Supplementary Material for:

Surprisingly Facile C-H Activation in the Course of Oxime-Directed Catalytic Asymmetric Hydroboration

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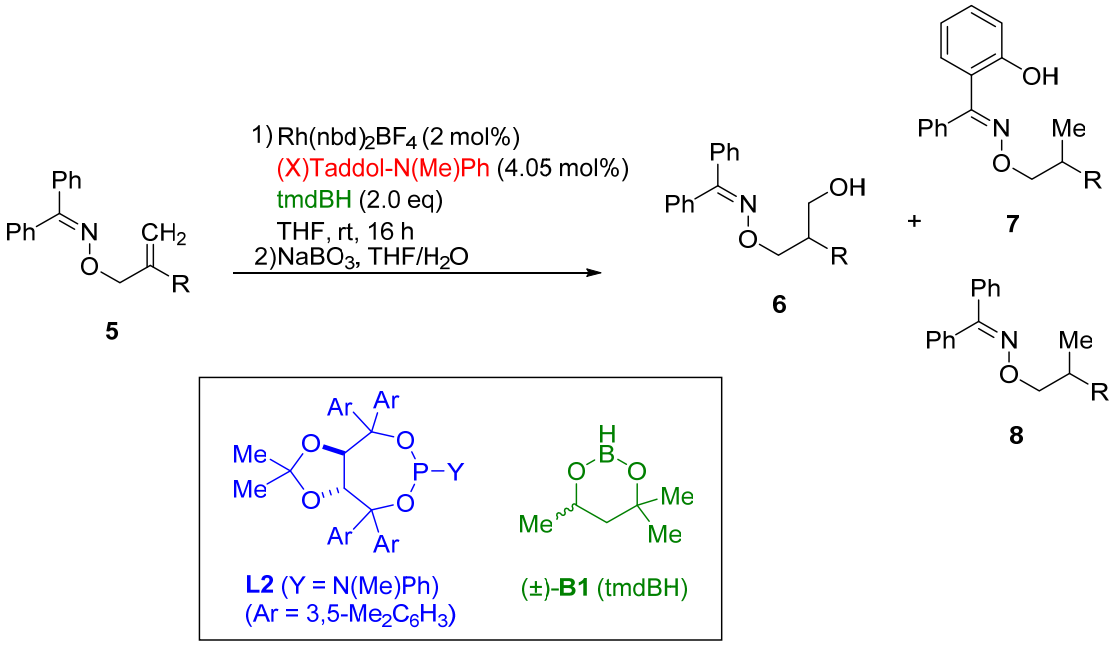
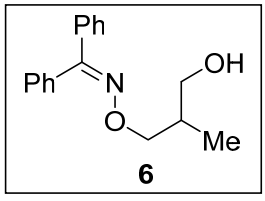
General information

Reactions were carried out in a dry atmosphere (N_2). Dichloromethane (DCM), tetrahydrofuran (THF), and methanol (MeOH) were freshly distilled under the following conditions: DCM from calcium hydride, THF from sodium metal and benzophenone, and MeOH from Mg. All synthesized compounds were purified with flash chromatography with the indicated solvents using EMD Silica Gel 60 Geduran ®. Thin layer chromatography analyses were performed on Analtech Silica Gel HLF (0.25 m) precoated analytical plates and visualized with use of handheld short wavelength UV light, vanillin stain (ethanol, H_2SO_4, and vanillin), and ninhydrin stain (ethanol, acetic acid, and ninhydrin). All reactions were performed in a chemical fume hood or in a glovebox with a nitrogen environment. NMR spectra were recorded on either a 400 MHz or a 300 MHz Bruker Advance NMR spectrometer using $CHCl_3$ (δ 7.27 ppm), $CDCl_3$ (δ 77.0 ppm), or CH_2Cl_2 (δ 5.30 ppm) for reference. Gas chromatography analysis was performed with a CP-Chirasil-Dex CB column (I.D. = 0.25 mm) using a temperature program of 140-200 ^{o}C at 1 ^{o}C/min). Peaks are expressed as m (unresolved multiplet), q (quartet), t (triplet), d (doublet), s (singlet), bs (broad singlet). IR spectra were recorded using an Avatar 360 FT-IR. Optical rotations were measured in solutions, 1.0 g/100 mL CH_3Cl unless indicated otherwise, and recorded using an Autopol III automatic polarimeter. HRMS analyses were performed by the Nebraska Center for Mass Spectrometry. All phenolic tethers were prepared using procedures described in the literature.

Typical Rh-CAHB reaction

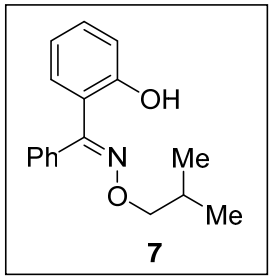


To a vial containing $Rh(nbd)_2BF_4$ (3.0 mg, 7.93 μmol) was added **L2** (11.4 mg, 16.0 μmol) in THF (1 mL) and stirred for 1 hour for complexation (solution changes from colorless to yellow instantaneously). A 1 mL aliquot of the resulting $Rh[(\mathbf{L2})_2(nbd)]BF_4$ solution was added to a 50 mL round bottom flask with stir bar. The resulting yellow solution was added β,γ-unsaturated oxime **5a** (66.3 mg, 0.26 mmol) as a solution in THF (2 mL). The reaction mixture was stirred for 30 minutes at RT and then cooled in an ice bath. To the cooled solution (0 °C) was added dropwise (over the course of 20 minutes) a solution of 4,4,6-trimethyl-1,3,2-dioxaborinane (tmdBH, **B1**, 67.6 mg, 0.53 mmol) in THF (1 mL). The mixture was allowed to warm to room temperature and stirred for 4 hours. Afterwards, the reaction mixture was concentrated and reduced product **8** was separated via flash chromatography on silica gel (20:80 EtOAc/hexanes) as a clear oil. The inseparable ortho-borylated and γ-borylated products were concentrated and added a 1:3 water/THF mixture. $NaBO_3$-monohydrate (300 mg, 300 mmol) was added and the reaction mixture was stirred vigorously. After a 6 hour stir, the resultant mixture was extracted with EtOAc (3 x 15 mL) and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified via flash chromatography on silica gel (20:80 EtOAc/hexanes) afforded **6** and **7** as colorless oils.



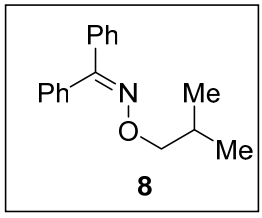
Benzophenone O-(3-hydroxy-2-methylpropyl) oxime (γ-hydroxylated product **6**) β,γ-unsaturated substrate **5a** (66.3 mg, 0.24 mmol) was converted to γ-hydroxylated product **6** (40.7 mg, 57%) as a colorless oil. TLC analysis (30:70 EtOAc/hexanes) showed a spot at Rf 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.33 (10H, m), 4.29 and 4.13 (2H, ddd, J_1 = 4.6= Hz, J_2 = 7.5

Hz), 3.64-3.52 (2H, m), 2.18-2.11 (1H, m), 2.01 (1H, t, J = 5.5 Hz), 0.94 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 136.1, 133.3, 129.5, 128.9, 128.9, 128.3, 128.2, 127.8, 77.9, 66.3, 35.8, 13.5; IR (neat) 3360 (O-H stretch), 3041 (C-H aromatic stretch), 2924 (C-H aliphatic), 1585 (C=N stretch), 1434 (N-O stretch), 989 (C-O stretch) cm^{-1}.



7

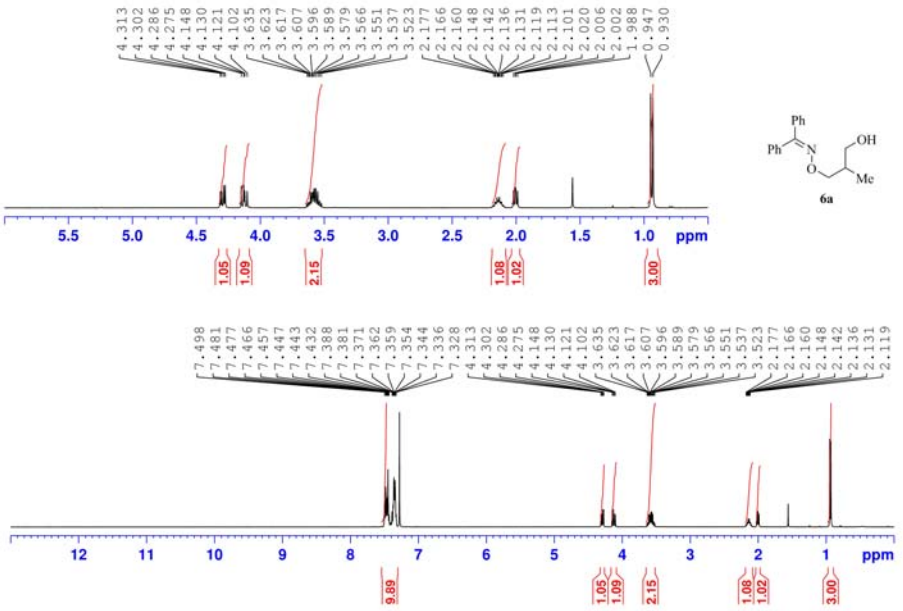
(2-hydroxyphenyl)(phenyl methanone O-isobutyl oxime (*Ortho*-hydroxylated and reduced product **7**) β,γ-unsaturated substrate **5a** (66.3 mg, 0.24 mmol) was converted to *ortho*-hydroxylated / reduced product **7** (22.3 mg, 31%) as a colorless oil. TLC analysis (10:90 EtOAc/hexanes) showed a spot at Rf 0.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (1H, s), 7.52-7.47 (3H, m), 7.32-7.24 (3H, m), 7.03 (1H, d, *J* = 8.9 Hz), 6.84-6.77 (1H, m), 6.73 (1H, t, *J* = 8.0 Hz), 3.94 (2H, d, *J* = 6.9 Hz), 2.10-2.00 (1H, m), 0.90 (2H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 158.2, 132.0, 130.7, 130.5, 128.9, 128.4, 128.3, 118.8, 118.8, 117.1, 81.5, 27.9, 19.0; IR (neat) 3055 (C-H aromatic stretch), 2958 (C-H aliphatic), 1588 (C=N stretch), 1438 (N-O stretch), 996 (C-O stretch) cm^{-1}.



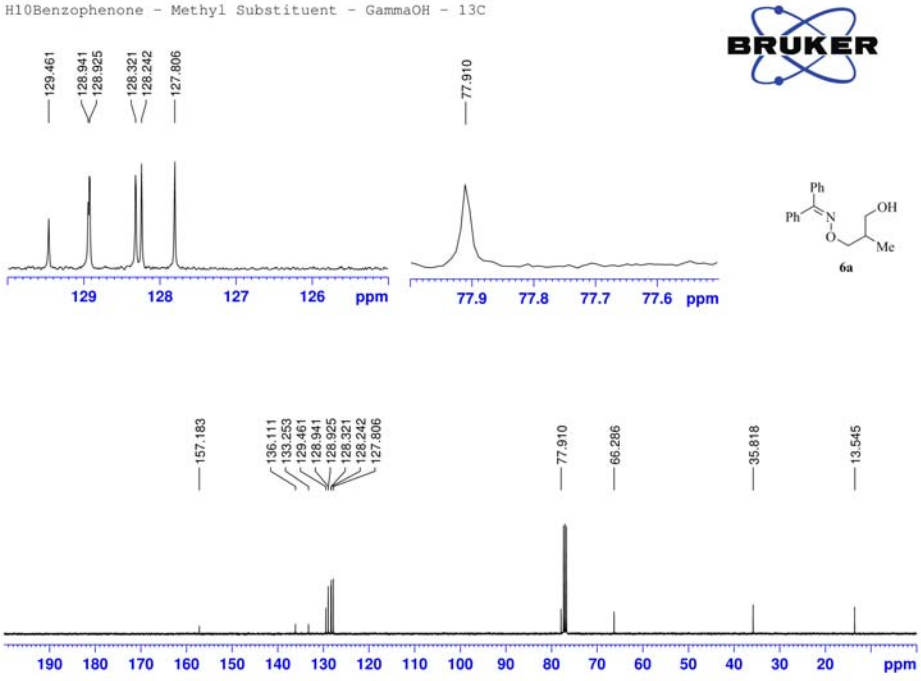
8

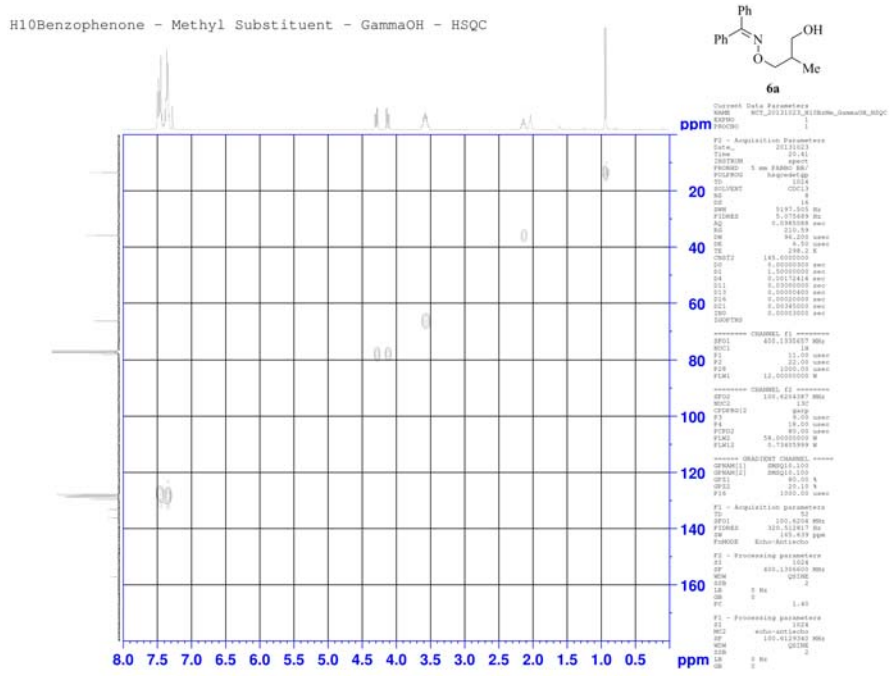
Benzophenone O-isobutyl oxime (Reduced product **8**) β,γ-unsaturated substrate **5a** (66.3 mg, 0.24 mmol) was converted to reduced product **8** (6.8 mg, 10%) as a colorless oil. TLC analysis (10:90 EtOAc/hexanes) showed a spot at Rf 0.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.31 (10H, m), 3.98 (2H, d, *J* = 6.8 Hz), 2.12-2.02 (1H, m), 0.93 (6H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 136.44, 135.6, 129.3, 129.1, 128.6, 128.2, 128.0, 127.8, 81.2, 28.1, 19.2; IR (neat) 3054 (C-H aromatic stretch), 2958 (C-H aliphatic), 1588 (C=N stretch), 1438 (N-O stretch), 996 (C-O stretch) cm^{-1}.

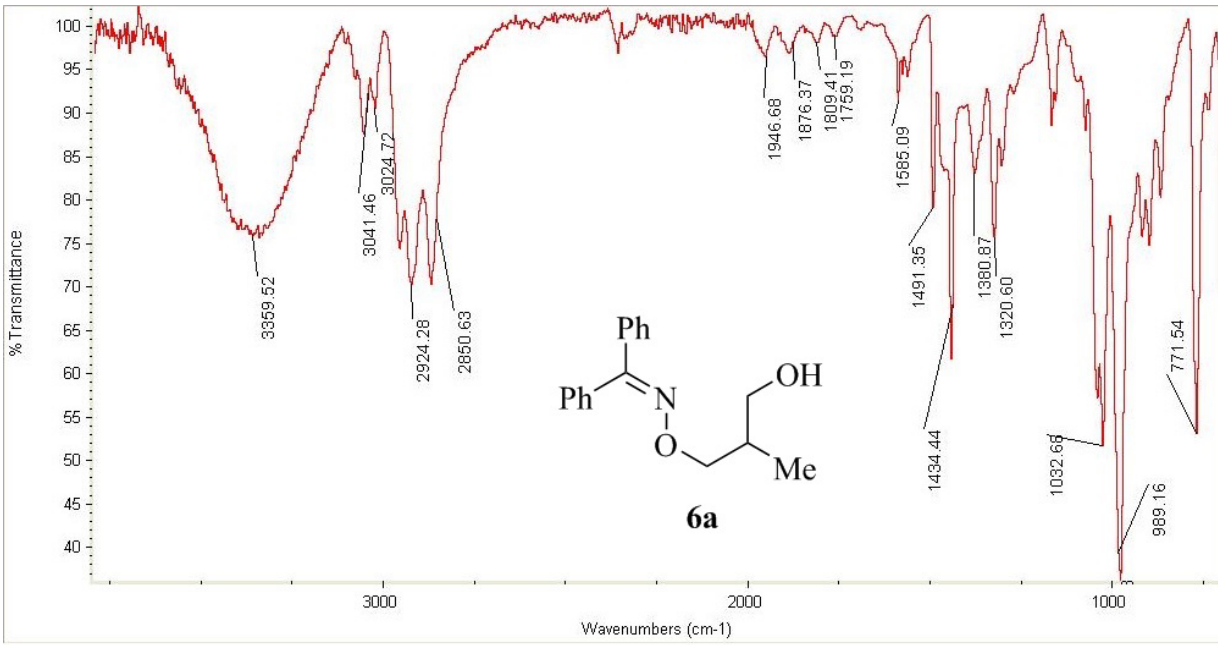
benzophenone oxime- Me substituent-gammaOH-1H



H10Benzophenone - Methyl Substituent - GammaOH - 13C




H10Benzophenone - Methyl Substituent - GammaOH - HSQC
Ph
Ph
N
O
OH
Me
6a
ppm
20
40
60
80
100
120
140
160
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
3359.52
3041.46
3024.72
2924.28
2850.63
1946.68
1876.37
1809.41
1759.19
1585.09
1491.35
1434.44
1380.87
1320.60
1032.68
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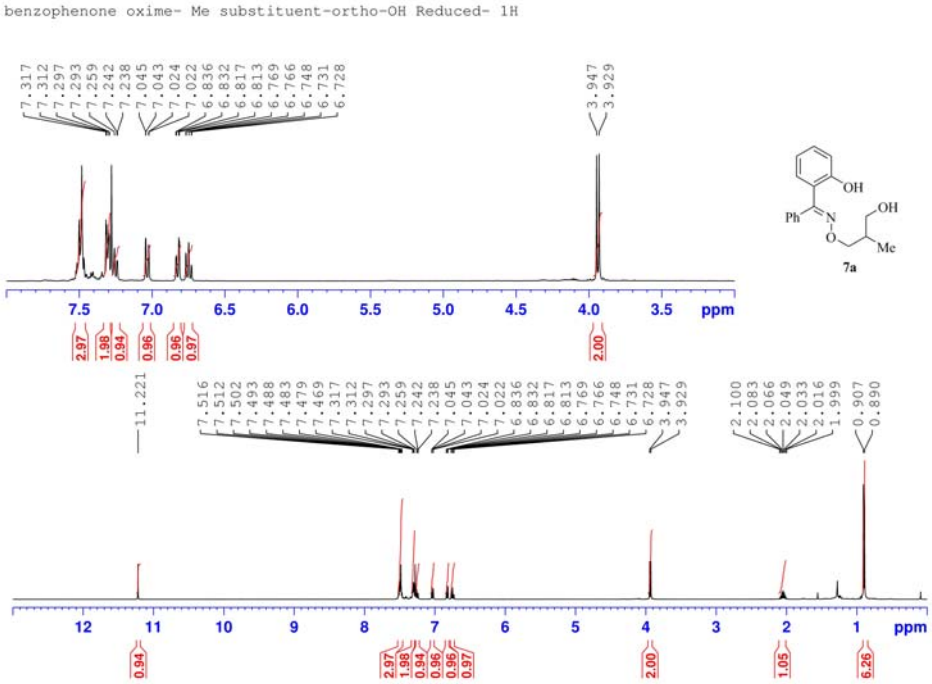
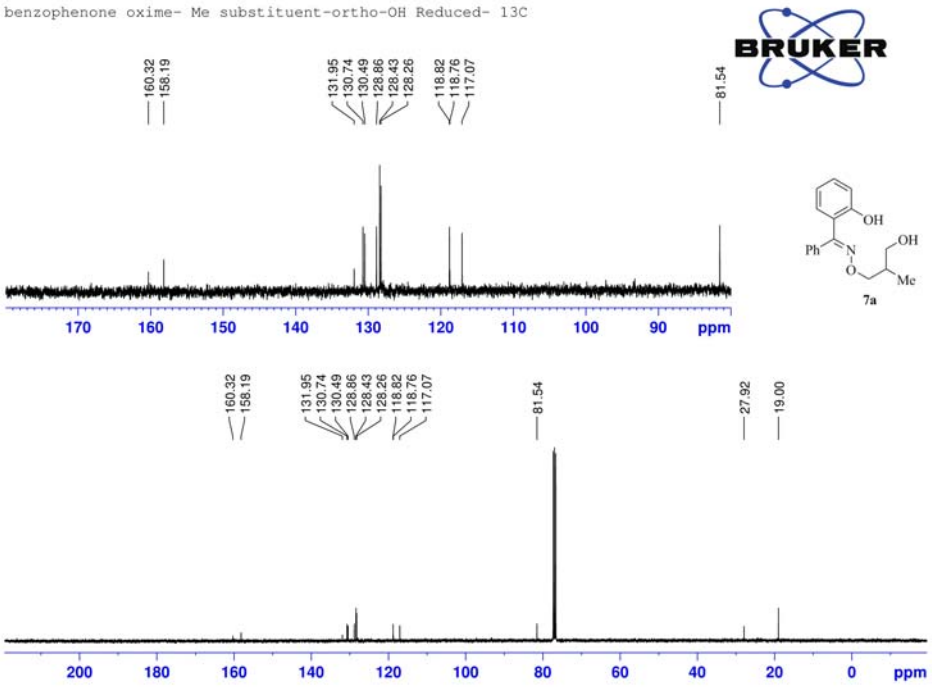
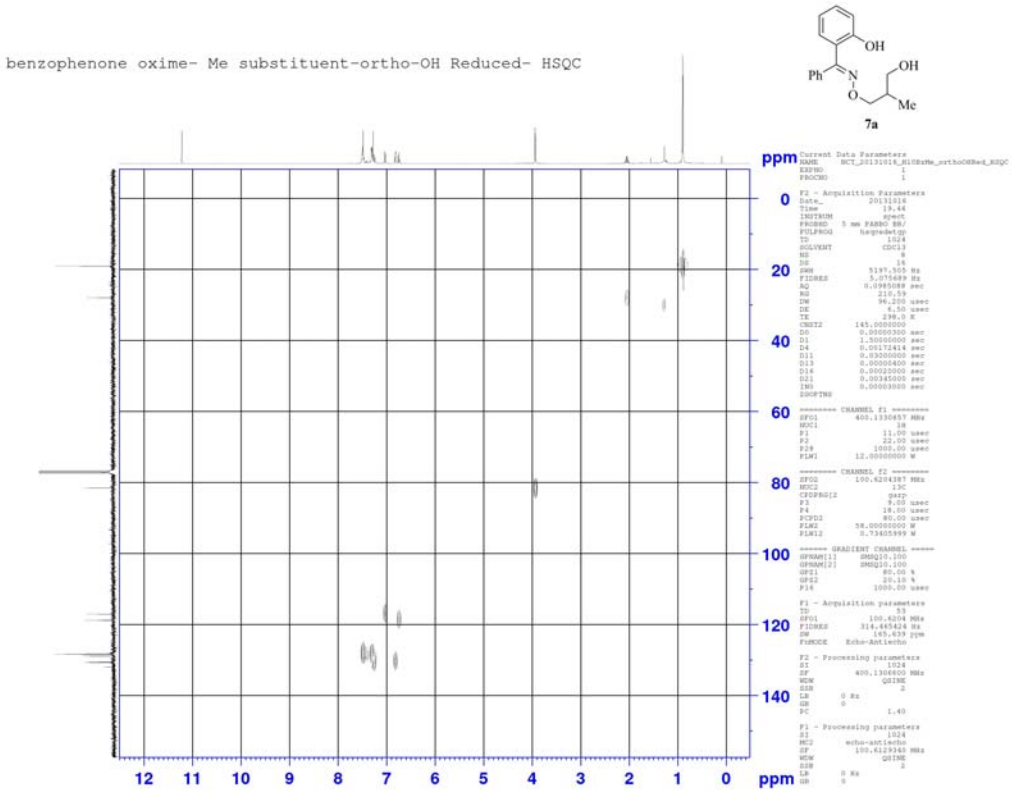
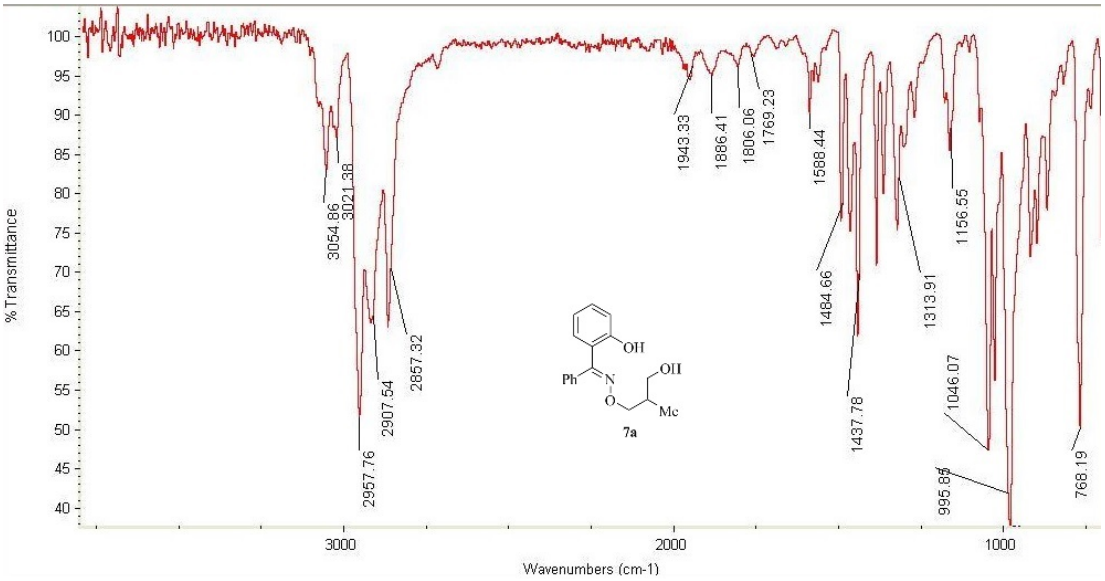
771.54
Ph
Ph
N
O
OH
Me
6a
3000
2000
1000
Wavenumbers (cm-1)

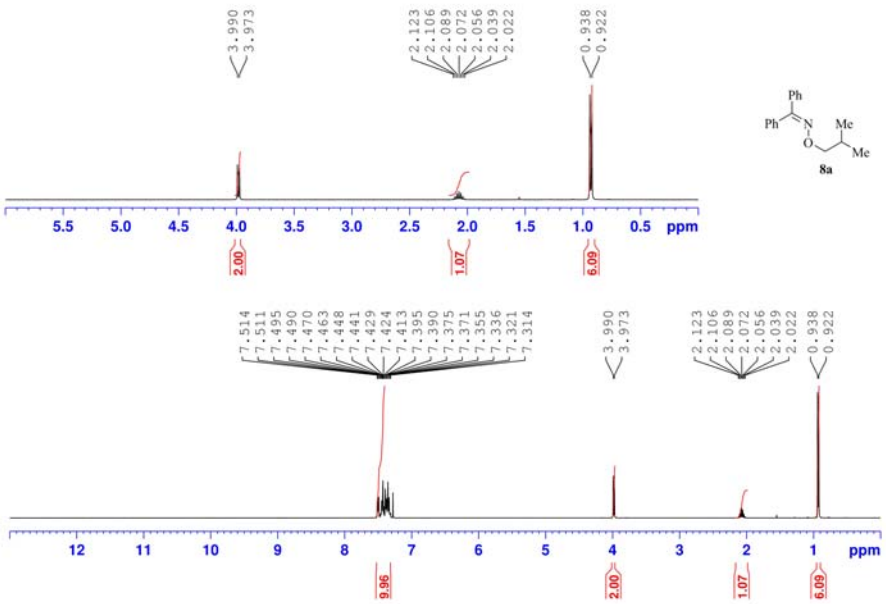

benzophenone oxime- Me substituent-ortho-OH Reduced- 1H
7.317
7.312
7.297
7.293
7.259
7.242
7.238
7.045
7.043
7.024
7.022
6.836
6.832
6.817
6.813
6.769
6.766
6.748
6.731
6.728
3.947
3.929
OH
Ph
N
O
OH
Me
7a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
2.97
1.98
0.94
0.96
0.96
0.97
2.00
11.221
7.516
7.512
7.502
7.493
7.488
7.483
7.479
7.469
7.317
7.312
7.297
7.293
7.259
7.242
7.238
7.045
7.043
7.024
7.022
6.836
6.832
6.817
6.813
6.769
6.766
6.748
6.731
6.728
3.947
3.929
2.100
2.083
2.066
2.049
2.033
2.016
1.999
0.907
0.890
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.94
2.97
1.98
0.94
0.96
0.96
0.97
2.00
1.05
6.26


benzophenone oxime- Me substituent-ortho-OH Reduced- 13C
BRUKER
160.32
158.19
131.95
130.74
130.49
128.86
128.43
128.26
118.82
118.76
117.07
81.54
OH
Ph
N
O
OH
Me
7a
170
160
150
140
130
120
110
100
90
ppm
160.32
158.19
131.95
130.74
130.49
128.86
128.43
128.26
118.82
118.76
117.07
81.54
27.92
19.00
200
180
160
140
120
100
80
60
40
20
0
ppm

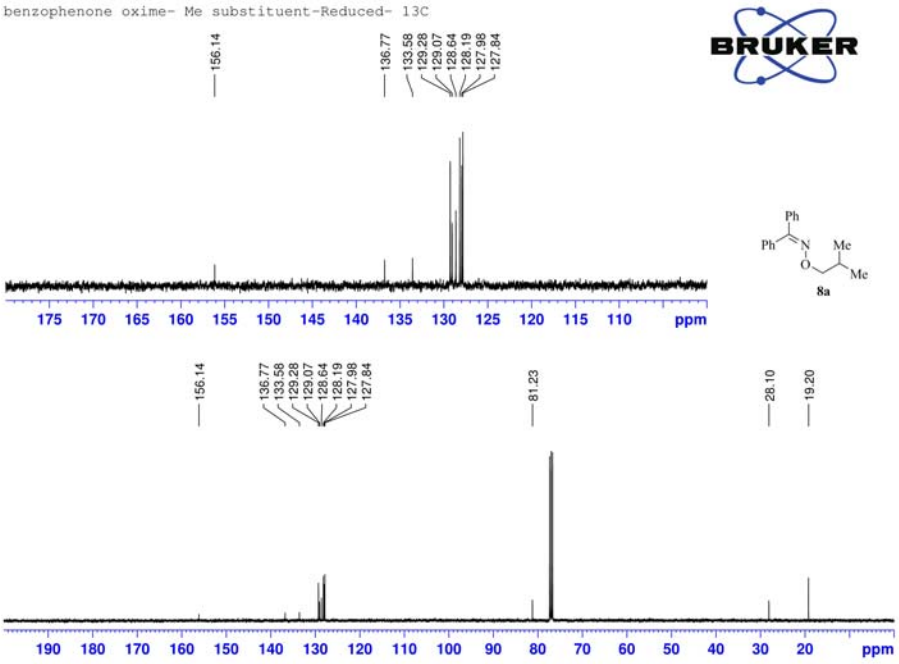

benzophenone oxime- Me substituent-ortho-OH Reduced- HSQC
OH
Ph
N
O
OH
Me
7a
ppm
0
20
40
60
80
100
120
140
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

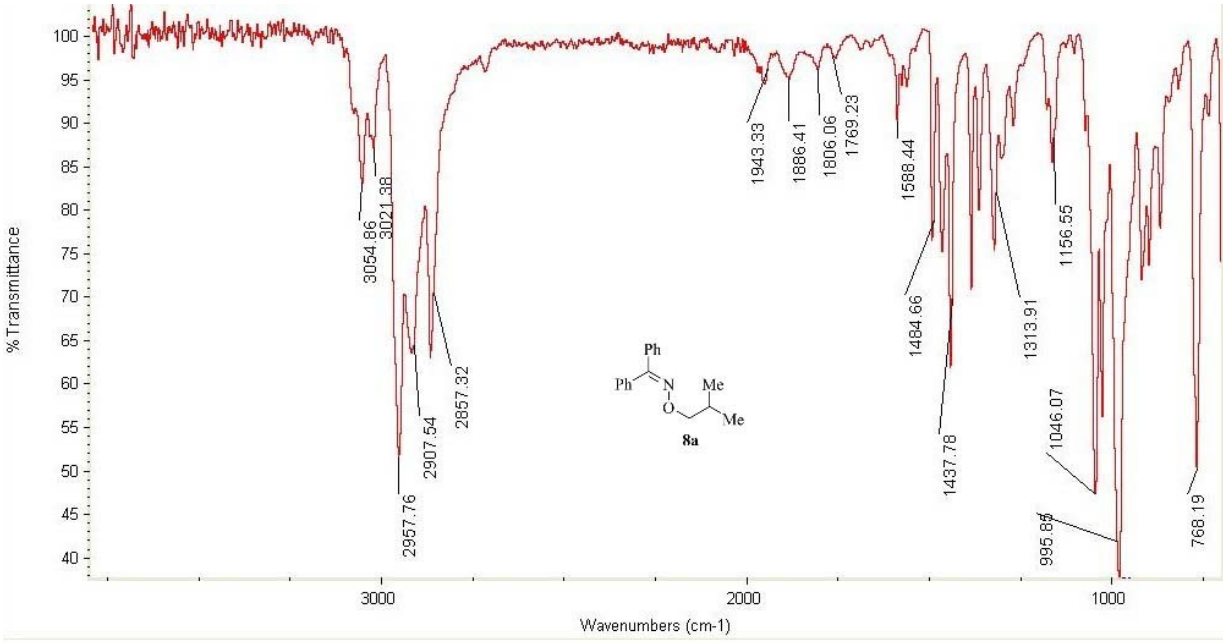

% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
3054.86
3021.38
2957.76
2907.54
2857.32
1943.33
1886.41
1806.06
1769.23
1588.44
1484.66
1437.78
1313.91
1156.55
1046.07
995.85
768.19
OH
Ph
N
O
OH
Me
7a
3000
2000
1000
Wavenumbers (cm-1)

benzophenone oxime- Me substituent-Reduced- 1H



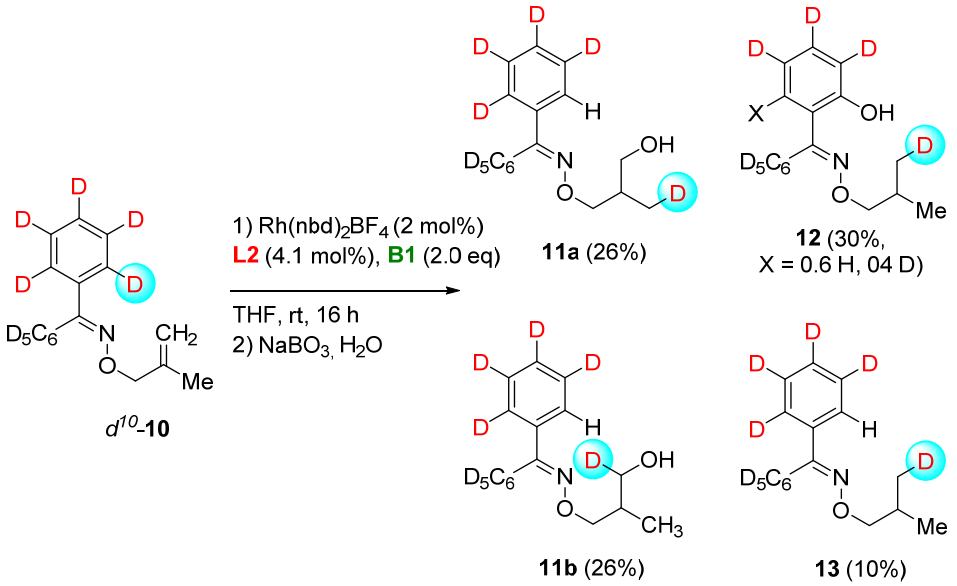
benzophenone oxime- Me substituent-Reduced- 13C

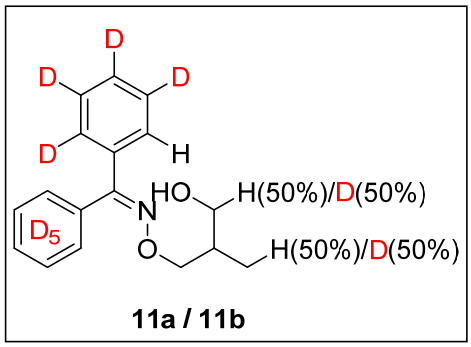



% Transmittance
Wavenumbers (cm-1)
3054.86
3021.38
2957.76
2907.54
2857.32
1943.33
1886.41
1806.06
1769.23
1588.44
1484.66
1437.78
1313.91
1156.55
1046.07
995.85
768.19
Ph
Ph
N
O
Me
Me
8a

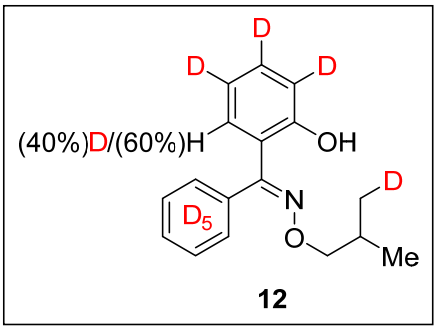
Rh-CAHB of deuterated benzophenone derivatives with tmdB-H

Using a procedure for typical Rh-CAHB with deuterium-labeled substrate d[10]-**10** and tmdBH, the products isolated as described below.



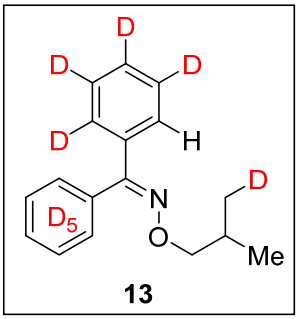


d[9]H-Benzophenone O-(2-hydroxymethyl)-4-methylpentyl oxime (γ-hydroxylated products **11a/11b**) β,γ-unsaturated substrate d[10]-**10** (69.1 mg, 0.24 mmol) was converted to γ-hydroxylated products **11a/11b** (38.7 mg, 52%) as a colorless oil. TLC analysis (30:70 EtOAc/hexanes) showed a spot at Rf 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, s), 4.30 and 4.13 (2H, ddd, J_1 = 4.5 Hz, J_2 = 10.9 Hz), 3.62-3.53 (1.5H, m), 2.17-2.10 (1H, m), 2.04 (1H, bs), 0.95-0.92 (2.5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.7, 77.9, 66.3, 35.8, 13.5; IR (neat) 3339 (O-H stretch), 2924 (C-H aliphatic), 1595 (C=N stretch), 1454 (N-O stretch), 972 (C-O stretch) cm^{-1}.



12

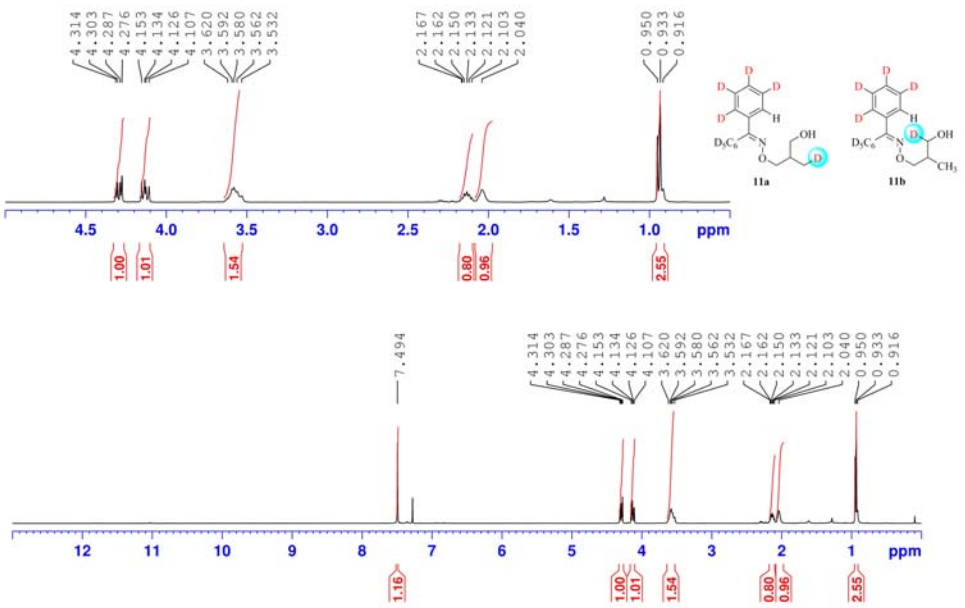
(2-hydroxyphenyl)(phenyl methanone O-isobutyl oxime (*ortho*-hydroxylated and reduced product **12**) β,γ-unsaturated substrate d[10]**-10** (69.1 mg, 0.24 mmol) was converted to *ortho*-hydroxylated product **12** (22.2 mg, 30%) as a colorless oil. TLC analysis (30:70 EtOAc/hexanes) showed a spot at Rf 0.85; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (1H, s), 6.83 (0.6H, s), 3.94 (2H, d, J = 6.9 Hz), 2.09-1.99 (1H, m), 0.91-0.88 (4.7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 158.2, 131.8, 130.4, 128.3, 128.0, 127.8, 127.5, 118.8, 118.7, 81.5, 27.9, 27.8, 19.0, 18.9, 18.7, 18.5; IR (neat) 3085 (O-H phenol), 2920 (C-H aliphatic), 1585 (C=N stretch), 1441 (N-O stretch), 1025 (C-O stretch) cm^{-1}.



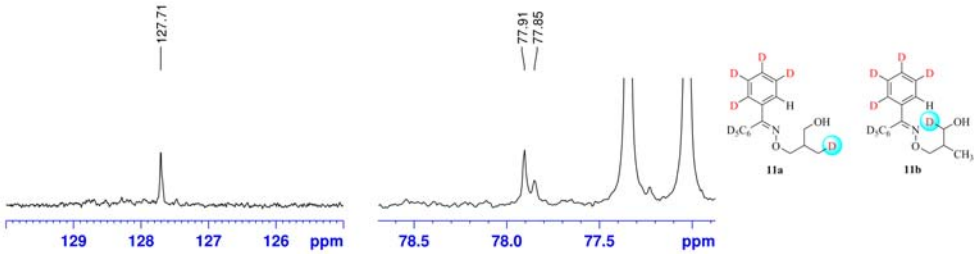
13

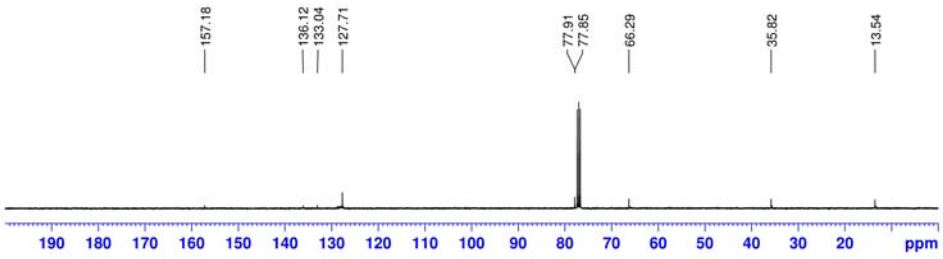
(d[9]H)-Benzophenone O-isobutyl oxime (reduced product **13**) β,γ-unsaturated substrate d[10]**-10** (69.1 mg, 0.24 mmol) was converted to reduced product **13** (6.82 mg, 10%) as a colorless oil. TLC analysis (30:70 EtOAc/hexanes) showed a spot at Rf 0.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, s), 3.98 (2H, d, J = 6.7 Hz), 2.11-2.02 (1H, m), 0.94-0.90 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.7, 81.2, 28.0, 19.2.

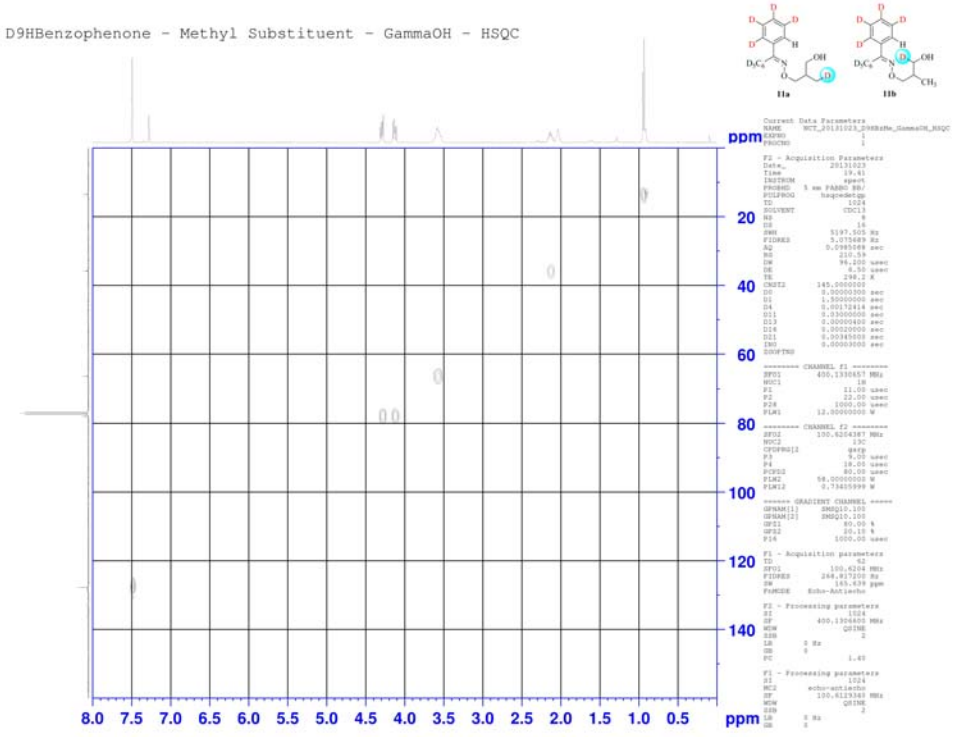
D9HBenzophenone - Methyl Substituent - GammaOH - 1H

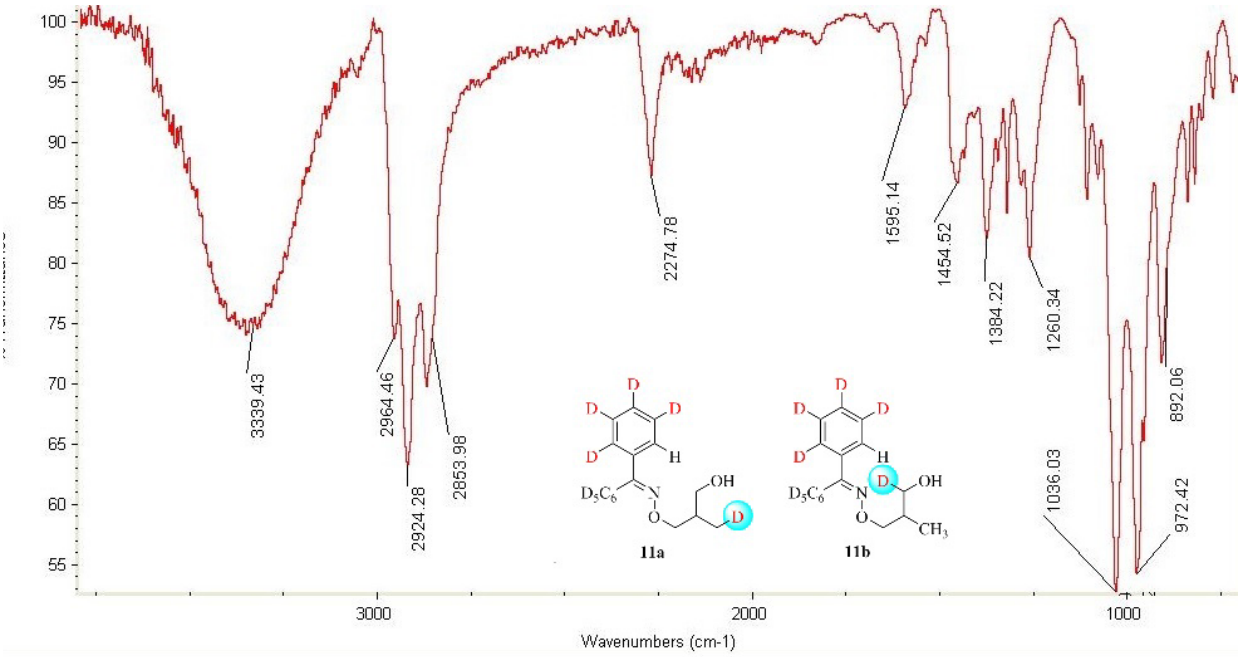


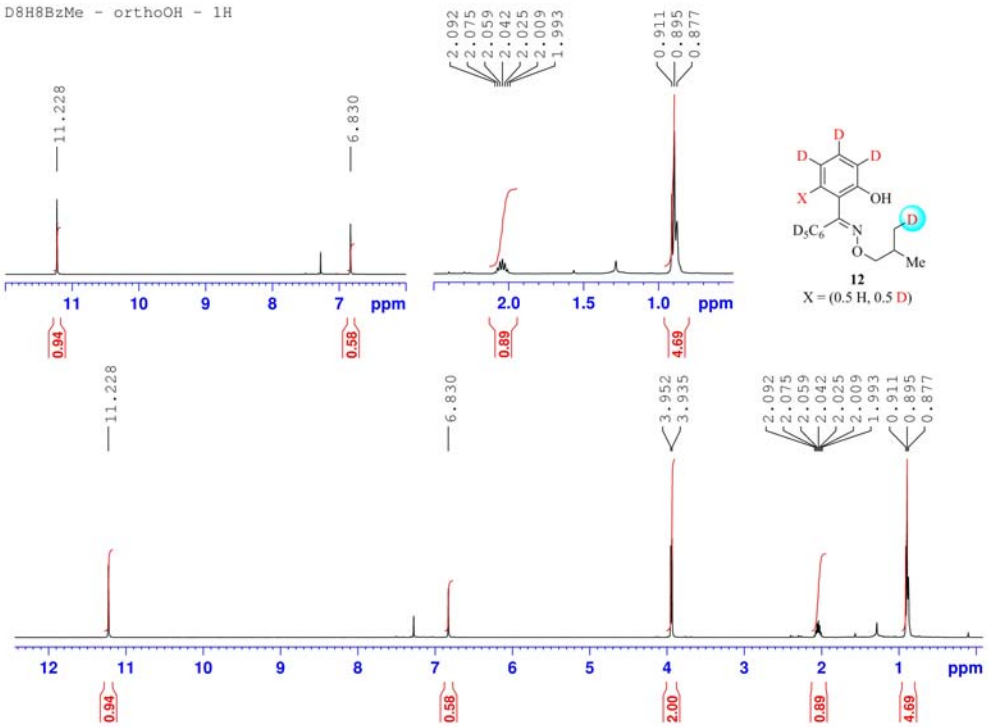
D9HBenzophenone - Methyl Substituent - GammaOH - 13C

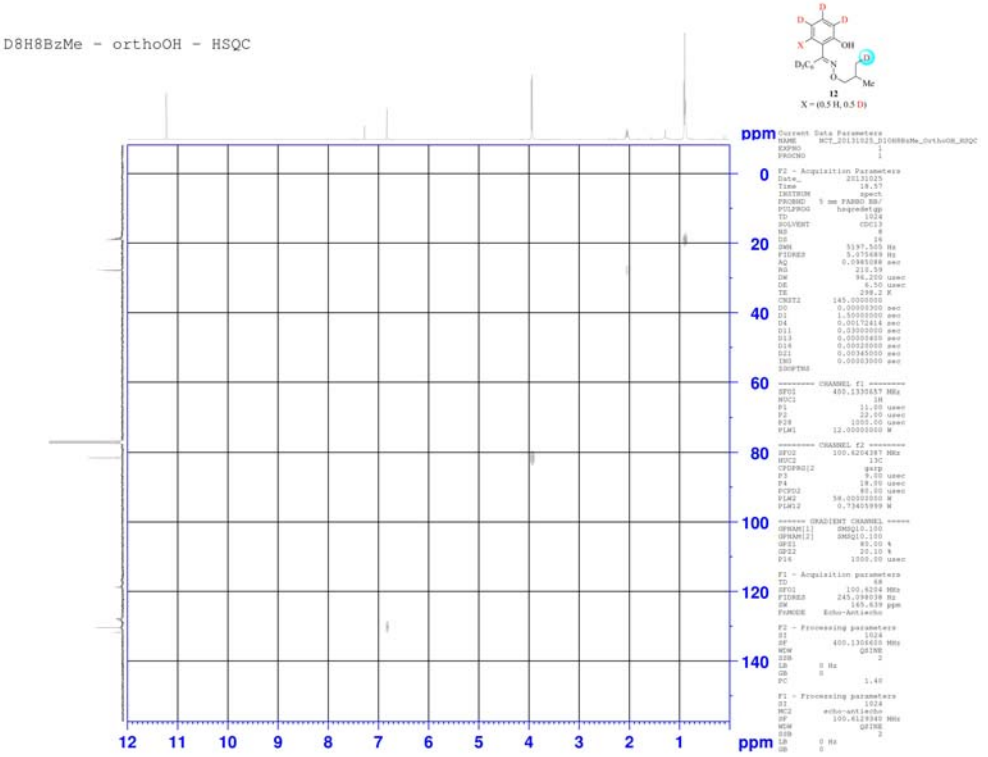


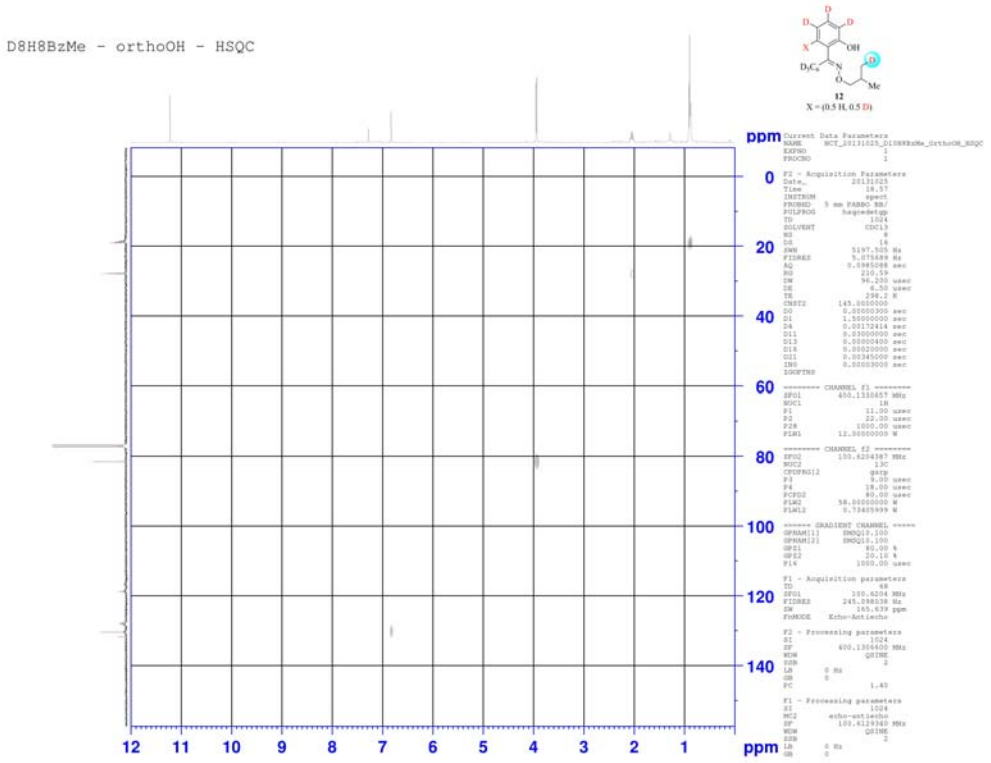


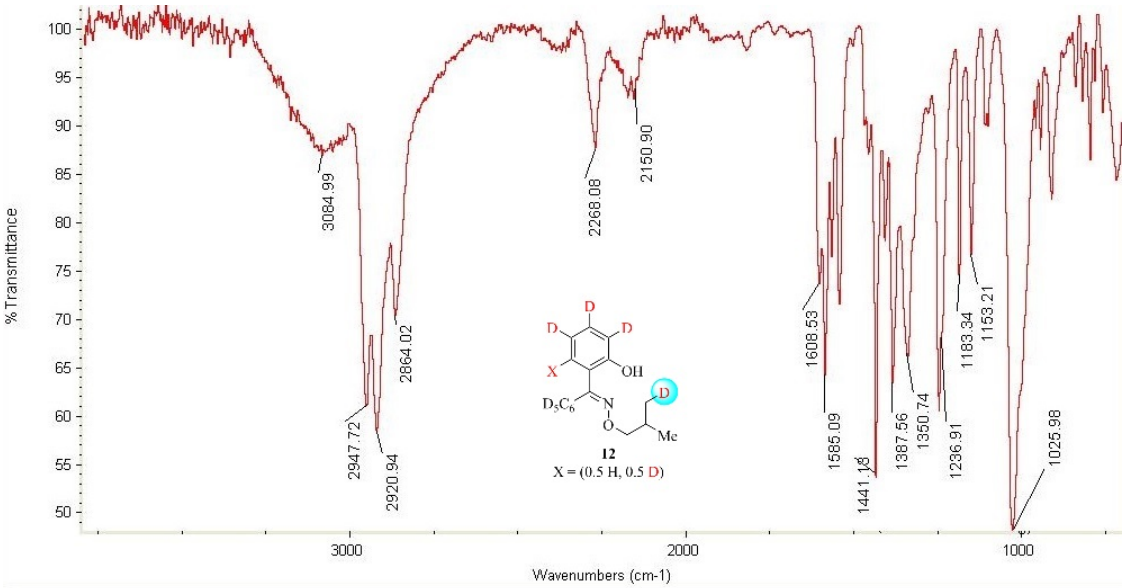

D9HBenzophenone - Methyl Substituent - GammaOH - HSQC
11a
11b
ppm
20
40
60
80
100
120
140
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

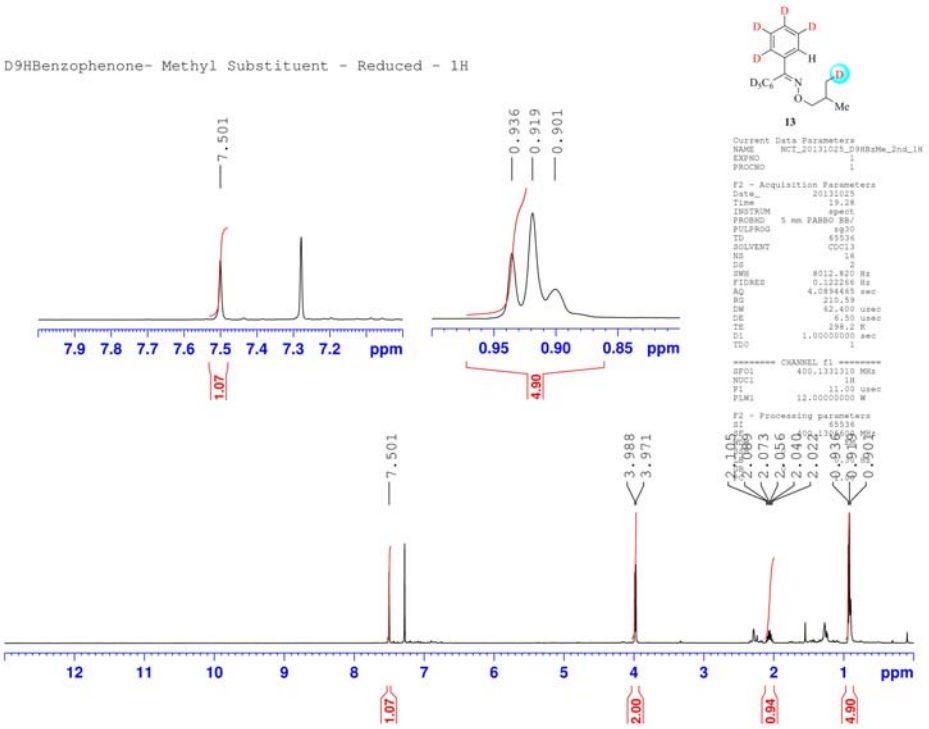

100
95
90
85
80
75
70
65
60
55
3339.43
2964.46
2924.28
2853.98
2274.78
1595.14
1454.52
1384.22
1260.34
1036.03
892.06
972.42
11a
11b
3000
2000
1000
Wavenumbers (cm-1)

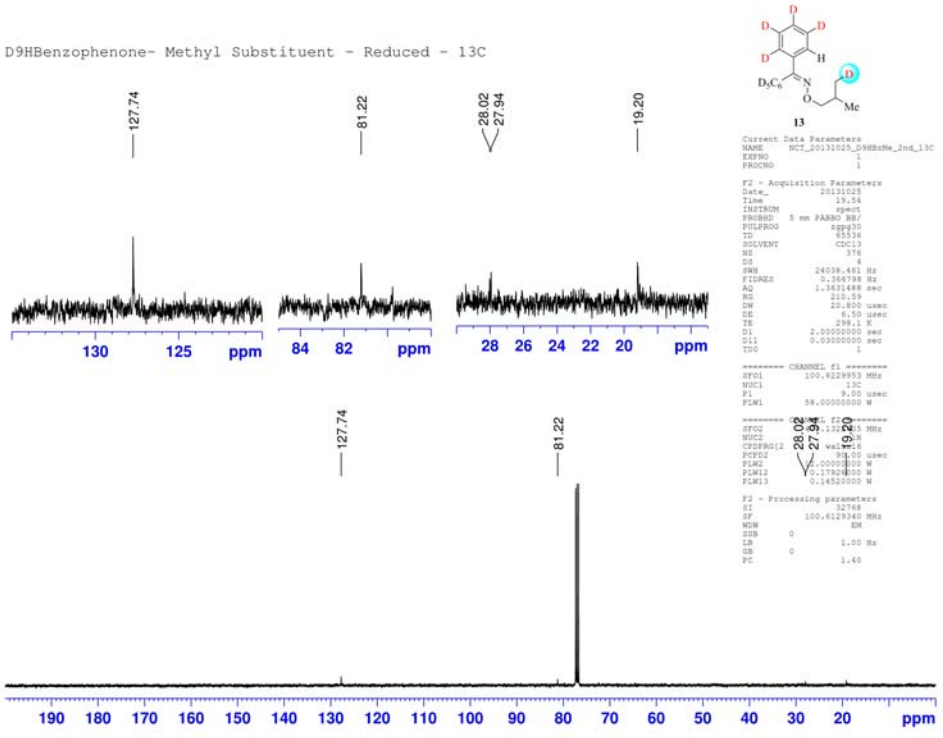

D8H8BzMe - orthoOH - 1H
11.228
6.830
2.092
2.075
2.059
2.042
2.025
2.009
1.993
0.911
0.895
0.877
ppm
0.94
0.58
0.89
4.69
12
X = (0.5 H, 0.5 D)
3.952
3.935
2.00

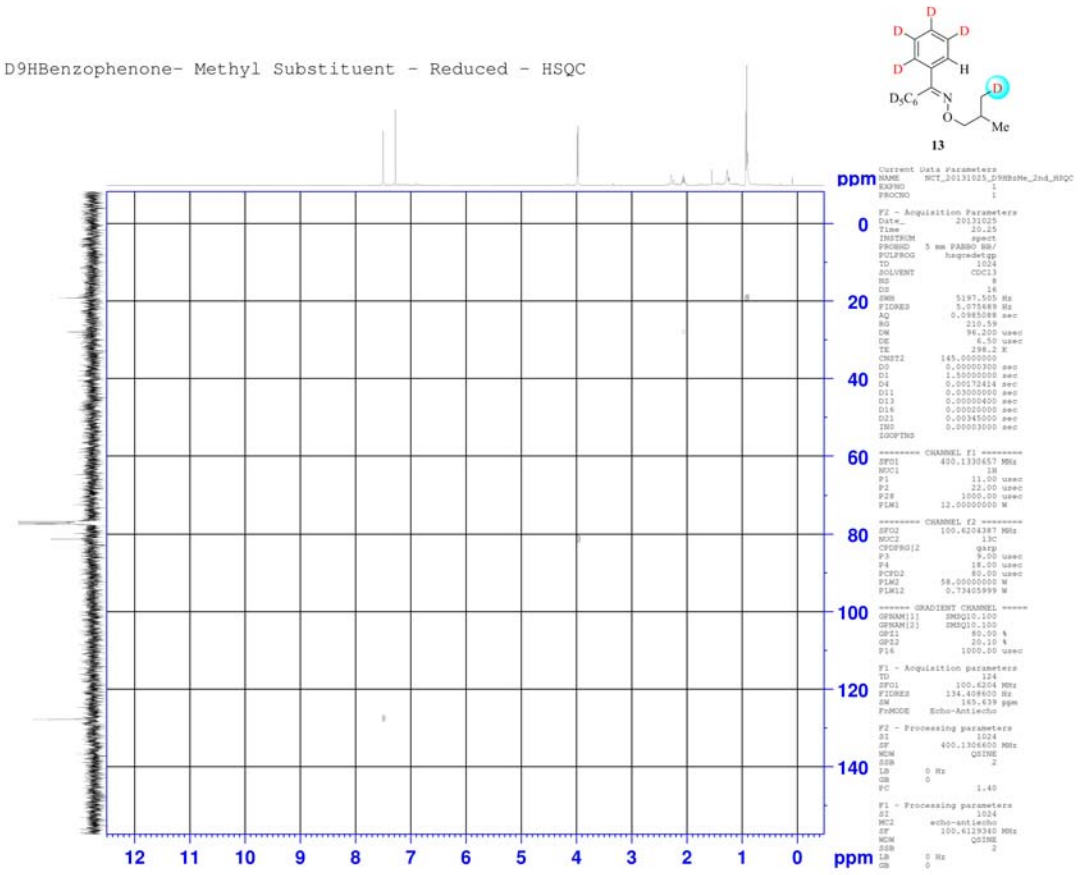

D8H8BzMe - orthoOH - HSQC
ppm
12
X = (0.5 H, 0.5 D)


D8H8BzMe - orthoOH - HSQC
ppm
0
20
40
60
80
100
120
140
12 11 10 9 8 7 6 5 4 3 2 1 ppm
12
X = (0.5 H, 0.5 D)


% Transmittance
Wavenumbers (cm-1)
3084.99
2947.72
2920.94
2864.02
2268.08
2150.90
1608.53
1585.09
1441.18
1387.56
1350.74
1236.91
1183.34
1153.21
1025.98
12
X = (0.5 H, 0.5 D)


D9HBenzophenone- Methyl Substituent - Reduced - 1H
7.501
0.936
0.919
0.901
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 ppm
0.95 0.90 0.85 ppm
1.07
4.90
13
7.501
3.988
3.971
12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.07
2.00
0.94
4.90


D9HBenzophenone- Methyl Substituent - Reduced - 13C
127.74
81.22
28.02
27.94
19.20
130 125 ppm
84 82 ppm
28 26 24 22 20 ppm
13
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


D9HBenzophenone- Methyl Substituent - Reduced - HSQC
D
D
D
D
H
D
D_5C_6
N
O
Me
13
ppm
0
20
40
60
80
100
120
140
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm