A Convenient Method for the Preparation of Weinreb Amides via Pd-Catalyzed Aminocarbonylation of Aryl Bromides at Atmospheric Pressure

*Joseph R Martinelli, Dominique M. M. Freckmann and Stephen L. Buchwald**

Department of Chemistry, Massachusetts Institute of Technology

Cambridge, Massachusetts, 02139.

Experimental Section

General. All reactions were carried out under a carbon monoxide atmosphere, Air Gas. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. Unless otherwise noted, THF, Et₂O, CH₂Cl₂ and toluene were purchased from J.T. Baker in CYCLE-TAINER[®] solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF and Et₂O) or through neutral alumina and copper (II) oxide (for toluene and CH₂Cl₂).¹ Unless otherwise stated, commercially obtained materials were used without further purification.

The following aryl bromides were purchased from Acros: 3-bromothiophene (filtered through basic alumina prior to use) and 2-bromo-3-methylpyridine. The following aryl bromides were purchased from Lancaster: 3-bromonitrobenzene, 4-bromo-2-fluorobenzonitrile, methyl 3-bromobenzoate and 1-bromo-2-cyclohexylbenzene. The following aryl bromides were purchased from Alfa Aesar: 3-bromobenzonitrile (Avocado Organics), 4-chloro-bromobenzene (Avocado Organics), 4-bromoanisole (filtered through basic alumina prior to use), 1-bromonaphthalene (Avocado Organics), 2-bromobenzonitrile, 2-bromobenzotrifluoride (filtered through basic alumina prior to use) and 2-bromoanisole (Avocado Organics; filtered through basic alumina prior to use). The following aryl bromides were purchased from Aldrich: 4-bromoveratrole (filtered through basic alumina prior to use), 4-bromobiphenyl, 2-(3-bromophenyl)-1,3-dioxolane (filtered through basic alumina prior to use), 2-bromo-*p*-xylene, methyl 2-bromobenzoate and 4-chlorobenzonitrile. The following compound was purchased from PCR Inc.: 2,5-difluorobromobenzene (filtered through basic alumina prior to use). *tert*-Butyl *N*-(4-bromophenyl)carbamate was prepared following literature procedures² using 4-bromoaniline (Aldrich), Di-*tert*-butyl dicarbonate (Aldrich) and Iodomethane (Alfa). *N*, *O*-dimethylhydroxylamine hydrochloride was purchased from Aldrich and Alfa Aesar. Xantphos was purchased from Strem and used without further purification. Pd(OAc)₂ was purchased from Strem, Inc. or supplied by Englehard. Sodium Carbonate was purchased from Mallinckrodt. *Anhydrous tribasic potassium phosphate was purchased from Fluka Chemical Co. and used as supplied.* The source (and thus the particle size) of the base employed may be critical for achieving efficient reactions.

All products of aminocarbonylation reactions were characterized by ¹H NMR, ¹³C NMR, and IR spectroscopy, as well as elemental analysis (Atlantic Microlab, Inc). Two new compounds

failed to give satisfactory elemental analyses. For these copies of ^1H and ^{13}C NMR spectra are included. Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300. Infrared spectra were recorded using a Perkin-Elmer 2000 FT-IR. All ^1H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane (internal standard) and were measured relative to the signals for residual chloroform (7.26 ppm), methylene chloride (5.32 ppm) or benzene (7.16 ppm) in the deuterated solvents. All ^{13}C NMR spectra are reported in ppm relative to deuteriochloroform (77.23 ppm), deuteromethylene chloride (54.00 ppm) or deuterobenzene (128.39 ppm), and all were obtained with ^1H decoupling. All ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (0 ppm). All ^{19}F NMR spectra are reported in ppm relative to trichlorofluoromethane (0 ppm). Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus. Gas Chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatography instrument with an FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

The conversions in Table 1 were determined by G.C. using dodecane as an internal standard, added during reaction workup. The yields in Table 1, entries 1 – 9 were also determined by G.C. using dodecane as an internal standard. The yield in Table 1, entry 10, is an isolated yield (average of two runs) and the procedure is given below. The yields in Tables 2 and 3 are isolated yields (average of two runs). All compounds isolated were estimated to be $\geq 95\%$ pure as determined by ^1H NMR and GC analysis and/or combustion analysis. The procedures described in this section are representative, and thus the yields may differ from those shown in Tables 1 - 3.

Synthesis of Weinreb Amides

General Procedure A: Synthesis of Wienreb Amides via Pd-Catalyzed Aminocarbonylation.

An oven-dried culture tube (18 x 150 mm, VWR) equipped with a Teflon[®] coated magnetic stir bar was sealed with a 14/20 rubber septum (inverted), evacuated, backfilled with nitrogen and cooled under nitrogen. All solid reagents were added by briefly removing the rubber septum: Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), and Na₂CO₃ (3 mmol, 3 equiv., 318 mg). Then, all liquid reagents were added dropwise via syringe: aryl bromide (1 mmol, 1 equiv.; aryl bromides which were solids at room temperature were added during the initial charge) and toluene (2 mL). After the addition of all reagents, the rubber septum was secured with several wrappings of electrical tape. Then, the reaction was purged for ~ 30 seconds with CO_(g); following the gas purge a balloon was connected to the reaction using a short length of rubber tubing (~ 1 in.), a needle adapter and a 20 G needle. This balloon was then inflated with CO_(g) and the reaction tube was submerged in a 80 °C preheated oil bath. The reaction mixture was heated at 80 °C with vigorous stirring until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate (~ 10 mL), filtered through a plug of celite (eluting with ethyl acetate) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

General Procedure B: Synthesis of Wienreb Amides via Pd-Catalyzed Aminocarbonylation of *ortho*-Substituted Aryl Halides.

An oven-dried culture tube (18 x 150 mm, VWR) equipped with a Teflon[®] coated magnetic stir bar was sealed with a 14/20 rubber septum (inverted), evacuated, backfilled with nitrogen and cooled under nitrogen. All solid reagents were added by briefly removing the rubber septum: Pd(OAc)₂ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %,

0.05 mmol, 0.05 equiv., 28.9 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), and K_3PO_4 (3 mmol, 3 equiv., 637 mg). Then, all liquid reagents were added dropwise via syringe: aryl bromide (1 mmol, 1 equiv.; aryl bromides which were solids at room temperature were added during the initial charge) and solvent (2 mL, toluene or *m*-xylene). After the addition of all reagents, the rubber septum was secured with several wrappings of electrical tape. Then, the reaction was purged for ~ 30 seconds with $CO_{(g)}$; following the gas purge a balloon was connected to the reaction using a short length of rubber tubing (~ 1 in.), a needle adapter and a 20 G needle. This balloon was then inflated with $CO_{(g)}$ and the reaction tube was submerged in a 100 - 120 °C preheated oil bath. The reaction mixture was heated at 100 - 120 °C with vigorous stirring until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate (~ 10 mL), filtered through a plug of celite (eluting with ethyl acetate) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

3-Cyano-*N*-methoxy-*N*-methylbenzamide (Table 2, entry 1).

Following general procedure A, a mixture of 3-bromobenzonitrile (1mmol, 0.182 g), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 8 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a viscous light orange oil (181 mg, 95 %). 1H NMR (300 MHz, $CDCl_3$) δ : 8.04-8.01 (m, 1H), 7.97-7.93 (dm, *J* for the d = 7.98 Hz, 1H), 7.78-7.73 (dm, *J* for the d = 7.70 Hz, 1H), 7.55 (ddd, *J* = 0.55, 7.70, 7.98 Hz, 1H), 3.54 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 167.06, 135.02, 133.74, 132.48, 131.84, 128.93, 118.01, 112.10, 61.19, 33.06. IR (neat, cm^{-1}): 3075, 2975, 2938, 2821, 2232, 1647, 1602, 1578, 1486, 1460, 1436, 1412, 1384, 1178, 986, 799, 734, 684. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30. Found: C, 62.74; H, 5.22. The 1H and ^{13}C NMR spectra follow.

STANDARD 1H OBSERVE

exp1	std1h
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
12	12
13	13
14	14
15	15
16	16
17	17
18	18
19	19
20	20
21	21
22	22
23	23
24	24
25	25
26	26
27	27
28	28
29	29
30	30
31	31
32	32
33	33
34	34
35	35
36	36
37	37
38	38
39	39
40	40
41	41
42	42
43	43
44	44
45	45
46	46
47	47
48	48
49	49
50	50
51	51
52	52
53	53
54	54
55	55
56	56
57	57
58	58
59	59
60	60
61	61
62	62
63	63
64	64
65	65
66	66
67	67
68	68
69	69
70	70
71	71
72	72
73	73
74	74
75	75
76	76
77	77
78	78
79	79
80	80
81	81
82	82
83	83
84	84
85	85
86	86
87	87
88	88
89	89
90	90
91	91
92	92
93	93
94	94
95	95
96	96
97	97
98	98
99	99
100	100

SAMPLE	date	Mar 7 2006	DEC. & VI
solvent	CDCl3	dn	300.100
file	exp	dn	300.100
ACQUISITION	exp	dn	300.100
in	300.100	dm	300.100
at	H1	dm	300.100
at	1.995	dmf	300.100
at	1.994	dmf	300.100
np	12984	dmf	300.100
sw	4506.5	dmf	300.100
fb	not used	dmf	300.100
bs	16	dmf	300.100
tpwr	54	dmf	300.100
pw	7.0	dmf	300.100
dl	1.000	dmf	300.100
tof	0	dmf	300.100
rt	16	dmf	300.100
rt	16	dmf	300.100
rt	16	dmf	300.100
gain	not used	dmf	300.100
FLAGS	not used	dmf	300.100
ii	n	dmf	300.100
in	n	dmf	300.100
dp	y	dmf	300.100
DISPLAY	-302.0	dmf	300.100
sp	3677.2	dmf	300.100
wp	151	dmf	300.100
sc	0	dmf	300.100
sc	0	dmf	300.100
wc	250	dmf	300.100
hzmax	11.7.1	dmf	300.100
h1	438.03	dmf	300.100
rf1	716.6	dmf	300.100
rfp	45	dmf	300.100
th	100.000	dmf	300.100
ins	100.000	dmf	300.100
nmr	cdc	dmf	300.100
ph		dmf	300.100

JRMVII-75

13C OBSERVE

exp1 std13c

SAMPLE		DEC. & VT	
date	Mar 7 2006	dfrq	300.100
solvent	CDCl3	dn	H1
file	exp	dpwr	39
ACQUISITION		dm	0
sfrq	75.467	dm	yyv
tn	C13	dm	w
at	2.501	dmf	11000
np	113148	PROCESSING	
sw	22624.4	lb	0.50
fb	12400	wtfile	ft
bs	16	proc	262144
tpwr	55	fn	
pw	7.0	werr	
d1	2.000	wexp	
tof	-26.0	wbs	
nt	128	wnt	
ct	32		
alock	n	not used	
gain	not used		
il	n		
in	n		
dp	Y		
DISPLAY			
sp	-3737.7		
wp	22624.3		
vs	151		
sc	6		
wc	250		
hzmm	90.50		
is	500.00		
rfl	9625.6		
rfl	5827.8		
th	19		
ins	100.000		
nm	no	ph

4-Cyano-3-fluoro-N-methoxy-N-methylbenzamide (Table 2, entry 2).

Following general procedure A, a mixture of 4-bromo-2-fluorobenzonitrile (1mmol, 0.200 g), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na₂CO₃ (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 18 hours. The crude product mixture was purified by flash column chromatography on silica gel (20 % - 50 % ethyl acetate in hexanes) to provide the title compound as a light yellow-orange solid (181 mg, 95 %), mp 43 - 44 °C. ¹H NMR (300 MHz, CDCl₃) δ: 7.71-7.66 (m, 1H), 7.60-7.52 (m, 2H), 3.54 (s, 3H), 3.38 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 166.38, 164.23, 160.79, 140.84, 140.74, 133.36, 124.70, 124.65, 116.64, 116.35, 113.42, 103.26, 103.06, 61.59, 33.17 (observed complexity due to C-F splitting; definitive assignments have not yet been made). ¹⁹F NMR (282 MHz, CDCl₃) δ: -106.1. IR (neat, cm⁻¹): 3090, 2977, 2940, 2823, 2239, 1652, 1622, 1566, 1503, 1459, 1428, 1386, 1251, 1198, 1182, 1115, 990, 941, 887, 835, 750, 733, 714, 682, 668. Anal. Calcd for C₁₀H₉FN₂O₂: C, 57.69; H, 4.36. Found: C, 57.64; H, 4.37.

3-Nitro-N-methoxy-N-methylbenzamide (Table 2, entry 3).

Following general procedure A, a mixture of 3-bromonitrobenzene (1mmol, 0.202 g), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na₂CO₃ (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 8 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a tan colored solid (185 mg, 88 %), mp 41 - 43 °C. ¹H NMR (300 MHz, CDCl₃) δ: 8.60-8.58 (t, *J* = 19 Hz, 1H), 8.35-8.31 (ddd, *J* = 1.1, 2.5, 8.2 Hz, 1H), 8.07-8.03 (dt, *J* = 1.4, 7.7 Hz, 1H), 7.65-7.59 (t, *J* = 8 Hz, 1H), 3.57 (s, 3H), 3.41 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 167.02, 147.62, 135.43, 134.29, 129.22, 125.17, 123.41, 61.31, 33.13. IR (neat, cm⁻¹): 3087, 2974, 2938, 2822, 1648, 1616, 1577, 1532, 1485, 1459, 1438, 1417, 1383, 1351, 1215, 1170, 1099, 983, 918, 858, 815, 715. Anal. Calcd for C₉H₁₀N₂O₄: C, 51.43; H, 4.80. Found: C, 51.43; H, 4.70.

Thiophene-3- N-methoxy-N-methyl carboxamide (Table 2, entry 4).

Following general procedure A, a mixture of 3-bromothiophene (1mmol, 0.163 g, 94 μL, filtered through basic alumina prior to use), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na₂CO₃ (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 21 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a very light yellow oil (155 mg, 90 %). ¹H NMR (300 MHz, CDCl₃) δ: 8.09-8.06 (dd, *J* = 1.1, 3.0 Hz, 1H), 7.59-7.57 (dd, *J* = 1.1, 5.1, 1H), 7.31-7.27 (dd, *J* = 3.0, 5.2 Hz, 1H), 3.66 (s, 3H), 3.37 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 163.57, 134.37, 130.79, 128.95, 124.77, 61.10, 33.17. IR (neat, cm⁻¹): 3109, 2970, 2936, 2819, 1627, 1518, 1458, 1427, 1387, 1350, 1217, 1182, 1153, 1078, 985, 931, 881, 851, 816, 792, 733, 707, 667, 621. Anal. Calcd for C₇H₅NO₂S: C, 49.10; H, 5.30. Found: C, 49.40; H, 5.40.

4-Chloro-*N*-methoxy-*N*-methylbenzamide (Table 2, entry 5).

Following general procedure A, a mixture of 4-chloro-bromobenzene (1mmol, 0.191 g), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na₂CO₃ (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 19 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (173 mg, 87 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.79-7.64 (m, 2H), 7.41-7.36 (m, 2H), 3.54 (s, 3H), 3.37 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 168.53, 136.62, 132.27, 129.82, 128.21, 61.06, 33.43. IR (neat, cm⁻¹): 3067, 2970, 2935, 2818, 1917, 1643, 1594, 1567, 1490, 1460, 1416, 1380, 1275, 1213, 1176, 1148, 1111, 1091, 1016, 995, 979, 887, 840, 746, 691, 656, 627. Anal. Calcd for C₉H₁₀ClNO₂: C, 54.15; H, 5.05. Found: C, 54.23; H, 4.92.

***tert*-butyl *N*-methyl-*N*-(4-(*N*-methoxy-*N*-methylbenzamide)carbamate (Table 2, entry 6).**

Following general procedure A, a mixture of *tert*-Butyl *N*-(4-bromophenyl)carbamate (1mmol, 0.285 g), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na₂CO₃ (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 13 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a light brown oil (210 mg, 95 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.73-7.66 (m, 2H), 7.33-7.28 (m, 2H), 3.57 (s, 3H), 3.37 (s, 3H), 3.29 (s, 3H), 1.48 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ: 169.01, 154.18, 145.69, 130.13, 128.71, 124.15, 80.58, 60.89, 36.83, 33.62, 28.14, 27.70. IR (neat, cm⁻¹): 2976, 2934, 2819, 1791, 1703, 1644, 1607, 1569, 1512, 1477, 1456, 1422, 1367, 1315, 1300, 1279, 1254, 1216, 1153, 1109, 1065, 1018, 995, 977, 889, 851, 807, 770, 758, 734, 700. Anal. Calcd for C₁₅H₂₂N₂O₄: C, 61.21; H, 7.53. Found: C, 60.91; H, 7.75.

4-*N*-Dimethoxy-*N*-methylbenzamide (Table 2, entry 7).

Following general procedure A, a mixture of 4-bromoanisole (1mmol, 0.187 g, 125 μL, filtered through basic alumina prior to use), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na₂CO₃ (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 8 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (210 mg, 95 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.77-7.70 (m, 2H), 6.94-6.88 (m, 2H), 3.85 (s, 3H), 3.57 (s, 3H), 3.36 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 169.21, 161.39, 130.39, 125.84, 113.11, 60.73, 55.16, 33.74. IR (neat, cm⁻¹): 3074, 3002, 2966, 2936, 2840, 2559, 2048, 1639, 1608, 1575, 1512, 1462, 1421, 1375, 1304, 1255, 1216, 1173, 1112, 1064, 1029, 994, 977, 888, 842, 796, 756, 703, 676, 631, 593. Anal. Calcd for C₁₀H₁₃NO₃: C, 61.53; H, 6.71. Found: C, 61.29; H, 6.69.

***N*-Methoxy-*N*-methyl-isophthalamic acid methyl ester (Table 2, entry 8).** Following general procedure A, a mixture of methyl 3-bromobenzoate (1mmol, 0.215 g), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5

equiv., 146 mg), Na₂CO₃ (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 24 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (196 mg, 88 %). ¹H NMR (300 MHz, CDCl₃) δ: 8.38-8.33 (t, *J* = 1.7 Hz, 1H), 8.17-8.10 (ddd, *J* = 1.4, 1.7, 7.9 Hz, 1H), 7.91-7.84 (ddd, *J* = 1.4, 1.7, 7.7 Hz, 1H), 7.54-7.46 (dt, *J* = 1.7, 7.7 Hz, 1H), 3.94 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 168.69, 166.18, 134.32, 132.41, 131.37, 129.88, 129.19, 128.13, 60.99, 52.13, 33.30. IR (neat, cm⁻¹): 3072, 2953, 1725, 1645, 1582, 1487, 1435, 1381, 1300, 1278, 1208, 1170, 1109, 1085, 991, 972, 922, 824, 772, 724, 665, 633, 575. Anal. Calcd for C₁₁H₁₃NO₄: C, 59.19; H, 5.87. Found: C, 58.98; H, 5.78.

3-[1,3]Dioxolan-2-yl-*N*-methoxy-*N*-methyl-benzamide (Table 2, entry 9). Following general procedure A (a screw-capped test tube with a Teflon-lined septum was used in place of the culture tube and rubber septum), a mixture of 2-(3-bromophenyl)-1,3-dioxolane (1mmol, 151 mL, filtered through basic alumina prior to use),

Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), triethylamine (3 mmol, 3 equiv., 420 mL), and toluene (1 mL) was heated at 80 °C for 15 hours. The crude product mixture was purified by flash column chromatography on silica gel (67 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (220 mg, 93 %). ¹H NMR (400 MHz, CDCl₃) 7.78 (s, 1 H), 7.67 (d, 1 H, *J* = 7.5 Hz), 7.56 (d, 1 H, *J* = 7.5 Hz), 7.41 (dd, 1 H, *J* = 7.5 Hz), 5.83 (s, 1 H), 4.00-4.14 (m, 4 H), 3.53 (s, 3 H), 3.33 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃) δ 169.4, 138.0, 134.1, 128.8, 128.6, 128.0, 126.3, 103.1, 65.2, 60.9, 33.6. IR (CDCl₃, cm⁻¹) 2972, 2937, 2892, 1639. Anal. Calcd. for C₁₂H₁₅NO₄: C, 60.75, H: 6.37; Found C: 60.37, H: 6.35.

3,4,*N*-Trimethoxy-*N*-methyl-benzamide (Table 2, entry 10).

Following general procedure A (a screw-capped test tube with a Teflon-lined septum was used in place of the culture tube and rubber septum), a mixture of 4-bromoveratrole (1mmol, 144 μL, filtered through basic alumina prior to use), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), triethylamine (3 mmol, 3 equiv., 420 μL), and toluene (1 mL) was heated at 80 °C for 15 hours. The crude product mixture was purified by flash column chromatography on silica gel (67 % ethyl acetate in hexanes) to provide the title compound as a colorless solid (202 mg, 90 %), mp 55 – 57 °C. ¹H NMR (400 MHz, CDCl₃) 7.39 (dd, 1 H, *J* = 2 Hz, 8 Hz), 7.32 (d, 1 H, *J* = 2 Hz), 6.87 (d, 1 H, *J* = 8 Hz), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.58 (s, 3 H), 3.36 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃) δ 168.9, 150.8, 148.0, 125.9, 121.8, 111.7, 109.9, 60.7, 55.7, 55.6, 33.7. IR (CDCl₃, cm⁻¹) 2966, 2937, 1631, 1517. m. p. 56 - 57 °C. Anal. Calcd. for C₁₁H₁₅NO₄: C, 58.66, H: 6.71; Found C: 58.61, H: 6.77.

Biphenyl-4- N-methoxy-N-methyl carboxamide (Table 2, entry 11).³

Following general procedure A (a screw-capped test tube with a Teflon-lined septum was used in place of the culture tube and rubber septum), a mixture of 4-bromobiphenyl (1mmol, 0.233 g), Pd(OAc)₂ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), triethylamine (3 mmol, 3 equiv., 420 μ L), and toluene (1 mL) was heated at 80 °C for 15 hours. The crude product mixture was purified by flash column chromatography on silica gel (40 % ethyl acetate in hexanes) to provide the title compound as a colorless solid (226 mg, 94 %), mp 80 – 82 °C, lit. mp 77 – 78 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.77-7.81 (m, 2 H), 7.61-7.67 (m, 4 H), 7.37-7.50 (m, 3 H), 3.61 (s, 3 H), 3.40 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃) δ 169.5, 143.2, 140.0, 132.7, 128.8, 128.7, 127.8, 127.1, 126.6, 61.0, 33.7. IR (CDCl₃, cm⁻¹) 2971, 2936, 1632.

N-Methoxy-2,5,N-trimethyl-benzamide (Table 3, entry 1).

Following general procedure B, a mixture of 2-bromo-*p*-xylene (1mmol, 0.185 g, 138 μ L), Pd(OAc)₂ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) of the title compound as a colorless oil (166 mg, 86 %). ¹H NMR (300 MHz, CDCl₃) δ : 7.12-7.06 (m, 3H), 3.56 (brs, 3H), 3.31 (brs, 3H), 2.32 (s, 3H), 2.29 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ : 169.8, 134.5, 133.9, 130.6, 129.2, 129.2, 129.0, 125.8, 59.9, 31.9, 19.8, 17.7. IR (neat, cm⁻¹): 3018, 2969, 2932, 2818, 2736, 1903, 1844, 1651, 1612, 1577, 1502, 1459, 1422, 1375, 1287, 1242, 1181, 1157, 1126, 1062, 1041, 998, 980, 922, 887, 838, 816, 777, 746, 706, 694, 642, 597. Anal. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82. Found: C, 68.28; H, 7.86.

Naphthalene-1- N-methoxy-N-methyl carboxamide (Table 3, entry 2).

Following general procedure B, a mixture of 1-bromonaphthalene (1mmol, 0.207 g, 139 μ L), Pd(OAc)₂ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) of the title compound as a light orange oil (208 mg, 97 %). ¹H NMR (300 MHz, CDCl₃) δ : 7.94-7.85 (m, 3H), 7.58-7.47 (m, 4H), 3.4 (brs, 6H). ¹³C NMR (75 MHz, CDCl₃) δ : 169.1, 132.7, 129.1, 128.9, 127.8, 126.3, 125.3, 124.3, 124.2, 123.7, 60.5, 32.4. IR (neat, cm⁻¹): 3280, 3056, 3005, 2971, 2935, 2817, 1947, 1820, 1651, 1592, 1580, 1508, 1474, 1439, 1422, 1374, 1266, 11232, 1183, 1167, 1102, 1027, 1014, 975, 891, 865, 801, 779, 740, 697, 647, 629, 580. Anal. Calcd for C₁₃H₁₃NO₂: C, 72.54; H, 6.09. Found: C, 72.16; H, 6.12.

2-Cyano-*N*-methoxy-*N*-methyl-benzamide (Table 3, entry 3). Following general procedure B, a mixture of 2-bromobenzonitrile (1mmol, 0.182 g), Pd(OAc)₂ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) the title compound as a colorless oil (161 mg, 84 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.74-7.70 (ddd, *J* = 0.55, 1.38, 7.7 Hz, 1H), 7.69-7.50 (m, 3H), 3.52 (brs, 3H), 3.40 (brs, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 166.5, 138.2, 132.4, 132.3, 129.7, 127.3, 116.6, 109.9, 61.0, 32.3. IR (neat, cm⁻¹): 3292, 3071, 2976, 2938, 2822, 2229, 1657, 1595, 1572, 1492, 1459, 1445, 1421, 1385, 1289, 1219, 1191, 1168, 1117, 1062, 1036, 982, 891, 772, 759, 720, 687, 634. Anal. Calcd for C₁₀H₁₀N₂O₂: C, 63.15; H, 5.30. Found: C, 63.42; H, 5.29.

***N*-Methoxy-*N*-methyl-phthalamic acid methyl ester (Table 3, entry 4).** Following general procedure B, a mixture of methyl 2-bromobenzoate (1mmol, 0.215 g, 140 μL), Pd(OAc)₂ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (20 - 50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (186 mg, 83 %). ¹H NMR (300 MHz, CDCl₃) δ: 8.04-7.97 (d, *J* = 7.7 Hz, 1H), 7.63-7.55 (dt, *J* = 1.4, 7.4 Hz, 1H), 7.52-7.45 (dt, *J* = 1.4, 7.7 Hz, 1H), 7.45-7.38 (d, *J* = 7.4 Hz, 1H), 3.91 (s, 3H), 3.74 (brs, 3H), 3.35 (brs, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 172.0, 166.1, 137.2, 132.3, 129.7, 128.9, 127.7, 126.9, 60.9, 52.4, 33.1. IR (neat, cm⁻¹): 3067, 2953, 2939, 2904, 2820, 2845, 1726, 1662, 1599, 1578, 1492, 1459, 1413, 1435, 1379, 1280, 1211, 1192, 1166, 1130, 1091, 1062, 1040, 991, 964, 883, 828, 802, 777, 739, 723, 703, 667, 631, 576. Anal. Calcd for C₁₁H₁₃NO₄: C, 59.19; H, 5.87. Found: C, 59.17; H, 5.90.

2, *N*-Dimethoxy-*N*-methyl-benzamide (Table 3, entry 5).⁴ Following general procedure B, a mixture of 2-bromoanisole (1mmol, 0.187 g, 125 μL, filtered through basic alumina prior to use), Pd(OAc)₂ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) of the title compound as a colorless plates (174 mg, 89 %), mp 47 – 49 °C. ¹H NMR (300 MHz, CDCl₃) δ: 7.40-7.32 (ddd, *J* = 1.6, 7.4, 8.2 Hz, 1H), 7.30-7.24 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.01-6.95 (dt, *J* = 0.8, 7.4 Hz, 1H), 6.95-6.90 (d, *J* = 8.3 Hz, 1H), 3.84 (s, 3H), 3.49 (brs, 3H), 3.33 (brs, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 168.8, 155.2, 130.1, 126.9, 124.7, 119.9, 110.6, 60.4, 55.1, 31.6. IR (neat, cm⁻¹): 3067, 3003, 2970, 2938, 2939, 1651, 1601, 1584, 1495, 1465, 1437, 1418, 1381,

1284, 1249, 1209, 1182, 1164, 1116, 1064, 1045, 1022, 987, 940, 884, 795, 758, 697, 630. Anal. Calcd for C₁₀H₁₃NO₃: C, 61.53; H, 6.71. Found: C, 61.46; H, 6.76.

4-Cyano-*N*-methoxy-*N*-methylbenzamide (Table 3, entry 6).

Following general procedure B, a mixture of 4-chlorobenzonitrile (1mmol, 0.146 g), Pd(OAc)₂ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 105 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (149 mg, 78 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.81-7.64 (m, 4H), 3.53 (s, 3H), 3.38 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 167.7, 138.2, 131.7, 128.6, 118.0, 113.8, 61.2, 33.0. IR (neat, cm⁻¹): 3093, 3066, 2974, 2938, 2821, 2230, 1937, 1651, 1609, 1560, 1507, 1461, 1422, 1383, 1286, 1215, 1180, 1149, 1115, 1065, 1020, 980, 889, 851, 7777, 754, 703, 668, 638, 575. Anal. Calcd for C₁₀H₁₀N₂O₂: C, 63.15; H, 5.30. Found: C, 63.12; H, 5.33.

2-trifluoromethyl-*N*-Methoxy-*N*-methylbenzamide (Table 3, entry 7).

Following general procedure B, a mixture of 2-bromobenzotrifluoride (1mmol, 0.225 g, 136 μL, filtered through basic alumina prior to use), Pd(OAc)₂ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and *m*-xylene (2 mL) was heated at 110 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (20 - 50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil and a 1.1:1 mixture of rotamers (214 mg, 92 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.75-7.67 (d, J = 7.4 Hz, 1H), 7.65-7.50 (m, 2H), 7.46-7.40 (m, 1H), 3.89 (brs, 0.6H), 3.42 (s, 2.4H), 3.37 (s, 2.3H), 3.05 (brs, 0.7H). ¹³C NMR (75 MHz, CDCl₃) δ: 169.1, 164.4, 133.7, 132.1, 131.3, 129.5, 128.9, 127.2, 126.8, 126.2, 1259, 125.3, 121.6, 118.0, 60.4, 59.7, 36.1, 31.9 (observed complexity due to C-F splitting; definitive assignments have not yet been made). ¹⁹F NMR (282 MHz, CDCl₃) δ: -60.2. IR (neat, cm⁻¹): 3071, 2977, 2941, 2823, 1667, 1606, 1584, 1503, 1426, 1445, 1416, 1384, 1317, 1272, 1213, 1171, 1130, 1077, 1049, 1034, 991, 961, 891, 879, 772, 742, 708, 655, 632. Anal. Calcd for C₁₀H₁₀F₃NO₂: C, 51.51; H, 4.32. Found: C, 51.61; H, 4.36.

3-Methylpyridine-2-*N*-methoxy-*N*-methylcarboxamide (Table 3, entry 8).

Following general procedure B, a mixture of 2-bromo-3-methylpyridine (1mmol, 0.172 g, 111 μL), Pd(OAc)₂ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and *m*-xylene (2 mL) was heated at 110 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 - 60 % ethyl acetate in hexanes) to provide the title compound as a light yellow oil and a 1:1 mixture of rotamers (140 mg, 77 %). ¹H NMR (300 MHz, CDCl₃) δ: 8.44-8.36 (dd, J = 0.8, 4.7 Hz, 1H), 7.60-7.48 (d, J = 7.1 Hz, 1H), 7.27-7.16 (dd, J = 4.9, 7.7 Hz, 1H), 3.89 (brs, 0.6H), 3.52 (s, 2.4H), 3.37 (s, 2.4H), 3.13 (brs, 0.6H). ¹³C NMR (75 MHz, CDCl₃) δ: 168.8, 153.3, 145.7, 137.5,

129.8, 123.4, 61.1, 31.4, 17.1. IR (neat, cm^{-1}): 3055, 2977, 2938, 2821, 1655, 1575, 1485, 1446, 1407, 1384, 1274, 1260, 1238, 1186, 1169, 1119, 1072, 983, 896, 889, 818, 800, 743, 692, 639, 580. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$: C, 59.99; H, 6.71. Found: C, 59.53; H, 6.72. The ^1H and ^{13}C NMR spectra follow.

STANDARD 1H OBSERVE

exp2 std1h

date Jul 12 2006 DEC. & VT
 solvent CDCl3 d1 300.100
 file /data/export/* d1 30
 home/slbuch/41m/mr~ dof 0
 hat/jrm9-123-H.fid dm nnn
 ACQUISITION dnm C
 sfrq 300.100 dmf 200
 in H1
 at 1.995 wfile
 np 1.7984 proc
 sw 4596.5 fn not used
 fb not used
 bs 16 verr
 tpwr 54 wexp
 pw 7.0 wbs
 d1 1.000 vnt
 tof 0
 nt 16
 ct 16
 alock n
 gain not used
 flags n
 il n
 in n
 dp n
 DISPLAY y
 SP -255.0
 WP 3260.8
 VS 151
 SC 0
 WC 250
 hzmm 13.08
 ts 286.09
 rfl 2898.6
 rfp 2181.7
 th 20
 ins 100.000
 nm cdc ph

13C OBSERVE

exp2 std13c

SAMPLE DEC. & VT
 date Jul 12 2006 dtrq 300.100
 solvent CDCl3 dn H1
 file /data/export/~ dpwr 39
 home/slbuch/tjm/mr~ dof 0
 hat/jrm9-123-c.fid dn yyy
 ACQUISITION dem 11000
 sfrq 75.167 dmf 11000
 tn C13
 at 2.501 lb PROCESSING 0.50
 np 113148 vifile
 ew 26521.4 proc ft
 fb 12100 fn 262144
 bs 16
 tpwr 55 verr
 pw 7.0 vexp
 dt 2.000 vst
 tof -20.0 vnt
 nt 128
 ct 96
 alock not used n
 gain FLAGS
 ll n
 in n
 dp DISPLAY y
 sp -1468.3
 wp 18827.0
 vs 151
 sc 0
 wc 250
 hznm 67.31
 fs 500.00
 rfl 9644.6
 rfp 5827.8
 th 20
 ins 100.000
 nm no ph

2-Cyclohexyl-*N*-methoxy-*N*-methylbenzamide (Table 3, entry 9).

Following general procedure B, a mixture of 1-bromo-2-cyclohexylbenzene (1mmol, 0.239 g), Pd(OAc)₂ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and *m*-xylene (2 mL) was heated at 120 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (30 - 50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) of the title compound as a viscous colorless oil (213 mg, 86 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.41-7.30 (m, 2H), 7.24-7.14 (m, 2H), 3.85 (brs, 1H), 3.38 (brs, 5H), 2.75 (brs, 1H), 1.60-1.95 (m, 5H), 1.2-1.58 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ: 171.1, 143.9, 134.2, 128.7, 125.6, 125.4, 124.8, 60.2, 41.0, 33.6, 31.6, 26.3, 25.5. IR (neat, cm⁻¹): 3292, 3061, 3025, 2926, 2851, 2817, 2668, 1651, 1599, 1575, 1489, 1448, 1410, 1378, 1264, 1218, 1193, 1168, 1140, 1117, 1093, 1060, 1044, 989, 893, 884, 863, 829, 771, 755, 705, 644, 634, 625, 577, 530. Anal. Calcd for C₁₅H₂₁NO₂: C, 72.84; H, 8.56. Found: C, 72.66; H 8.54.

2,5-Difluoro-*N*-methoxy-*N*-methylbenzamide (Table 3, entry 10).

Following general procedure B, a mixture of 2,5-difluorobromobenzene (1mmol, 0.193 g, filtered through basic alumina prior to use), Pd(OAc)₂ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N*, *O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K₃PO₄ (3 mmol, 3 equiv., 637 mg), and *m*-xylene (2 mL) was heated at 110 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (140 mg, 70 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.19-7.03 (m, 3H), 3.56 (brs, 3H), 3.36 (brs, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 164.7, 159.7, 156.4, 156.1, 152.9, 124.7, 124.6, 124.4, 124.3, 117.9, 117.6, 117.1, 117.0, 116.8, 116.7, 115.4, 115.1, 61.1, 31.9 (observed complexity due to C-F splitting; definitive assignments have not yet been made). ¹⁹F NMR (282 MHz, CDCl₃) δ: -118.8, -120.4. IR (neat, cm⁻¹): 3074, 2977, 2940, 2823, 1659, 1599, 1495, 1437, 1405, 1383, 1266, 1251, 1205, 1149, 1104, 1059, 992, 939, 879, 851, 822, 786, 735, 706, 690, 640, 604. Anal. Calcd for C₉H₅F₂NO₂: C, 53.73; H, 4.51. Found: C, 53.50; H, 4.55.

References

- ¹ (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.
- ² (a) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *64*, 6790. (b) Deetz, M. J.; Forbes, C. C.; Jonas, M.; Malerich, J. P.; Smith, B. D.; Wiest, S. *J. Org. Chem.* **2002**, *67*, 3949.
- ³ De Voss, J. J.; Sui, Z.; DeCamp, D. L.; Salto, R.; Babé, L. M.; Craik, C. S.; Ortiz de Montellano, P. R. *J. Med. Chem.* **1994**, *37*, 665.
- ⁴ Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20*, 1105.