 tof 64
 nt 64
 ct 64
 atlock
 gain not used
 FLAG
 11
 in n
 dp n
 gp 013W/AY
 sp 380.4
 wv 4011.4
 vs 147
 sc 0
 wc 250
 hzma 57.85
 f1 32.11
 f2 101.7
 rfp 0
 th 12
 ins 3.000
 res cdc ph

2-Me w/020

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date Jul 12 2004 DEC. & VT
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file exp exp 38
ACQUISITION 133
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pc 1.933
at 23936
np 6008.0
sv 1.000
wb not used
ts 4
ss 4
tpwr 55
pw 13.5
di 1.000
to 0
ct 84
alock not used
gain not used
flags
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  11 n
  dp n
  DISPLAY -282.0
  sp 4300.7
  wp 200
  vs 200
  sc 0
  sc 250
  hzmax 27.22
  ls 547.75
  rfl 1018.7
  rfp 0
  th 20
  ls 3.000
  me coc ph
  
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S17

suzuki-2-Me-C13
Pulse Sequence: zgpg30

S18

expl std13c

expl std13c

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          tn 0.013 dar 10860
          no 31235 dar PROCESSING
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          w0 10400 wirfile ft
          b0 16 proc fn not used
          twpr 7.68 n
          pw 1.146 warr
          tsf 0 wexp
          nt $000 Nos
          cf 5999 vnt
          gain n
          FLAG5 30
          i) n
          dp n
          DISPLAY y
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          ep 18761.7
          va 880
          vc 258
          wc .75-85
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          rff 1009.3
          rfp 3
          ins 100.500
          al no ph

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S20

021402-4-M

exp 22mu)

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SW	425.3	10		
ac	3.334	10		
pd	31256	11		
np	2880	10		
dt	10	10		
ds	1.036	10		
ct	5	10		
TRANSMITTER	H1	SP	DEPLA	156.5
trq	360.475	WD	SP	370.9
tof	245.7	WD	SP	272.5
cpw	57	rfp	SP	2172.6
pcouple	7.256	tp	SP	-18.6
pc	1.2	tp	SP	-23.2
dn	C13	WC	PLOT	254
de	mm	WC	PLOT	254
ds	41	WC	PLOT	116
ds	15693	WC	PLOT	226

021402-4-CL3

exp1 std13c

date Mar 10 2002
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 at 8.851
 acq 20721.7
 sb 18408
 bs 16
 is 16
 ipwr 7.5
 pw 1.25
 tof 588
 nt 4784
 ct 4784
 alock 58
 gain 58
 flabg 58
 il 58
 in 58
 of 58
 sp -1000.3
 wp 1075.12
 xc 512
 mc 250
 hzmax 75.05
 iq 588.08
 r2 1000.3
 t2p 4
 t2s 4
 lns 108.008
 a1 no bh

DEC. A VI
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 acq 18809
 sb 1.17
 bs 16
 is 16
 ipwr 7.5
 pw 1.25
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 nt 4784
 ct 4784
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 gain 58
 flabg 58
 il 58
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 of 58
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 r2 1000.3
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 lns 108.008
 a1 no bh