Proximity Effects in the Palladium-Catalyzed Substitution of Aryl Fluorides

Supplementary Material Part II (Experimental)

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Experimental Section

All melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a BRUKER-SPECTROSPIN 300 UltraShield instrument operating at 300 and 75.5MHz respectively using CDCl_3 or d_6 -DMSO as the solvent. Electron ionization low-resolution spectra were determined at an ionizing voltage of 70eV. Electron spray low-resolution spectra were determined at an ionizing voltage of 70eV. Column chromatography was carried out on Universal silica gel (32-63 μm) using the indicated solvents as eluents. HRMS data were determined on Micromass Q-TOF-2 mass spectrometer. All the starting materials and solvents were used as received without further purification. 4-Fluoro-3-nitrobenzonitrile, 2-fluoro-5-nitrobenzonitrile, 4-fluoro-3-nitrobenzaldehyde, 2-fluoro-5-nitrobenzaldehyde, 2-fluoro-5-nitrobenzoic acid, 2-fluorobenzoic acid, tributylphenyltin, tributyl(vinyl)tin, phenylboronic acid, 4-methoxyphenylboronic acid, triphenylphosphine, Cs_2CO_3 , Triton B (40% solution in water) and tetrakis(triphenylphosphine)palladium(0) were all purchased from Aldrich.

Methyl 2-fluoro-5-nitrobenzoate: A 200 mL round bottom flask, equipped with a stirring bar was charged with 5.00 g (27.0 mmol, 1.0 equiv.) of 2-fluoro-5-nitrobenzoic acid, 13.20 g (40.5 mmol, 1.5 equiv.) of Cs_2CO_3 and 50 mL of DMF. After stirring at room temperature for 10 min, 4.78 g (25.7 mmol, 0.95 equiv.) of methyl tosylate was added. The mixture was allowed to stir at room temperature for 18 hours, at which time HPLC of the aliquot indicated all the starting material was consumed. The mixture was partitioned between 100 mL of EtOAc and 100 mL of water. After layer separation, the aqueous layer was extracted once with 50 mL of EtOAc. The combined organic layers were washed for five times with 100 mL of water and concentrated *in vacuo* to afford 5.10 g of a yellow solid: m.p., 48-49 $^\circ\text{C}$; ^1H NMR CDCl_3 δ 4.00 (s, 3H), 7.36 (t, $J=9.3$ Hz, 1H), 8.39-8.47 (m, 1H), 8.81-8.88 (m, 1H); ^{13}C NMR CDCl_3 δ 52.9 (t), 118.4 (d), 119.7 (d), 128.1, 129.5 (d), 143.8, 162.9 (d), 166.8; IR (KBr), 1728, 1627, 1532, 1486, 1434, 1350, 1325. These properties agreed in all respects with those reported in the literature.¹

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Injection Date : 28-Aug-2003 1:47:11 PM Seq. Line : 1
Sample Name : SY4696-40-01 Location : Vial 27
Acq. Operator : Inj : 1
 Inj Volume : 20 µl
Sequence File : C:\HPCHEM\1\SEQUENCE\DEF_LC.S
Method : C:\HPCHEM\1\METHODS\TFASH.M
Last changed : 18-Jul-2003 4:44:08 PM
TFASH method
0.1% TFA/0.1% ACN Gradient
column: Phenomenex Prodigy 100x4.6, 3 micron
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Area Percent Report
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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.394	BV	0.1321	3.04391e4	3137.26538	98.5640
2	9.646	VB	0.1200	342.77353	38.56733	1.1099
3	10.730	BB	0.1172	70.17336	8.23276	0.2272
4	11.865	VB	0.0895	30.51873	4.96612	0.0988

Totals : 3.08825e4 3189.03160

Results obtained with standard integrator!

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*** End of Report ***

General procedure for Stille Couplings: a 100 mL three neck round bottom flask fitted with a magnetic stirring bar and a temperature probe was charged with 2.67 mmol (1.0 equiv) of the organotin starting material, 4.01 mmol of the fluoroarene (1.5 equiv), 1.58 mL of Triton B (40% solution in water, 4.01 mmol, 1.5 equiv) for entries 5, 6, 11, 12 and 14 in Table 2, 307 mg of Pd(PPh₃)₄ (0.267 mmol, 0.1 equiv)/280 mg of PPh₃ (1.07 mmol, 0.4 equiv) and 25 mL of DMF. The contents were degassed three times by alternately connecting to house vacuum (~55mmHg) and nitrogen. The contents were then heated at the temperature indicated in Table 2 and followed with HPLC (35°C, 25mM NH₄Ac/CH₃CN gradient 90/10 to 10/90, 254 nm detection) until the disappearance of the starting material or when the reaction stalled (all reactions were heated for at least 24 hours). After cooling, the reaction mixture was poured into 75 mL of water, acidified with 1.10 of KHSO₄ and extracted with methylene chloride (75 mL x 3). The combined organic layer was washed successively with water and brine and dried over MgSO₄. The solvent was removed *in vacuo*. The residue was pre-adsorbed onto silica gel and subjected to gradient flash chromatography using hexanes and ethyl acetate (6:1 to 1:1) to afford the enriched desired product; the materials were further purified with prep HPLC to afford the desired product, in quantity as indicated in Table 2.

5-Nitro-2-vinyl-benzoic acid: 0.185 g; m.p. 157-158 °C; ¹H NMR DMSO-d₆ δ 5.58 (d, J=11.3 Hz, 1H), 5.97 (d, J=17.5 Hz, 1H), 7.49 (dd, J=11.1, 17.5 Hz, 1H), 7.94 (d, J=8.6 Hz, 1H), 8.31 (dd, J=8.7, 2.6 Hz, 1H), 8.52 (d, J=2.6 Hz, 1H), 13.76 (br s, 1H); ¹³C NMR DMSO-d₆ δ 120.8, 125.0, 126.1, 128.3, 130.5, 133.7, 144.2, 146.3, 166.7; IR (KBr): 1127, 1256, 1347, 1477, 1521, 1606, 1693, 3088; MS (CI, Negative) m/z: 191 (M-1); HRMS Calcd for C₉H₆NO₄: 192.0297, Found: 192.0314.

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Injection Date	: 10-Jun-2004 2:24:32 PM	Seq. Line	: 2
Sample Name	: 2	Location	: Vial 2
Acq. Operator	: nm-agilent	Inj	: 1
		Inj Volume	: 20 µl

Sequence File : C:\HPCHEM\1\SEQUENCE\DEF_LC.S
Method : C:\HPCHEM\1\METHODS\TFASH.M
Last changed : 10-Jun-2004 2:23:54 PM by nm-agilent
(modified after loading)

TFASH method
0.1% TFA/0.1% ACN Gradient
column: Phenomenex Prodigy 100x4.6, 3 micron

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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.696	BB	0.1657	7167.85742	565.81122	98.9724
2	12.865	BB	0.1620	74.42035	7.26007	1.0276

Totals : 7242.27777 573.07129

Results obtained with standard integrator!

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*** End of Report ***

FOR: SHU. YU.

LV 14DEC04

TFAsh HPLC Method

HPLC Conditions

Column: Prodigy 3u ODS, 100 x 4.6 mm

Detector: 254 nm

Injection volume: 20 µL

Temperature: 35 °C

Flow rate: 1.0 ml/min

Mobile phase: A= 0.1% TFA in H2O B= 0.1% TFA in Acetonitrile

GRADIENT PROFILE

Time	%A	%B
0	90	10
10	35	65
12	10	90
15	10	90

Stop time: 15 min

Post time: 3 min

#11

Current Data Parameters
NAME SY7151-08-11
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters

Date_ 20040616
Time 18.03
INSTRUM DPX300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32

#11

Current Data Parameters
NAME SY7151-08-11
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040616
Time 21.03
INSTRUM DPX300
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2048
uc

170.43
147.24
146.94
134.68
129.19
128.23
127.81
127.11
121.32

77.58

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

4-Nitro-biphenyl-2-carboxylic acid: 0.189 g; m.p. 168-171 °C; ^1H NMR CDCl_3 δ 7.29-7.36 (m, 2H), 7.39-7.45 (m, 3H), 7.56 (d, $J=8.3$ Hz, 1H), 8.38 (dd, $J=8.5, 2.5$ Hz, 1H), 8.78 (d, $J=2.5$ Hz, 1H); ^{13}C NMR CDCl_3 δ 125.9, 126.4, 128.2, 128.4, 128.7, 130.5, 132.5, 138.8, 146.8, 149.5, 170.7; IR (KBr): 1447, 1521, 1609, 1703, 2860; MS (CI, Negative) m/z : 242 (M-1). These properties agree in all respects with those reported in the literature.²

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Injection Date	: 10-Jun-2004 3:59:34 PM	Seq. Line	: 7
Sample Name	: 7	Location	: Vial 7
Acq. Operator	: nm-agilent	Inj	: 1
		Inj Volume	: 20 µl

Sequence File : C:\HPCHEM\1\SEQUENCE\DEF_LC.S
Method : C:\HPCHEM\1\METHODS\TFASH.M
Last changed : 10-Jun-2004 3:58:54 PM by nm-agilent
(modified after loading)

TFASH method

0.1% TFA/0.1% ACN Gradient

column: Phenomenex Prodigy 100x4.6, 3 micron

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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.149	BB	0.1543	45.20761	4.49813	0.8013
2	10.072	BB	0.1751	5526.20752	406.29102	97.9497
3	12.858	BB	0.1642	70.46933	6.63228	1.2490

Totals : 5641.88446 417.42143

Results obtained with standard integrator!

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*** End of Report ***

FOR: SHU. YU.

LV 14DEC04

TFAsh HPLC Method

HPLC Conditions

Column: Prodigy 3u ODS, 100 x 4.6 mm

Detector: 254 nm

Injection volume: 20 μ L

Temperature: 35 $^{\circ}$ C

Flow rate: 1.0 ml/min

Mobile phase: A= 0.1% TFA in H₂O B= 0.1% TFA in Acetonitrile

GRADIENT PROFILE

Time	%A	%B
0	90	10
10	35	65
12	10	90
15	10	90

Stop time: 15 min

Post time: 3 min

General procedure for Suzuki Couplings: a 100 mL three neck round bottom flask fitted with a magnetic stirring bar and a temperature probe was charged with 2.67 mmol of the boronic acid (1.0 equiv), 4.01 mmol of the aryl fluoride (1.5 equiv), 1.96 g of Cs_2CO_3 (6.01 mmol, 2.25 equiv), 1.58 mL of Triton B (40% solution in water, 4.01 mmol, 1.5 equiv) for entries 5, 6, 11, 12 and 14 in Table 3, 307 mg of $\text{Pd}(\text{PPh}_3)_4$ (0.267 mmol, 0.1 equiv)/280 mg of PPh_3 (1.07 mmol, 0.4 equiv) and 25 mL of DMF. The contents were degassed three times by alternately connecting to house vacuum (~55mmHg) and nitrogen. The contents were then heated at the temperature indicated in Table 3 and followed with HPLC (35°C, 25mM $\text{NH}_4\text{Ac}/\text{CH}_3\text{CN}$ gradient 90/10 to 10/90, 254 nm detection) until the disappearance of the starting material or when the reaction stalled (all reactions were heated for at least 24 hours). After cooling, the reaction mixture was poured into 75 mL of water, acidified with 1.10 of KHSO_4 and extracted with methylene chloride (75 mL x 3). The combined organic layer was washed successively with water and brine and dried over MgSO_4 . The solvent was removed *in vacuo*. The residue was preadsorbed onto silica gel and subjected to gradient flash chromatography using hexanes and ethyl acetate (6:1 to 1:1) to afford the enriched desired product; the materials were further purified with prep HPLC to afford the desired product, in quantity as indicated in Table 3.

4-Nitro-biphenyl-2-carboxylic acid: 0.279 g; m.p. 168-171 °C; ^1H NMR CDCl_3 δ 7.29-7.36 (m, 2H), 7.39-7.45 (m, 3H), 7.56 (d, $J=8.3$ Hz, 1H), 8.38 (dd, $J=8.5, 2.5$ Hz, 1H), 8.78 (d, $J=2.5$ Hz, 1H); ^{13}C NMR CDCl_3 δ 125.9, 126.4, 128.2, 128.4, 128.7, 130.5, 132.5, 138.8, 146.8, 149.5, 170.7; IR (KBr): 1447, 1521, 1609, 1703, 2860. MS (CI, Negative) m/z : 242 (M-1). These properties agreed in all respects with those reported in the literature.²

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Injection Date   : 10-Jun-2004 2:05:33 PM      Seq. Line :    1
Sample Name      : 1                          Location  : Vial 1
Acq. Operator    : nm-agilent                 Inj       :    1
                                           Inj Volume: 20 µl

Sequence File    : C:\HPCHEM\1\SEQUENCE\DEF_LC.S
Method           : C:\HPCHEM\1\METHODS\TFASH.M
Last changed     : 28-Jan-2004 1:08:47 PM
TFASH method
0.1% TFA/0.1% ACN Gradient
column: Phenomenex Prodigy 100x4.6, 3 micron
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Area Percent Report
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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.032	BB	0.1560	5136.17334	429.55453	98.6266
2	12.841	BB	0.1587	71.52064	7.20451	1.3734

Totals : 5207.69398 436.75904

Results obtained with standard integrator!

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*** End of Report ***

FOR: SHU. YU.

LV 14DEC04

TFAsh HPLC Method

HPLC Conditions

Column: Prodigy 3u ODS, 100 x 4.6 mm

Detector: 254 nm

Injection volume: 20 μ L

Temperature: 35 $^{\circ}$ C

Flow rate: 1.0 ml/min

Mobile phase: A= 0.1% TFA in H₂O B= 0.1% TFA in Acetonitrile

GRADIENT PROFILE

Time	%A	%B
0	90	10
10	35	65
12	10	90
15	10	90

Stop time: 15 min

Post time: 3 min

4'-Methoxy-4-nitro-biphenyl-2-carboxylic acid: 0.219 g; m.p. 130-134 °C; ^1H NMR CDCl_3 δ 3.87 (s, 3H) 6.95 (d, $J=8.7$ Hz, 2H), 7.28 (d, $J=8.7$ Hz, 2H), 7.54 (d, $J=8.7$ Hz, 1H), 8.36 (dd, $J=8.5, 2.3$ Hz, 1H), 8.76 (d, $J=2.5$ Hz, 1H); ^{13}C NMR CDCl_3 δ 55.3, 114.1, 125.9, 126.4, 129.7, 130.3, 131.0, 132.3, 146.4, 149.1, 160.2, 170.8; IR (KBr): 1178, 1249, 1350, 1478, 1520, 1610, 1710, 2957; MS (CI, Negative) m/z : 272 (M-1) HRMS Calcd for $\text{C}_{14}\text{H}_{10}\text{NO}_5$: 272.0559, Found: 272.0572.

Reference:

- (1) Soundararajan, N.; Platz, Matthew S. *J. Org. Chem.* **1990**, *55*, 2034-44.
- (2) Ihama, T.; Fu, J. M.; Bourguignon, M.; Snieckus, V. *Synthesis* **1989**, 184-8.

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Injection Date	: 14-Dec-2004 5:58:15 PM	Seq. Line	: 1
Sample Name	: SY7151-08-06	Location	: Vial 11
Acq. Operator	: Agilent	Inj	: 1
		Inj Volume	: 20 µl

Sequence File : C:\HPCHEM\1\SEQUENCE\DEF_LC.S
Method : C:\HPCHEM\1\METHODS\TFASH.M
Last changed : 06-Oct-2004 1:45:27 PM by Agilent
TFASH method
0.1% TFA/0.1% ACN Gradient
column: Phenomenex Prodigy 100x4.6, 3 micron

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Area Percent Report
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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.500	BV	0.1589	119.69550	10.66138	0.8247
2	10.049	VB	0.1751	1.41096e4	1155.03796	97.2182
3	14.005	BB	0.1081	284.03860	36.45042	1.9571

Totals : 1.45133e4 1202.14977

Results obtained with standard integrator!

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*** End of Report ***

Recrystallized

Current Data Parameters
 NAME SY7151-08-06B
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20040726
 Time 17.50
 INSTRUM DPX300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 65536
 SOLVENT CDC13
 NS 16
 DS 2
 SWH 6172.839 Hz
 FIDRES 0.094190 Hz
 AQ 5.3084660 sec
 RG 456.1
 DW 81.000 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 8.00 usec
 PL1 -6.00 dB
 SFO1 300.1318534 MHz

F2 - Processing parameters
 SI 32768
 SF 300.1300290 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

Handwritten labels on the spectrum: CF_3 (pointing to the peak at ~7.9 ppm), CH_2 (pointing to the peak at ~3.7 ppm), and CH (pointing to the peak at ~2.5 ppm).

564

Recrystallized

Current Data Parameters
 NAME SY7151-08-06B
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20040727
 Time 4.40
 INSTRUM DPX300
 PROBHD 5 mm QNP 1H/1
 PULPROG zgpg30
 TD 65536
 SOLVENT CDC13
 NS 1024
 DS 4
 SWH 18832.393 Hz
 FIDRES 0.267360 Hz
 AQ 1.7400308 sec
 RG 574.7
 DW 26.550 usec
 DE 6.00 usec
 TE 300.0 K
 D1 3.50000000 sec
 d11 0.03000000 sec
 d12 0.0002000 sec

===== CHANNEL f1 =====
 NUC1 13C
 P1 10.00 usec
 PL1 0.00 dB
 SF01 75.4760200 MHz

===== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 80.00 usec
 PL2 -6.00 dB
 PL12 16.00 dB
 PL13 120.00 dB
 SF02 300.1312005 MHz

F2 - Processing parameters
 SI 32768
 SF 75.4677757 MHz
 EX 0
 WDW 0
 SSB 1.00 Hz
 LB 0
 GB 0
 PC 1.40

FOR: SHU. YU.

LV 14DEC04

TFash HPLC Method

HPLC Conditions

Column: Prodigy 3u ODS, 100 x 4.6 mm

Detector: 254 nm

Injection volume: 20 μ L

Temperature: 35 $^{\circ}$ C

Flow rate: 1.0 ml/min

Mobile phase: A= 0.1% TFA in H₂O B= 0.1% TFA in Acetonitrile

GRADIENT PROFILE

Time	%A	%B
0	90	10
10	35	65
12	10	90
15	10	90

Stop time: 15 min

Post time: 3 min