Regioselective Palladium-Catalyzed Arylation of 2-Furaldehyde

(Supporting Information)

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All commercial reagents were used as supplied with the exception of 2-furaldehyde which was freshly distilled over K_2CO_3 prior to use. Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C spectra were recorded on a Varian Unity-300 or Unity-400. IR spectra were recorded on a Nicolet 20DXC FT-IR spectrophotometer. Mass spectra were measured by Analytical Instrument Group, Inc. (Raleigh, NC).

General procedure for arylation of 2-furaldehyde: A solution of 2-furaldehyde (21 mmol), Bu_4NBr (2.1 mmol), KOAc (4.2 mmol), $PdCl_2$ (0.1 mmol), and Cy_3P (0.2 mmol) in 18 mL of DMF was degassed for 10 minutes by bubbling N_2 through the mixture before warming to 110 °C. To this mixture was added 2.1 mmol of aryl halide (**1**) in 3 mL of degassed DMF via syringe over 10 hrs. The cooled reaction mixture was poured into 100 mL of water and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and filtered through a short silica gel / Celite plug. The solvent was removed under reduced pressure to give a crude oil which was purified by silica gel chromatography using hexane / ethyl acetate mixtures to give the 5-aryl substituted furfural (**3**).

5-(4-chlorophenyl)-2-furaldehyde (3a): mp = 123-124 °C; IR (thin film) 1662, 1520, 1476, 1254cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.67 (s, 1H), 7.76 (AA'BB', 2H, J = 9 Hz), 7.44 (AA'BB', 2H, J = 9 Hz), 7.34 (d, 1H, J = 3 Hz), 6.84 (d, 1H, J = 3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz). δ 177.4, 158.4, 152.3, 135.8, 129.4, 127.6, 126.7, 123.8, 108.2; HRMS (PFAB) calculated for $C_{11}H_7ClO_2$ 207.0213, found: 207.0213.

5-(4-methoxyphenyl)-2-furaldehyde (3b): IR (thin film) 1662, 1608, 1478, 1387, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.63 (s, 1H), 7.80 (AA'BB', 2H, *J* = 9 Hz), 7.34 (d, 1H, *J* = 3 Hz), 6.99 (AA'BB', 2H, *J* = 9 Hz), 6.75 (d, 1H, *J* = 3 Hz), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 161.1, 160.0, 151.8, 127.2, 124.5, 122.0, 114.6, 106.5, 55.6; HRMS (PFAB) calculated for $C_{12}H_{10}O_3$ 203.0708, found: 203.0708.

5-(4-nitrophenyl)-2-furaldehyde (3c): mp = 199-200 °C; IR (thin film) 1666, 1599, 1512, 1341 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.76 (s, 1H), 8.33 (AA'BB', 2H, *J* = 9Hz), 7.99 (AA'BB', 2H, *J* = 9Hz), 7.39 (d, 1H, *J* = 3 Hz), 7.06 (d, 1H, *J* = 3 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 179.2, 156.1, 153.3, 148.0, 135.0, 126.6, 125.5, 125.2, 112.8; HRMS (PFAB) calculated for $C_{11}H_7NO_4$ 218.0451, found: 218.0451.

5-(4-methylphenyl)-2-furaldehyde (3d): mp = 55-56 °C; IR (thin film) 1665, 1529, 1480, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.65 (s, 1H), 7.74 (AA'BB', 2H, *J* = 9Hz), 7.34 (d, 1H, *J* = 3Hz), 7.27 (AA'BB', 2H, *J* = 9 Hz), 6.81 (d, 1H, *J* = 3 Hz), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3, 160.0, 152.0, 140.2, 129.9, 126.5, 125.5, 124.1, 107.3, 21.7; HRMS (PFAB) calculated for $C_{12}H_{10}O_2$ 187.0759, found: 187.0759.

5-(2-methylphenyl) -2-furaldehyde (3e): IR (thin film) 1669, 1513, 1465, 761 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.70 (s, 1H), 7.82 (m, 1H), 7.37 (d, 1H, *J* = 6 Hz), 7.32 (m, 4H), 6.77 (d, 1H, *J* = 6 Hz), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.6, 159.6, 151.9, 136.2, 131.7, 129.7, 128.7, 128.4, 126.5, 123.2, 111.3, 22.1; HRMS (PFAB) calculated for $C_{12}H_{10}O_2$ 187.0757, found: 187.0757.

5-(3-methylphenyl) -2-furaldehyde (3f): IR (thin film) 1669, 1517, 1469 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.66 (s, 1H), 7.68 (s, 1H), 7.64 (d, 1H, *J* = 7.6 Hz), 7.38-7.29 (m, 2H), 7.23 (d, 1H, *J* = 7.6 Hz), 6.86 (d, 1H, *J* = 3 Hz), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 177.4, 159.9, 152.2, 139.0, 130.8, 129.1, 126.1, 124.0, 122.8, 107.8, 21.6; HRMS (PFAB) calculated for $C_{12}H_{11}O_2$ 187.0757, found: 187.0757.

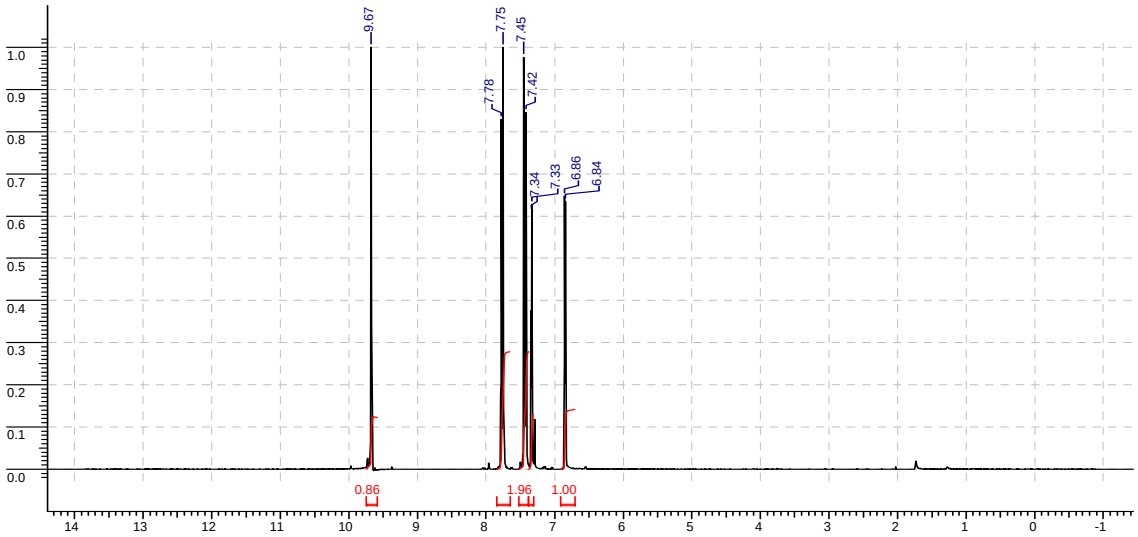
4-(5-formyl-2-furyl)benzonitrile (3g): mp = 155-156 °C; IR (thin film) 2222, 1666, 1528, 1480, 1255 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.73 (s, 1H), 7.93 (AA'BB', 2H, *J* = 9 Hz), 7.76 (AA'BB', 2H, *J* = 9 Hz), 7.38 (d, 1H, *J* = 3 Hz), 7.02 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7, 156.9, 153.0, 133.0 (2), 125.8, 123.2, 118.6, 112.9, 110.3; HRMS (PFAB) calculated for $C_{12}H_7NO_2$ 198.0556, found: 198.0556.

5-(3-trifluoromethylphenyl)-2-furaldehyde (3h): IR (thin film) 1672, 1328, 1121, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.71 (s, 1H), 8.06-7.99 (m, 2H), 7.67-7.56 (m, 2H), 7.36 (d, 1H, *J* = 3 Hz), 6.95 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 177.6, 157.7, 152.6, 131.7 (q, J_{CF} = 33 Hz), 129.9, 129.8, 128.5 (2), 126.2 (q, J_{CF} = 4 Hz), 123.9 (q, J_{CF} = 271 Hz), 122.2 (q, J_{CF} = 4 Hz), 109.0; HRMS (PFAB) calculated for $C_{12}H_{10}O_2F$ 241.0476, found: 241.0476.

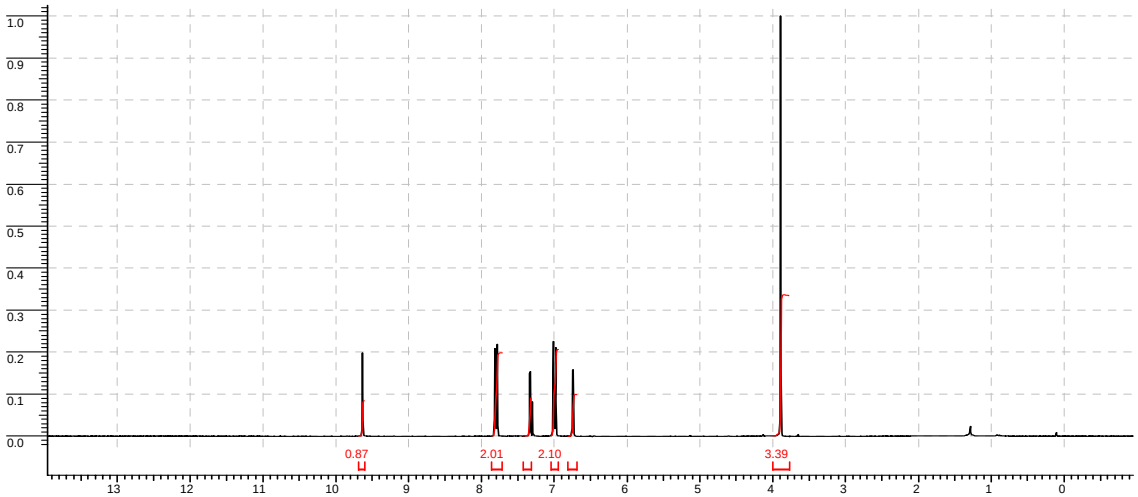
5-phenyl-2-furaldehyde (3i): IR (thin film) 1665, 1521, 1472, 1450, 1390, 1255; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.67 (s, 1H), 7.86-7.83 (m, 2H), 7.49-7.44 (m, 3H), 7.34 (d, 1H, *J* = 3 Hz), 6.86 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5, 159.7, 152.2, 129.9, 129.2, 125.5, 123.9, 107.9; HRMS (PFAB) calculated for $C_{11}H_8O_2$ 173.0603, found: 173.0603.

5-(5-formyl-2-furyl)-2-furaldehyde (3j): IR (thin film) 1661, 1439, 1263, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.72 (s, 2H), 7.36 (d, 2H, *J* = 4 Hz), 7.08 (d, 2H, *J* = 4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 179.1, 153.1, 148.8, 125.3, 112.6; HRMS (EI+) calculated for $C_{10}H_6O_4$ 190.0267, found: 190.0267.

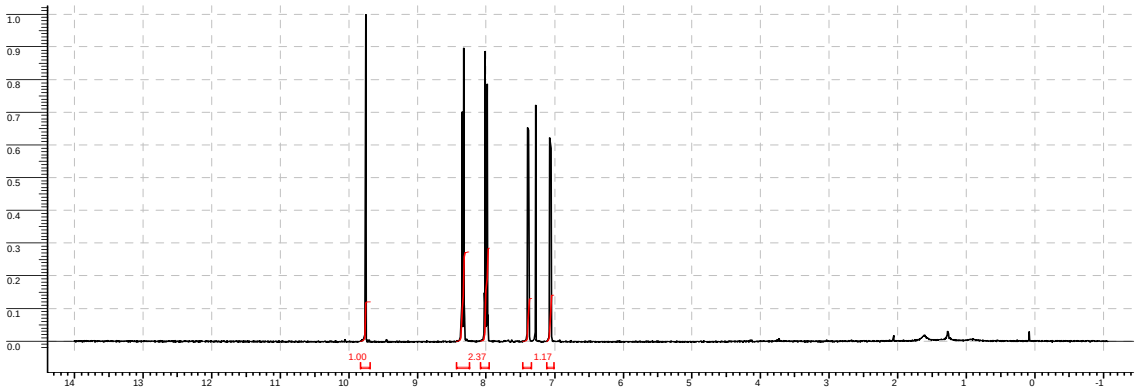
^{1}H NMR (3a):



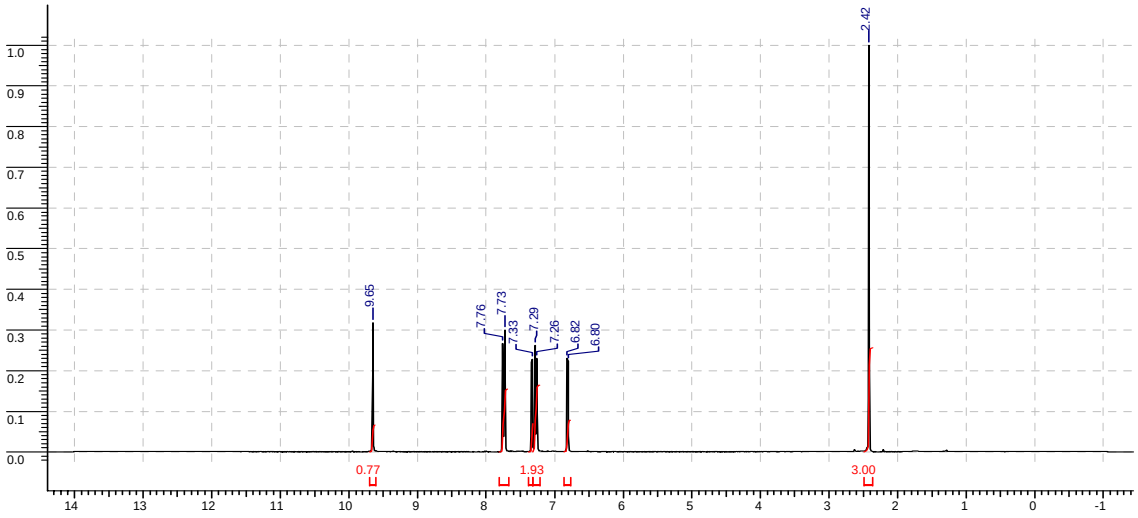
^{1}H NMR (3b):



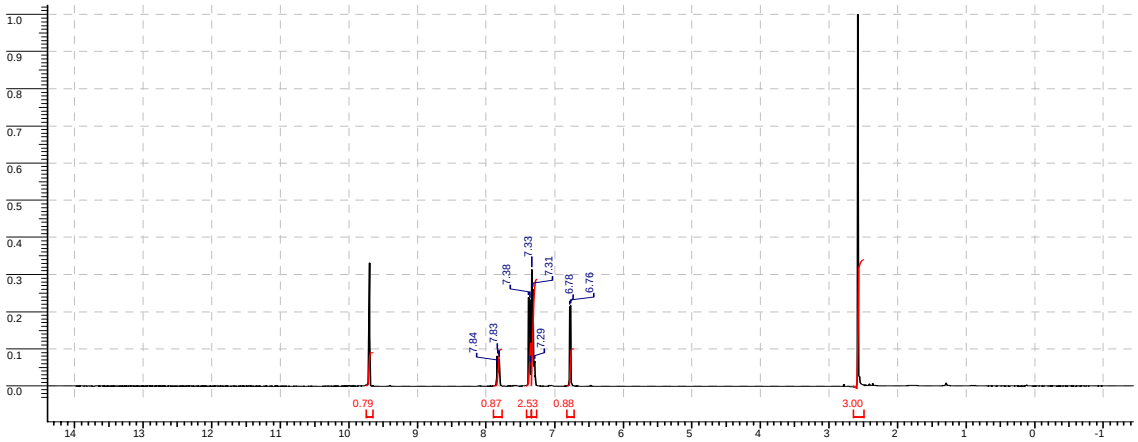
^{1}H NMR (3c):



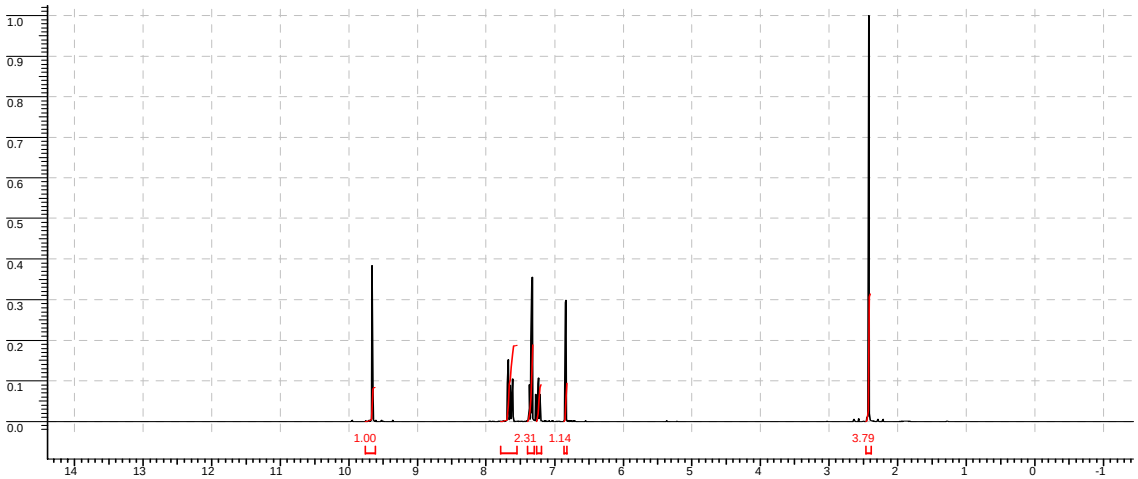
^{1}H NMR (3d):



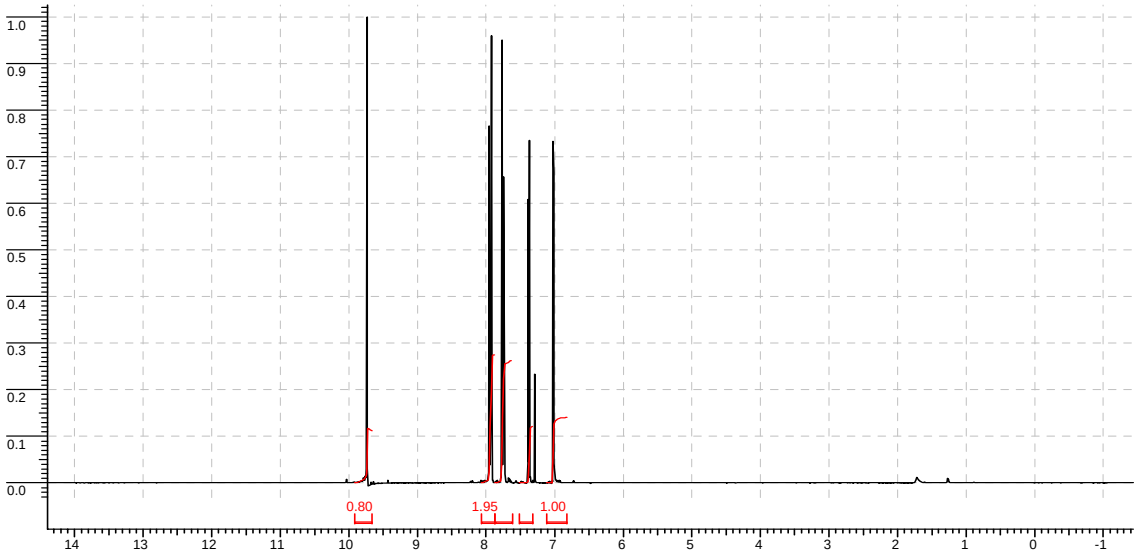
^{1}H NMR (3e):



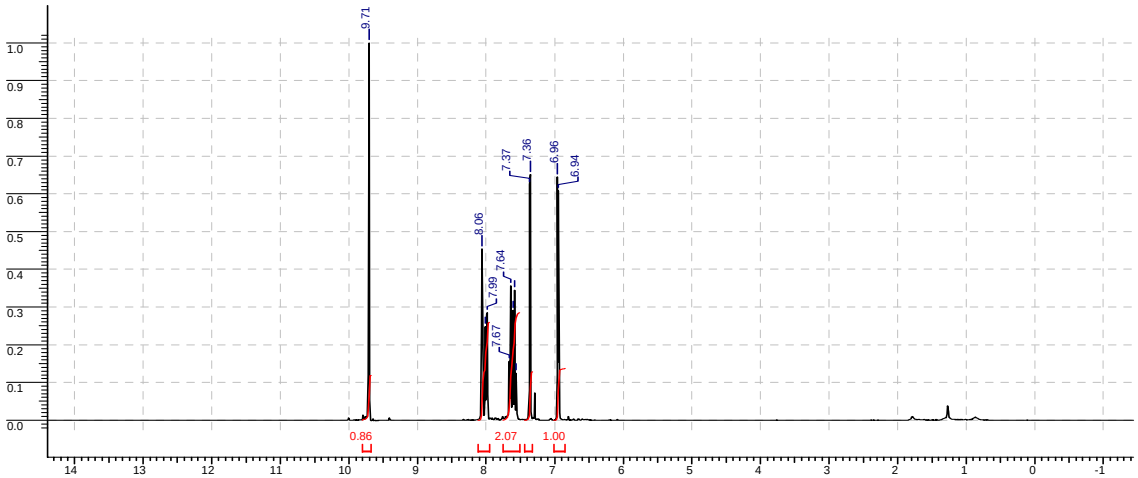
^{1}H NMR (3f):



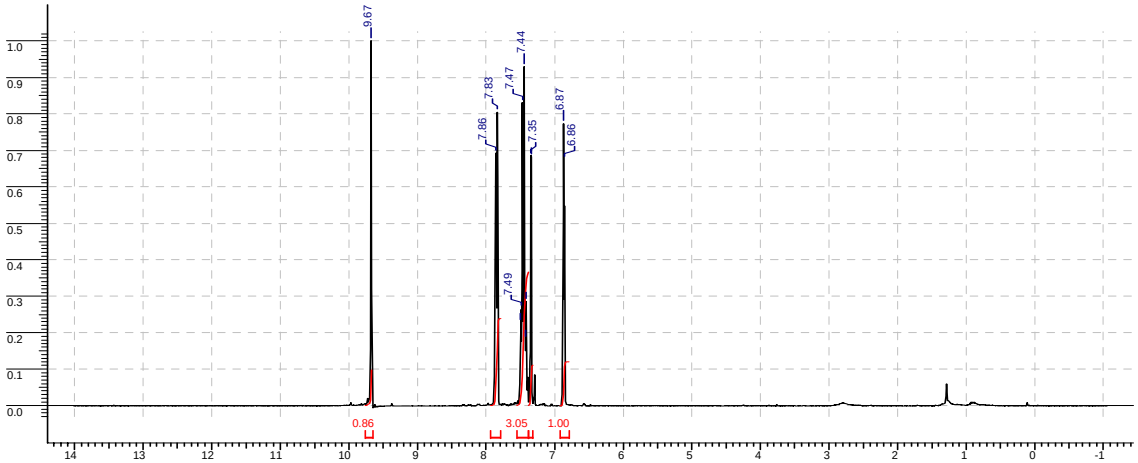
^{1}H NMR (3g):



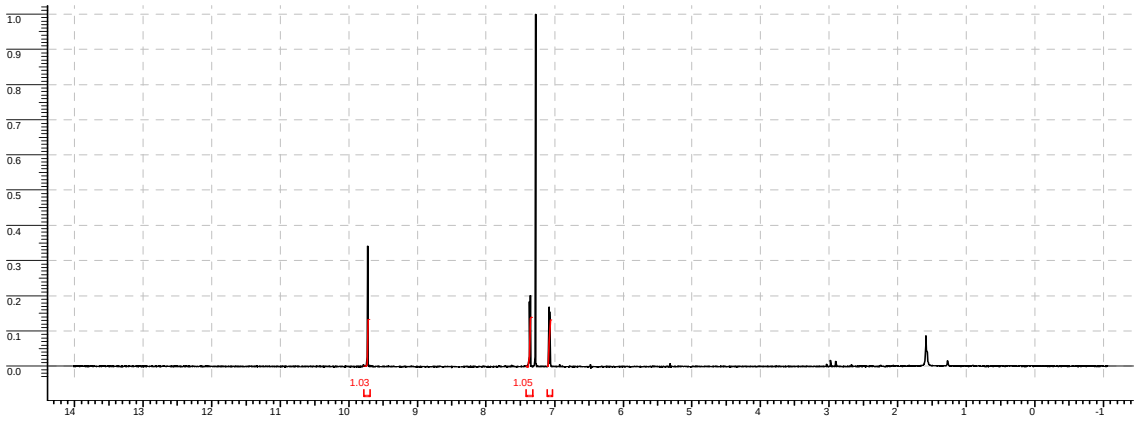
^{1}H NMR (3h):



^{1}H NMR (3i):



^{1}H NMR (3j):



Supplementary data for Table 1.:

A:Solvent	B:Additive	C:Phosphine	D:Catalyst	E:Base	% HC	% conversion	
DMA	Bu4NBr	No Phosphine	Pd(OAc)2	Hunigs	98.8	0.8	
CH3CN	Bu4NBr	No Phosphine	Pd(OAc)2	KOAc	4.0	14.6	
CH3CN	CuI	No Phosphine	Pd(OAc)2	Hunigs	1.6	0.3	
DMA	CuI	No Phosphine	Pd(OAc)2	KOAc	1.8	1.6	
CH3CN	Bu4NBr	P(o-Tol)3	Pd(OAc)2	Hunigs	90.0	8.3	
DMA	Bu4NBr	P(o-Tol)3	Pd(OAc)2	KOAc	2.0	17.9	
DMA	CuI	P(o-Tol)3	Pd(OAc)2	Hunigs	33.7	1.8	
CH3CN	CuI	P(o-Tol)3	Pd(OAc)2	KOAc	0.8	8.9	
CH3CN	Bu4NBr	No Phosphine	PdCl2	Hunigs	97.4	1.3	
DMA	Bu4NBr	No Phosphine	PdCl2	KOAc	18.6	40.8	
DMA	CuI	No Phosphine	PdCl2	Hunigs	9.3	0.6	
CH3CN	CuI	No Phosphine	PdCl2	KOAc	0.0	0.0	
DMA	Bu4NBr	P(o-Tol)3	PdCl2	Hunigs	99.0	1.0	
CH3CN	Bu4NBr	P(o-Tol)3	PdCl2	KOAc	13.4	24.6	
CH3CN	CuI	P(o-Tol)3	PdCl2	Hunigs	0.7	1.3	
DMA	CuI	P(o-Tol)3	PdCl2	KOAc	1.8	35.5	
		% HC = 100 x (area HC/HC+starting material+product)					
		% conversion = 100 x (area product/product+starting material+HC)					

Supplementary data for Figure 1.:

Phosphine	Catalyst	Solvent	%Conversion	% HC	
none	Pd/C dry	mibk	13.2	17.0	
o-tol3p	PdCl2	nmp	22.5	4.9	
tbu3p	Pd/C dry	dmf	0.0	0.0	
tbu3p	Pd/C	dmf	0.0	0.0	
cy3p	Pd/C	mibk	0.0	45.0	
o-tol3p	Pd/C dry	dmf	0.0	0.0	
none	Pd/C dry	nmp	0.0	0.0	
cy3p	Pd/C	nmp	7.7	0.0	
o-tol3p	PdCl2	mibk	43.7	24.6	
furyl3p	Pd/C dry	mibk	11.5	0.0	
o-tol3p	Pd/C dry	mibk	0.0	0.0	
furyl3p	Pd/C dry	nmp	0.0	0.0	
none	PdCl2	mibk	13.4	60.5	
furyl3p	Pd/C	dmf	33.6	20.4	
o-tol3p	Pd/C	dmf	4.9	0.0	
furyl3p	PdCl2	nmp	56.4	43.6	
tbu3p	PdCl2	nmp	55.6	44.4	
furyl3p	Pd/C	mibk	0.0	28.9	
none	PdCl2	dmf	56.9	43.1	
cy3p	Pd/C dry	dmf	4.4	0.0	
none	Pd/C	dmf	58.7	13.0	
furyl3p	PdCl2	dmf	61.0	31.7	
tbu3p	Pd/C dry	nmp	12.4	4.6	
cy3p	PdCl2	dmf	66.1	27.0	
cy3p	PdCl2	mibk	0.0	100.0	
tbu3p	Pd/C	mibk	0.0	0.0	
o-tol3p	Pd/C	nmp	39.3	9.3	
tbu3p	PdCl2	mibk	0.0	0.0	
none	Pd/C	nmp	63.5	36.5	
cy3p	Pd/C dry	nmp	9.1	0.0	
% HC = 100 x (area HC/HC+starting material+product)					
% conversion = 100 x (area product/product+starting material+HC)					