ESI for

A simple and efficient protocol for the palladium-catalyzed ligand-free Suzuki reaction at room temperature in aqueous DMF

Chun Liu,* Qijian Ni, Fanying Bao and Jieshan Qiu
State Key Laboratory of Fine Chemicals, Dalian University of Technology, Linggong Road 2, Dalian 116024, P R China, Fax: (+)86-411-84986182; email: chunliu70@yahoo.com

Contents

Materials and Methods

Unless stated otherwise, all the reactions were carried out under air. All aryl halides and arylboronic acids were purchased from Alfa Aesar, Avocado. All other chemicals were purchased from commercial sources and used without further purification. NMR spectra were recorded on a Varian Inova 400 spectrometer. Chemical shifts are reported in ppm relative to TMS. All products were isolated by short chromatography on a silica gel (200~300 mesh) column using petroleum ether (60~90 °C), unless otherwise noted.

Experimental Procedure

A mixture of aryl bromide (0.5 mmol), arylboronic acid (0.75 mmol), $PdCl_2$ (0.0025 mmol, 0.44 mg), K_2CO_3 (1 mmol), distilled water (2 mL) and DMF (2 mL) was stirred at room temperature under air for the indicated time. The mixture was added to brine (15 mL) and extracted four times with diethyl ether (4×15 mL). The solvent was concentrated under vacuum and the product was isolated by short chromatography on a silica gel (200~300 mesh) column.

Control Experiments in Different Conditions

The Suzuki Reaction of N-Heteroaryl Halides with Arylboronic Acids:

$PdCl_2$ (0.0075 mmol, 1.32 mg), $K_3PO_4 \cdot 7H_2O$ (1 mmol) were used instead of $PdCl_2$ (0.0025 mmol, 0.44 mg), K_2CO_3 (1 mmol) in the above procedure.

Suzuki reaction performed in nitrogen:

Both the solid materials such as aryl halides, arylboronic acids, base and catalyst and solvent (DMF and water) were all degassed for three times. And then the mixture of them was stirred at 25 °C for indicated time. The mixture was added to brine (15 mL)

and extracted four times with diethyl ether (4×15 mL). The solvent was concentrated under vacuum and the product was isolated by short chromatography on a silica gel (200~300 mesh) column.

Characterization Data

4-methoxybiphenyl[1]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.54 (t, J = 8.0 Hz, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.31 (d, J = 7.2 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), ppm.

4-methylbiphenyl[2]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.58 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 6.8 Hz, 1H), 7.25 (t, J = 3.2 Hz, 2H), 2.41 (s, 3H), ppm.

4-phenylbenzonitrile[2]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.00 (m, 4H), 7.59 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.2Hz, 2H), 7.45 (t, J = 9.2 Hz, 1H), ppm.

4-acetylbiphenyl[3,4]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.04 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 7.4 Hz, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.41 (t, J = 7.2 Hz, 1H), 2.62 (s, 3H), ppm.

4-methoxyl-4'-methylbiphenyl[5]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.48 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.36 (s, 3H), ppm.

4-methoxyl-3'-methylbiphenyl[6]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.52 (d, J = 9.2 Hz, 2H), 7.33 (m, 3H), 7.12 (d, J = 7.2 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 2.41 (s, 3H), ppm.

4,4'-dimethoxylbiphenyl[7]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.48 (d, J = 8.8 Hz, 4H), 6.96 (d, J = 8.8 Hz, 4H), 3.85 (s, 6H), ppm.

4-cyano-4'-methoxybiphenyl[4]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.67 (m, J = 6.0 Hz, 4H), 7.54 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), ppm.

4-methoxyl-4'-fluorobiphenyl[5]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.50 (m, 4H), 7.10 (t, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), ppm.

4-acetyl-4'-fluorobiphenyl[8]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.03 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 2.0 Hz, 2H), 7.59 (m, J = 3.2 Hz, 2H), 7.16 (t, J = 6.0 Hz, 2H), 2.54 (s, 3H), ppm.

4'-methoxy-4-biphenylaldehyde[5]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 10.05 (s, 1H), 7.95 (d, J =8.0 Hz, 2H), 7.70 (d, J =8.0 Hz, 2H), 7.60 (d, J =8.8 Hz, 2H), 7.0 (d, J =8.8 Hz, 2H), 3.85 (s, 3H), ppm.

2-methylbiphenyl[9]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.39-7.46 (m, 2H), 7.31-7.35 (m, 3H), 7.24-7.26 (m, 4H), 2.25 (s, 3H), ppm.

2-methoxylbiphenyl[2]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.60-6.95 (m, 9H), 3.81 (s, 3H), ppm.

2-phenylbenzonitrile[6]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.75 (d, J = 6.8 Hz, 1H), 7.63 (t, J = 8.4 Hz, 1H), 7.40 - 7.55 (m, 7H), ppm.

2-cyano-4'-methylbiphenyl[3]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.74 (d, J = 7.6 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.40 (t, J =7.6 Hz, 1H), 7.28 (d, J =8.0 Hz, 2H), 2.41 (s, 3H), ppm.

4-methoxyl-2'-methylbiphenyl[6]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.19 - 7.23 (m, 6H), 6.92 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 2.26 (s, 3H), ppm.

2,4'-dimethoxybiphenyl[5]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.47 (d, J = 9.2 Hz, 2H), 7.29 (t, J = 3.2 Hz, 2H), 6.93 - 7.03 (m, 4H), 3.84 (s, 3H), 3.81 (s, 3H), ppm.

2,2'-dimethoxybiphenyl[7]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.24-7.33 (m, 4H), 7.00 (m, 2H), 3.75 (s, 6H), ppm.

2-phenylpyridine[10]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.70 (d, J = 4.4 Hz, 1H), 7.99 (d, J = 7.2 Hz, 2H), 7.75 (m, 2H), 7.49-7.39 (m, 3H), 7.25 - 7.21 (m, 1H), ppm.

2-p-tolylpyridine[10]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.66 (d, J = 4.8 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.72 - 7.68 (m, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.21- 7.18 (m, 1H), 2.41 (s, 3H),

ppm.

2-(4-methoxyphenyl)pyridine[10]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.66 (d, J = 4.4 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.65 - 7.73 (m, 2H), 7.17 (t, J = 6.0 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), ppm.

2-(4-fluorophenyl)pyridine[10]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.66 (d, J = 4.8 Hz, 1H), 7.94 - 7.98 (m, 2H), 7.65 - 7.75 (m, 2H), 7.12 - 7.25 (m, 3H), ppm.

2-methoxyl-5-phenylpyridine[11]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.39 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.53 - 7.51 (m, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.98 (s, 3H), ppm.

2-methoxy-5-p-tolyl-pyridine
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.36 (d, J = 2.4 Hz, 1H), 7.28 (dd, 1H), 7.39 (d, J = 8.0 Hz, 2H), 6.96 (t, J = 4.0 Hz, 2H), 6.78 (d, J = 8.8 Hz, 1H), 3.96 (s, 3H), 2.96 (s, 3H), ppm; ^{13}C NMR δ 163.5, 144.8, 137.4, 137.2, 135.0, 130.1, 129.7, 126.6.1, 110.8, 53.6, 21.2, ppm.

2-methoxyl-5-(4-fluorophenyl)pyridine
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.33 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 8.4, 2.4 Hz, 1H), 7.49 - 7.45 (m, 2H), 7.15 - 7.11 (m, 2H), 6.81 (d, J = 8.4, 1H), 3.98 (s, 3H), ppm; ^{13}C NMR δ 163.6 (d, J = 8.0 Hz), 161.2, 144.8, 137.4, 134.1 (d, J = 3.0 Hz), 129.2, 128.3 (d, J = 8. 0 Hz), 115.9 (d, J = 22.0 Hz), 110.9, 53.57, ppm; MS (EI) m/z 203 (M^+, 100%): 204, 175, 172, 146, 133, 132, 107, 83, 63. Melting Point: 75℃.

2-methoxyl-5-(2-methyl phenyl)pyridine
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.13 (d, J = 2.8 Hz, 1H), 7.54 (dd, J = 8.8, 2.4 Hz, 1H), 7.28 - 7.19 (m, 4H), 6.79 (d, J = 8.4, 1H), 3.98 (s, 3H), 2.27 (s, 3H), ppm; 13C NMR δ 163.3, 146.7, 139.7, 138.3, 135.9, 130.7, 130.6, 130.1, 127.8, 126.2, 110.3, 53.6, 20.6, ppm; MS (EI) m/z 199 (M^+, 100%): 200, 198, 170, 169, 167,154, 141, 128, 127, 115, 102, 89, 77, 63, 48, 39.

2-phenylpyrazine[10]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.03 (s, 1H), 8.64 (s, 1H), 8.52 (d, J =2.4 Hz, 1H), 8.03 (d, J =7.6 Hz, 2H), 7.54 (m, 3H), ppm.

2-(4-methyl phenyl) pyrazine[10]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.01 (s, 1H), 8.61 (s, 1H), 8.48 (d, J = 2.4 Hz,

1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), ppm.

Reference

(1) C. Deng, S. Guo, Y. Xie and J. Li, *Eur. J. Org. Chem.*, 2007, 1457.

(2) D. Saha, K. Chattopadhyay and B. Ranu, *Tetrahedron Lett.*, 2009, **50**, 1003.

(3) A. Indolese, *Tetrahedron Lett.*, 1997, **38**, 3513.

(4) Z. Weng, L. Koh and T. Hor, *J. Organomet. Chem.*, 2004, **689**, 18.

(5) Y. Kitamura, A. Sakurai, T. Udzu, T. Maegawa, Y. Monguchi and H. Sajiki, *Tetrahedron*, 2007, **63**, 10596.

(6) L. Ackermann, C. Gschrei, A. Althammer and M. Riederer, *Chem. Commun.*, 2006, 1419.

(7) V. Courtois, R. Barhdadi, M. Troupel and J. Périchon, *Tetrahedron*, 1997, **53**, 11569.

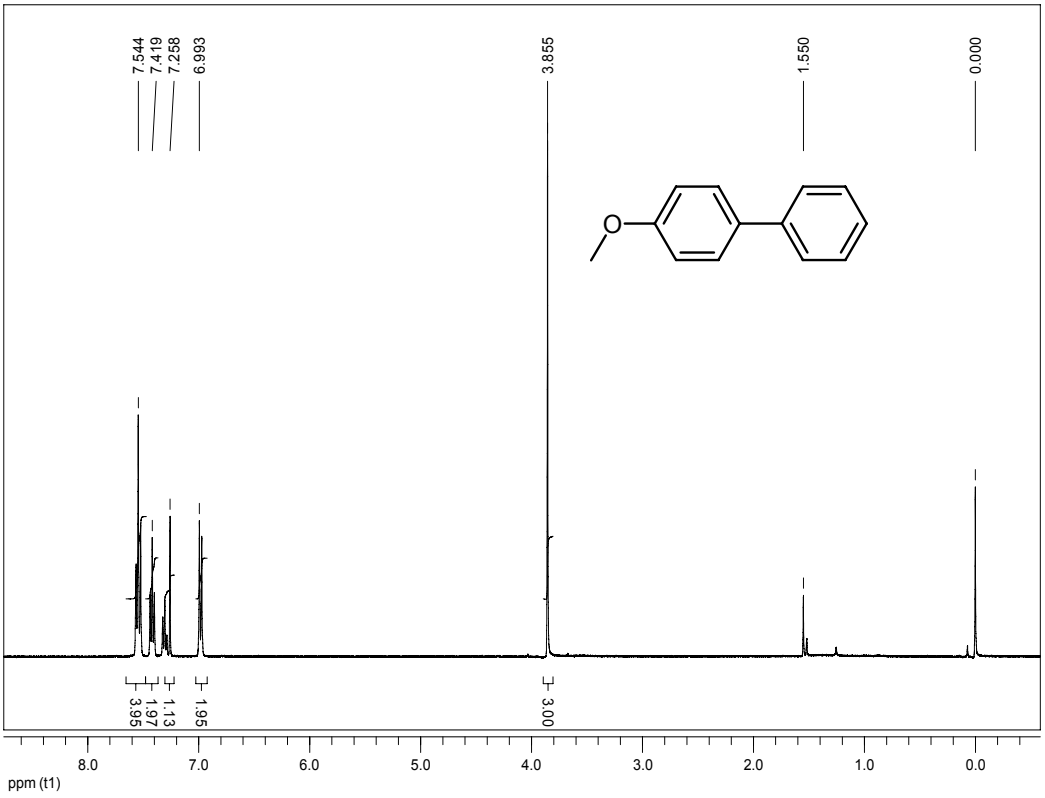
(8) N. Bumagin and V. Bykov, *Tetrahedron*, 1997, **53**, 14437.

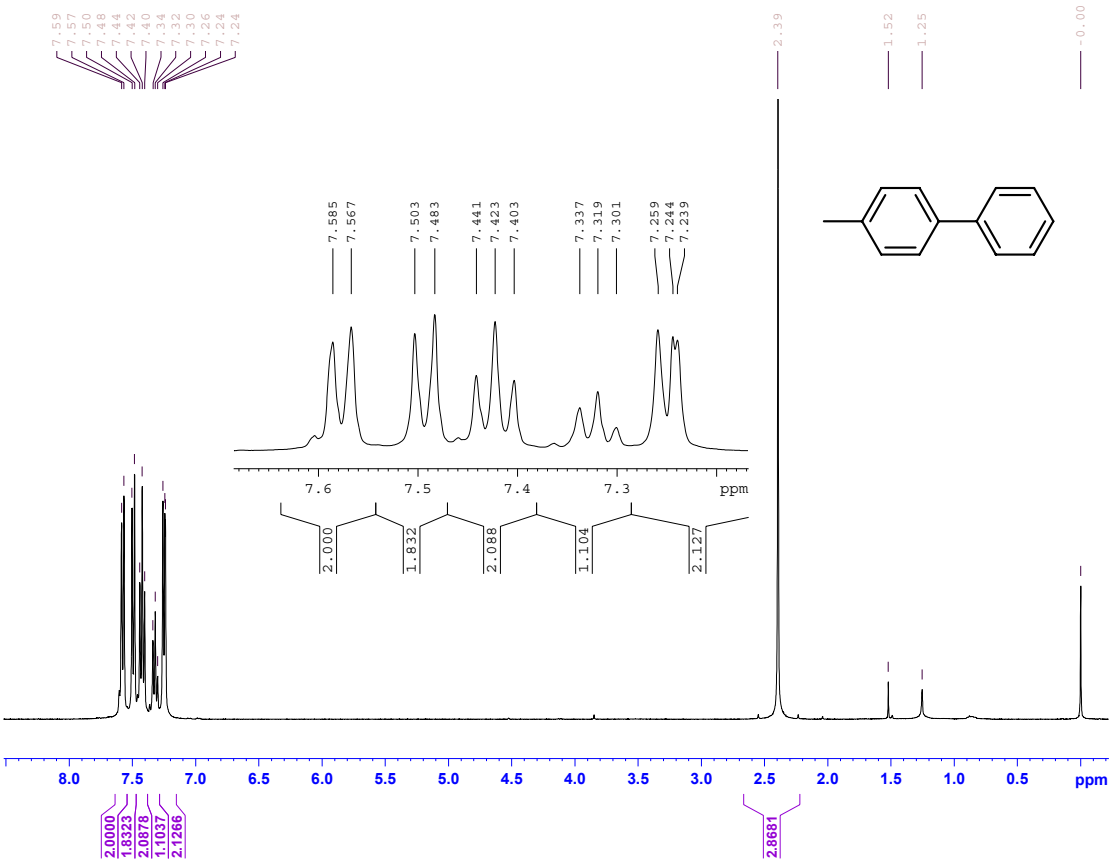
(9) T. Mino, Y. Shirae, M. Sakamoto and T. Fujita, *J. Org.Chem.*, 2005, **70**, 2191.

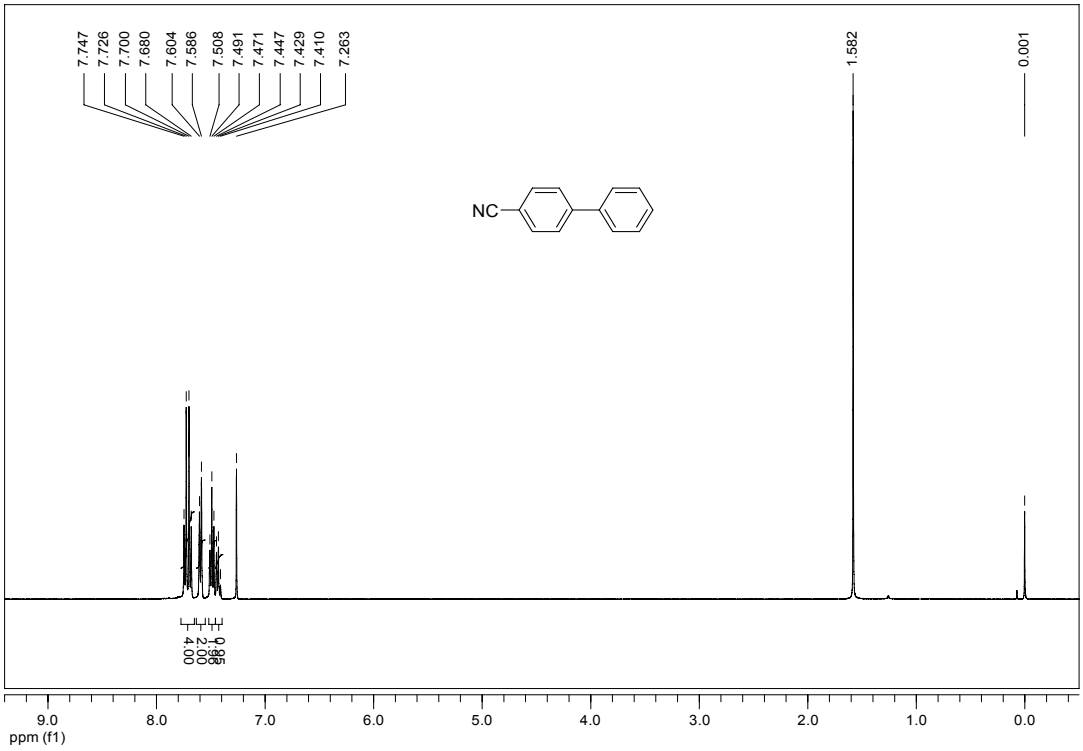
(10) C. Liu and W. Yang, *Chem. Commun.*, 2009, 6267.

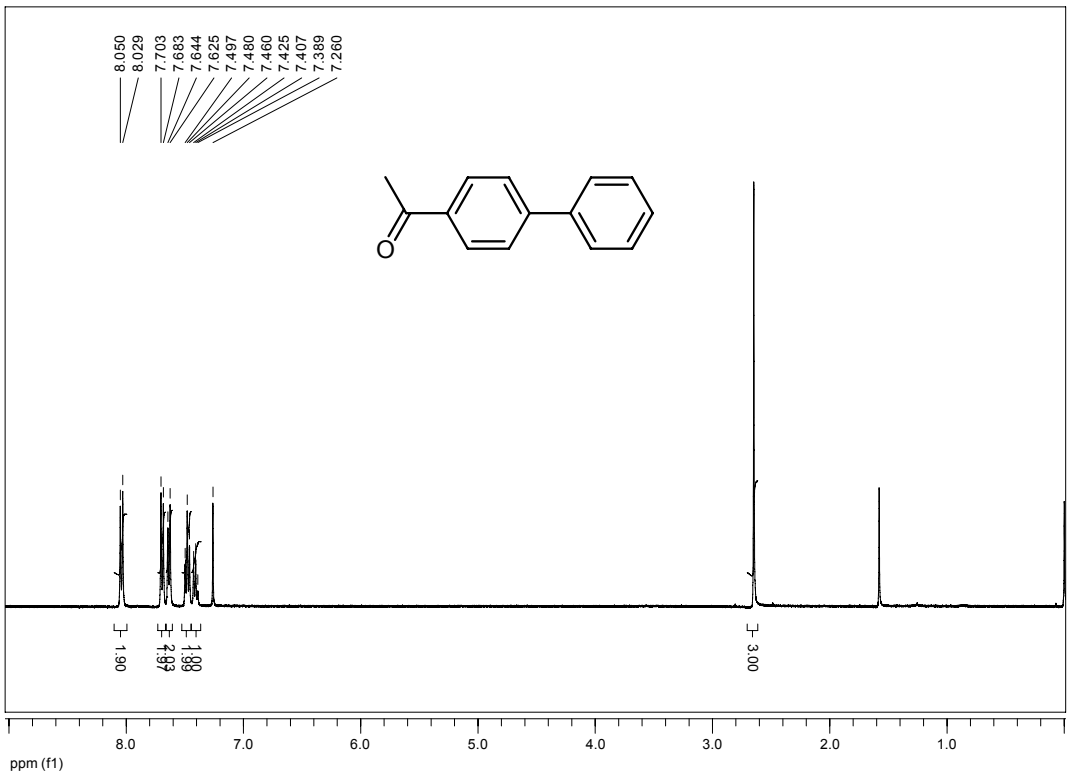
(11) J. Li, Q. Zhu and Y. Xie, *Tetrahedron*, 2006, **62**, 10888.

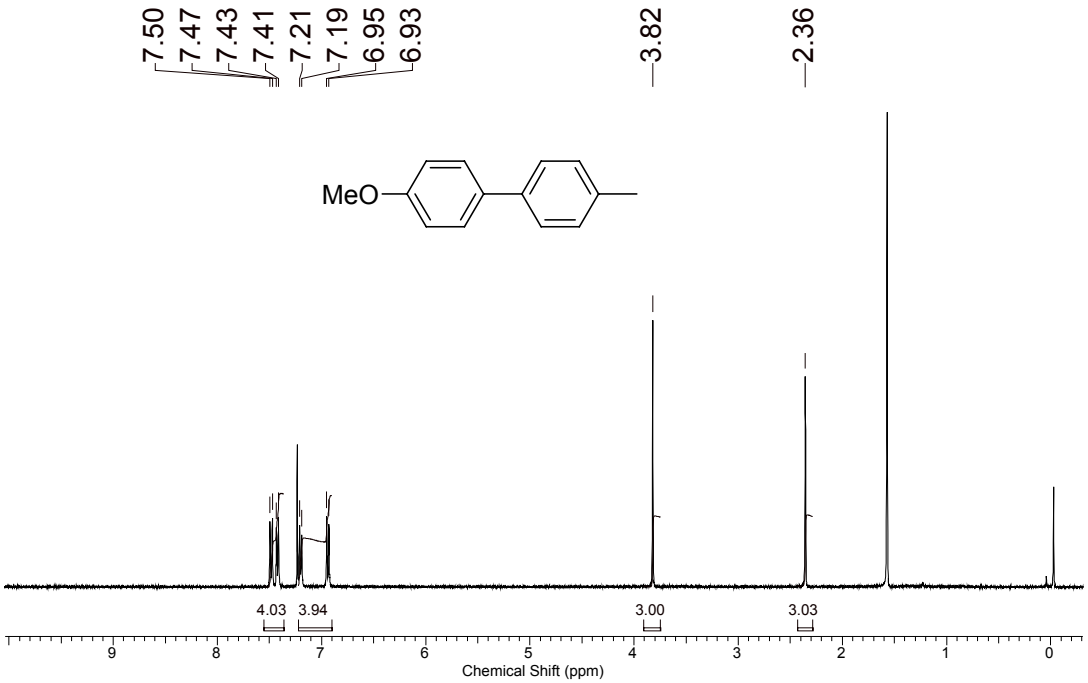
^{1}H NMR Spectra for all Cross-Coupling Products

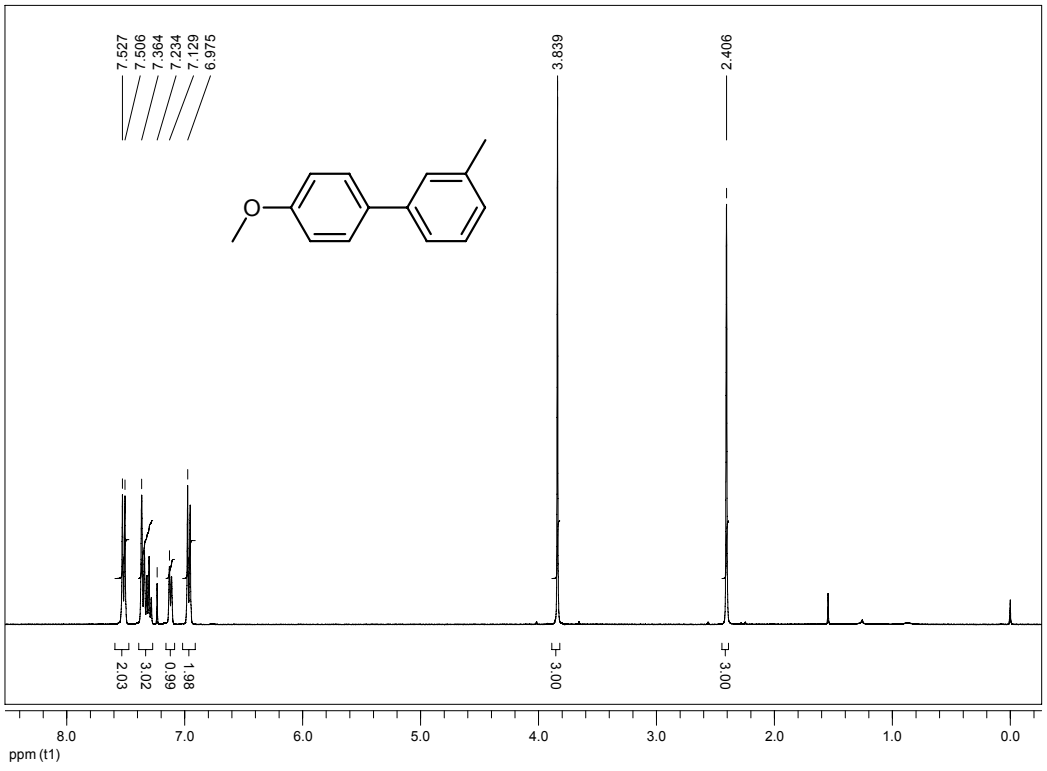


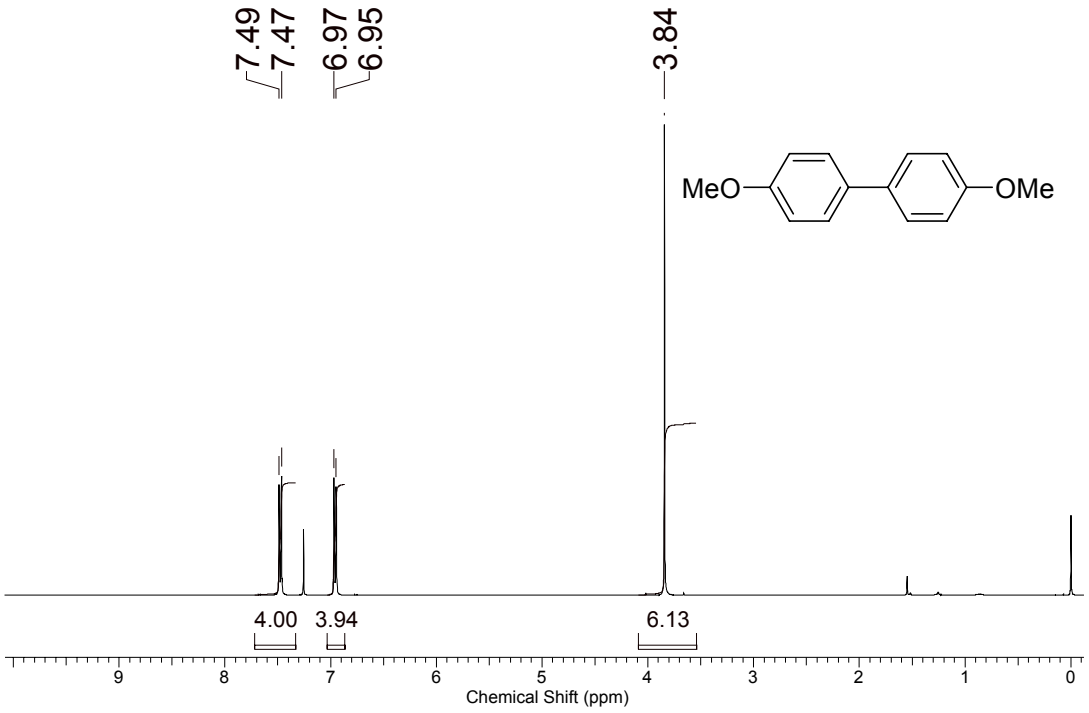


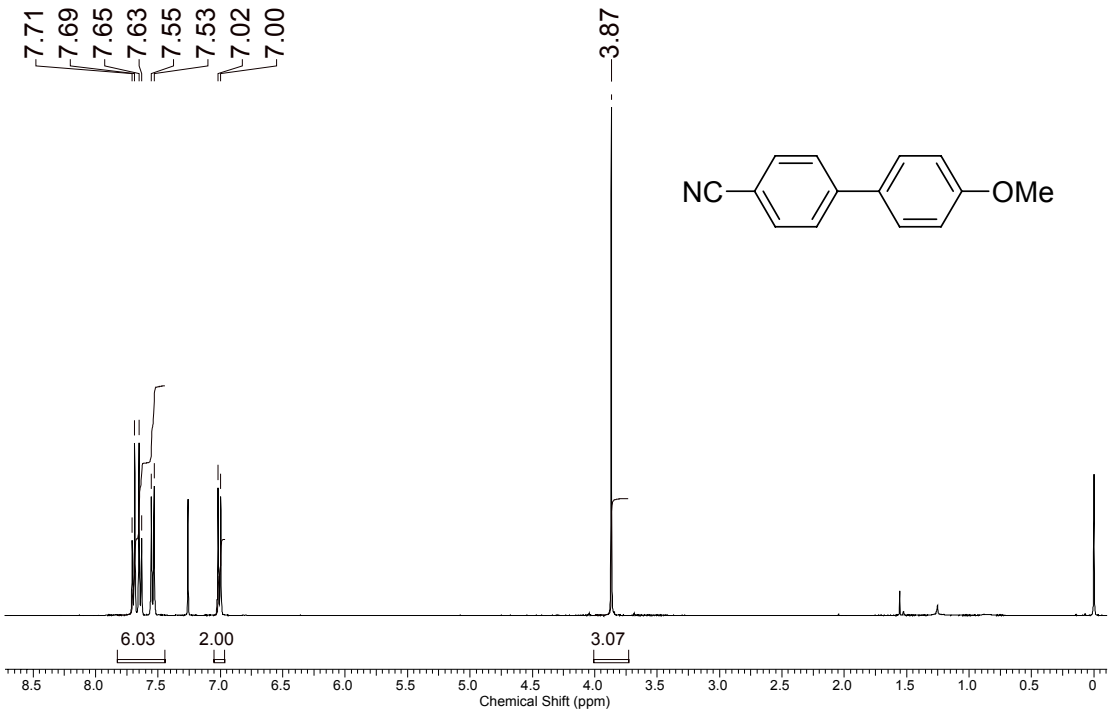

7.747
7.726
7.700
7.680
7.604
7.586
7.508
7.491
7.471
7.447
7.429
7.410
7.263
1.582
0.001
NC
4.00
2.00
9.05
ppm (f1)

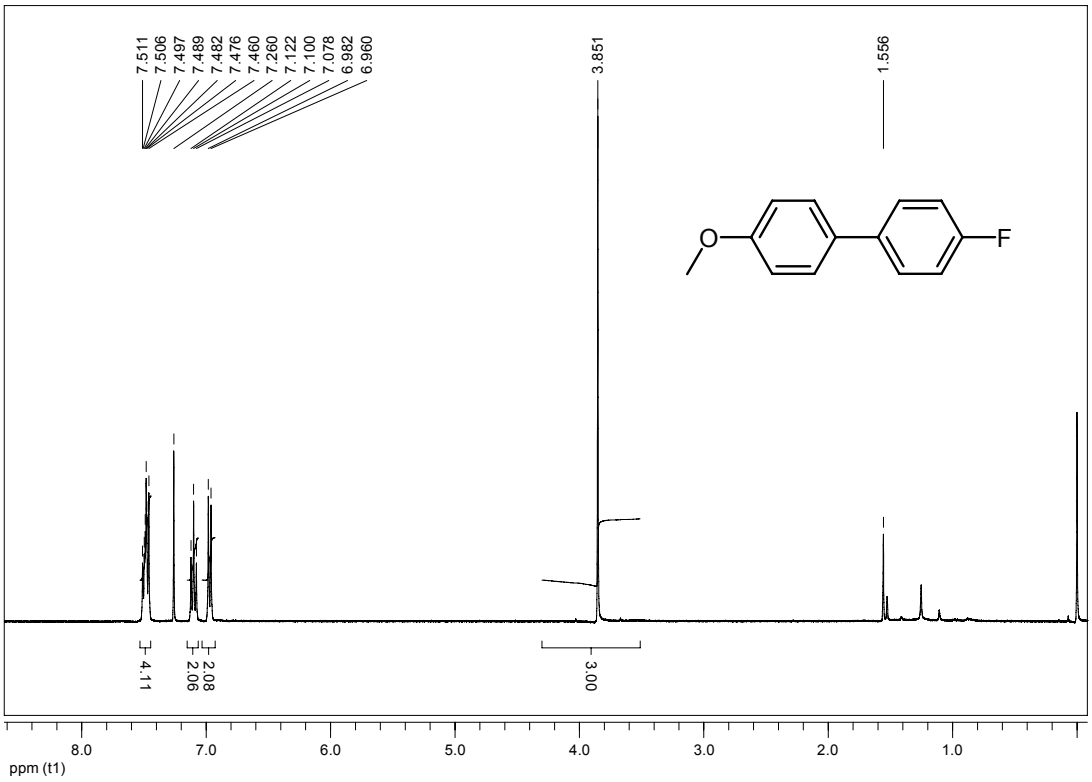

8.050
8.029
7.703
7.683
7.644
7.625
7.497
7.480
7.460
7.425
7.407
7.389
7.260
O
1.90
2.03
1.99
3.00
ppm (f1)

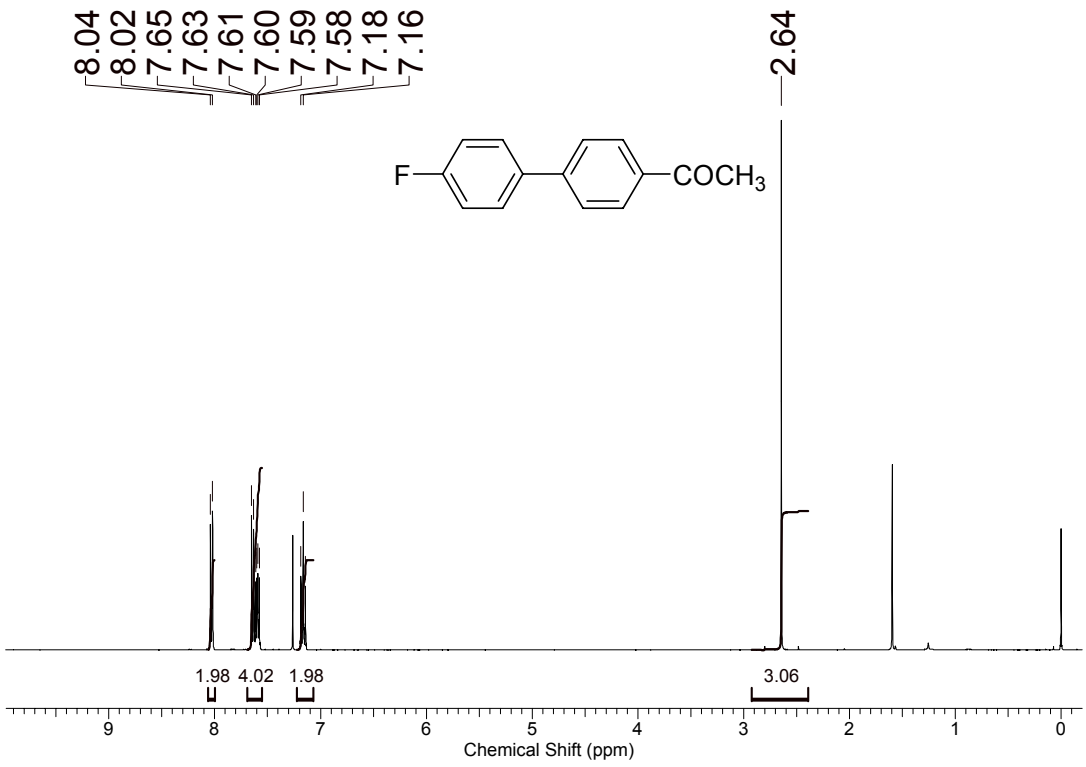

7.50
7.47
7.43
7.41
7.21
7.19
6.95
6.93
3.82
2.36
MeO
4.03
3.94
3.00
3.03
Chemical Shift (ppm)

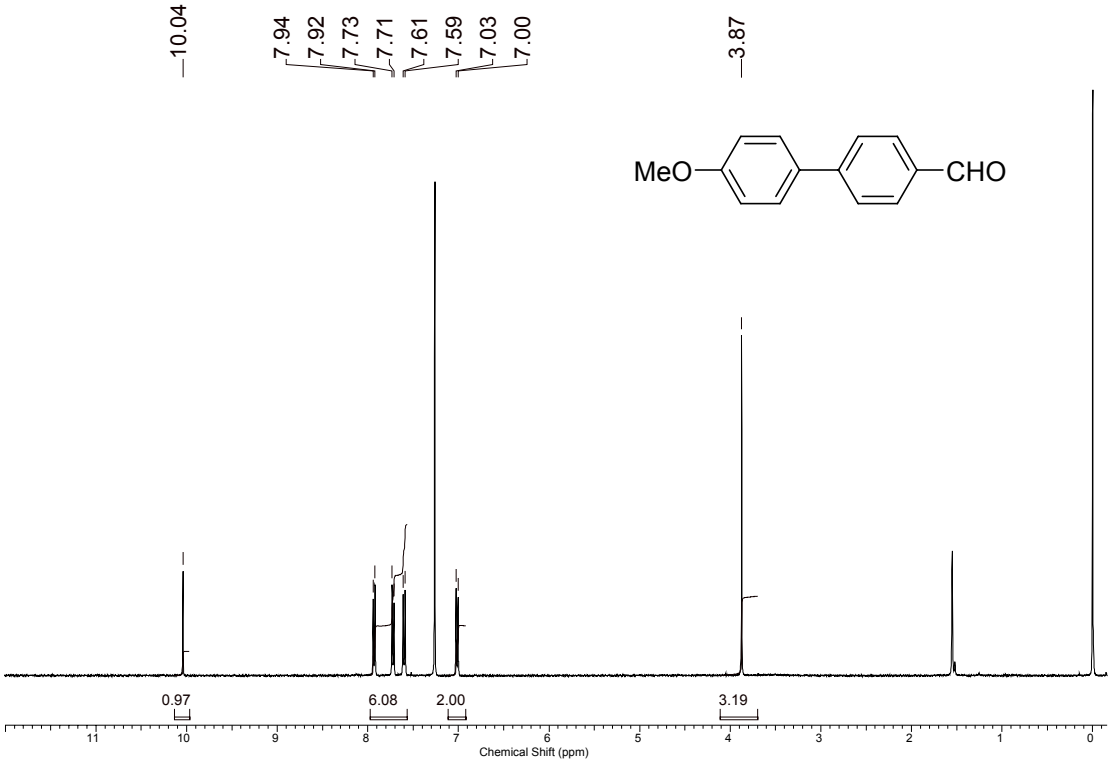

7.527
7.506
7.364
7.234
7.129
6.975
3.839
2.406
O
2.03
3.02
0.99
1.98
3.00
3.00
ppm (t1)

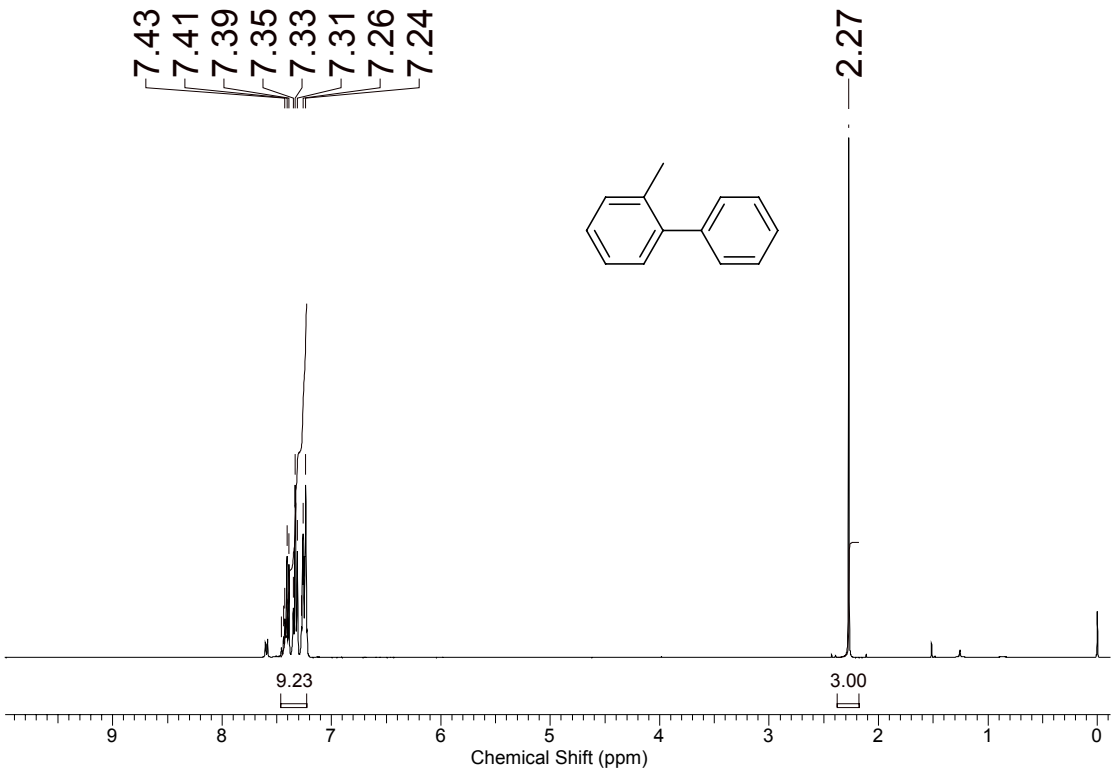

7.49
7.47
6.97
6.95
3.84
MeO
OMe
4.00
3.94
6.13
Chemical Shift (ppm)

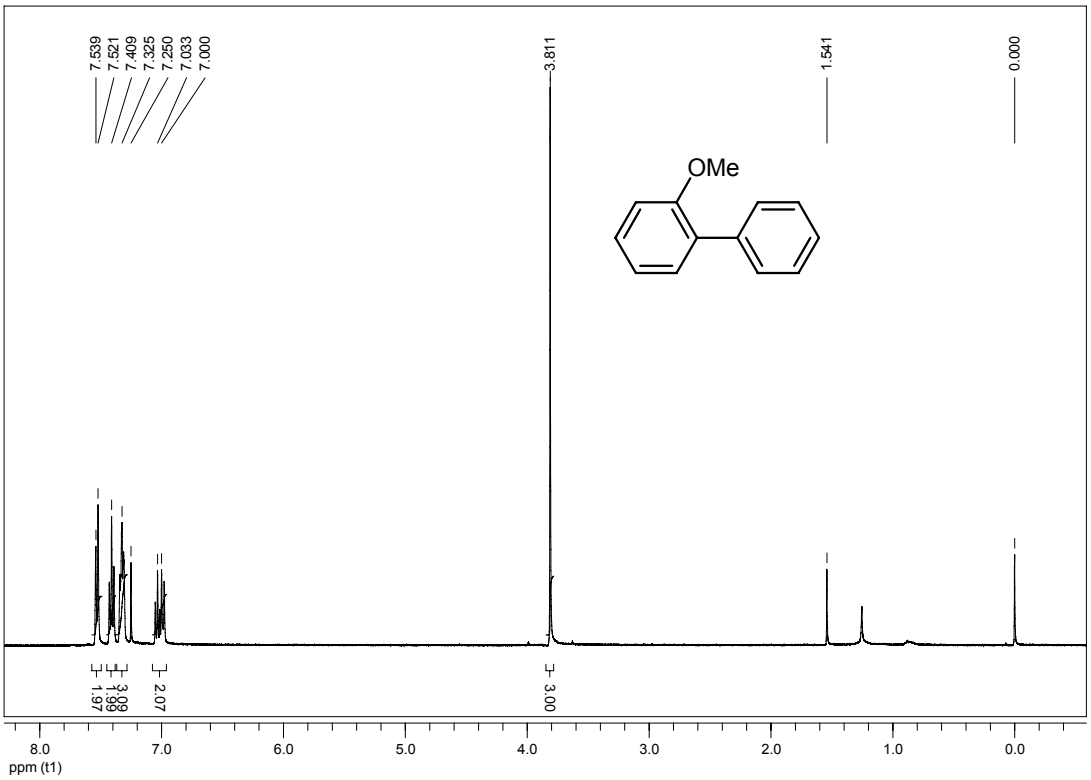

7.71
7.69
7.65
7.63
7.55
7.53
7.02
7.00
3.87
NC
OMe
6.03
2.00
3.07
Chemical Shift (ppm)

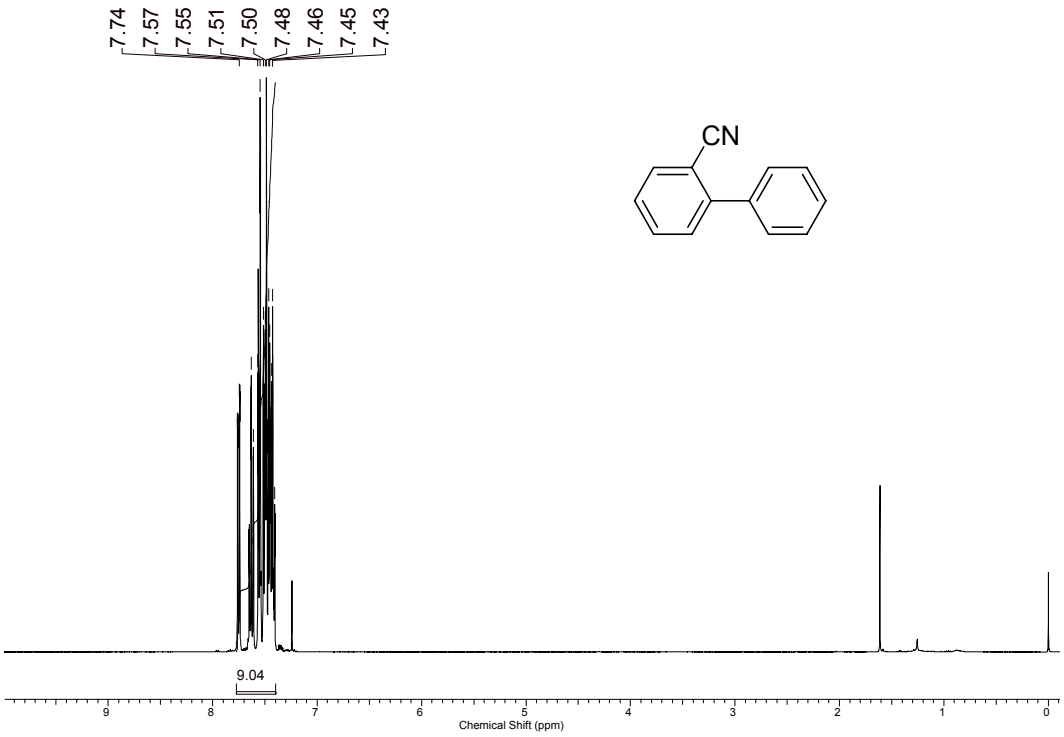

7.511
7.506
7.497
7.489
7.482
7.476
7.460
7.260
7.122
7.100
7.078
6.982
6.960
3.851
1.556
O
F
4.11
2.06
2.08
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

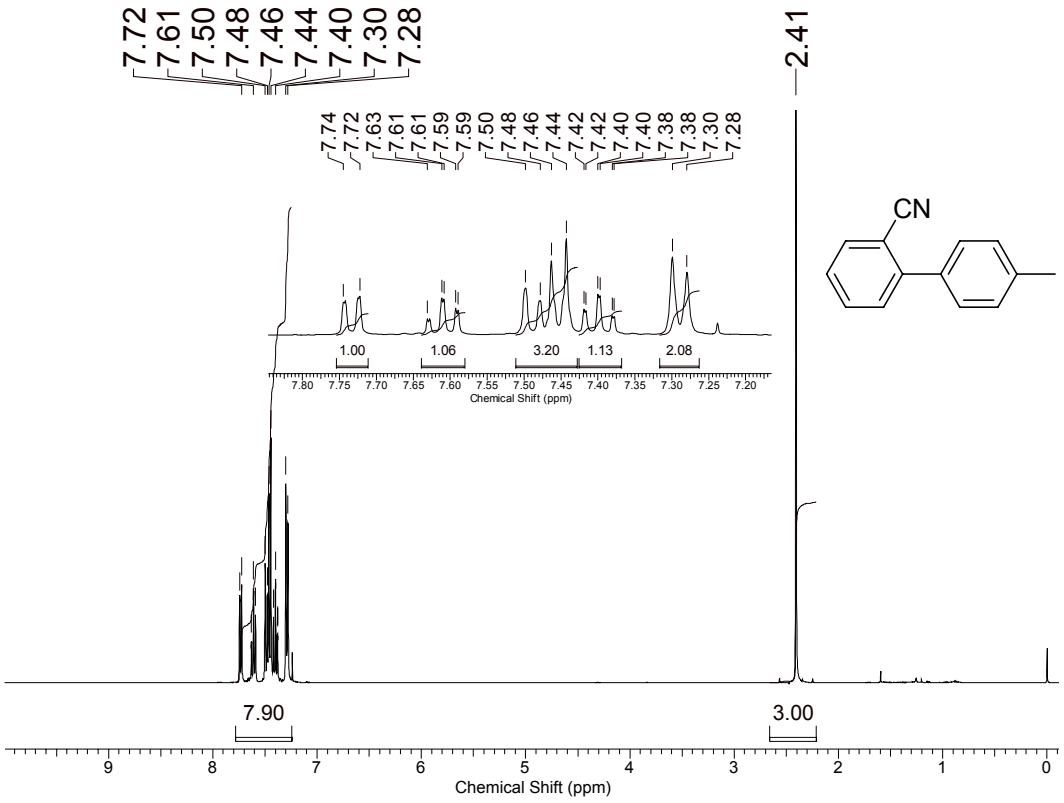

8.04
8.02
7.65
7.63
7.61
7.60
7.59
7.58
7.18
7.16
2.64
F
COCH3
1.98
4.02
1.98
3.06
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

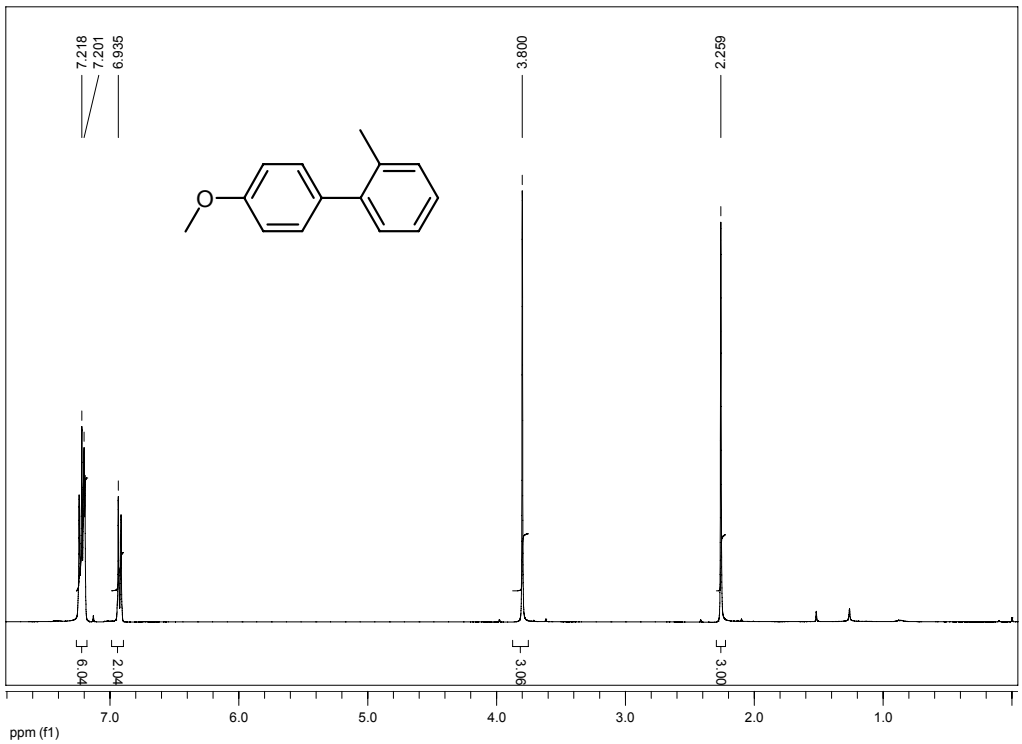

10.04
7.94
7.92
7.73
7.71
7.61
7.59
7.03
7.00
3.87
MeO
CHO
0.97
6.08
2.00
3.19
Chemical Shift (ppm)

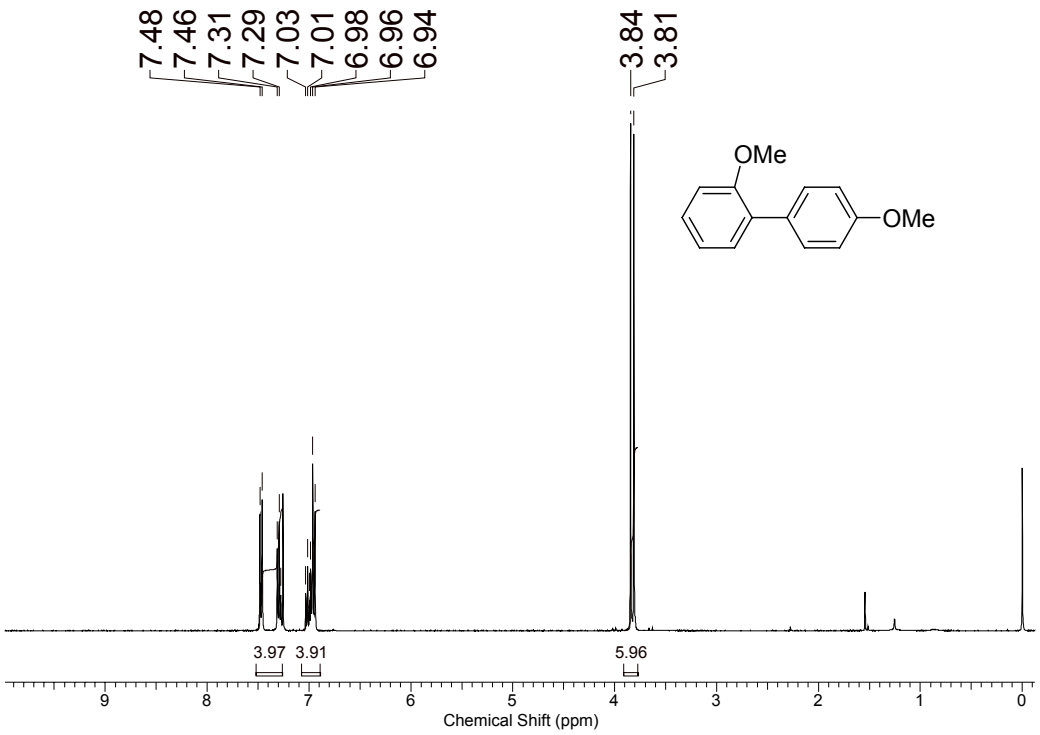

7.43
7.41
7.39
7.35
7.33
7.31
7.26
7.24
2.27
9.23
3.00
Chemical Shift (ppm)

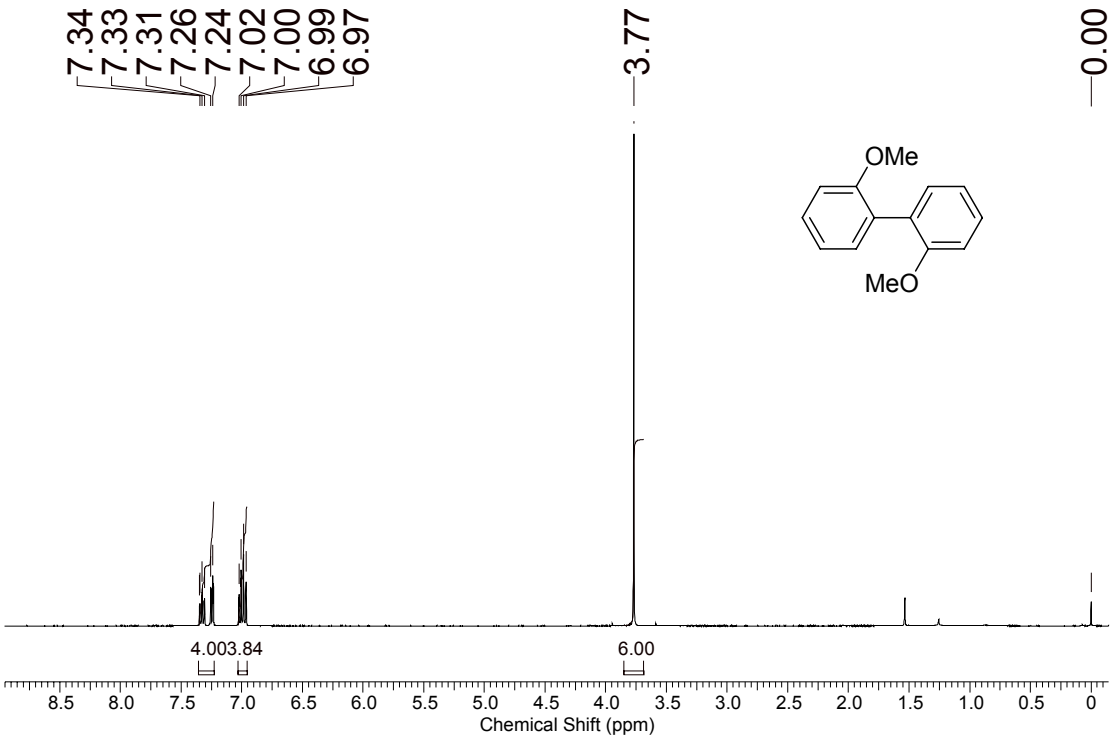

7.539
7.521
7.409
7.325
7.250
7.033
7.000
3.811
1.541
0.000
OMe
1.97
3.09
2.07
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

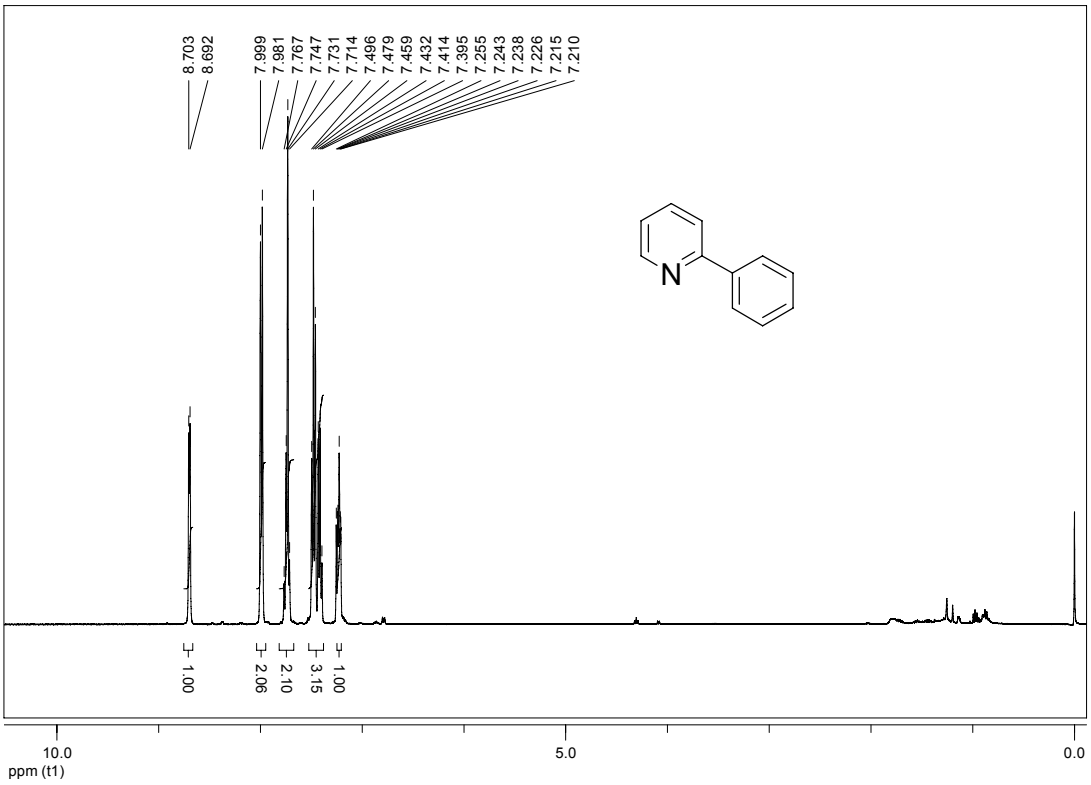

7.74
7.57
7.55
7.51
7.50
7.48
7.46
7.45
7.43
CN
9.04
Chemical Shift (ppm)

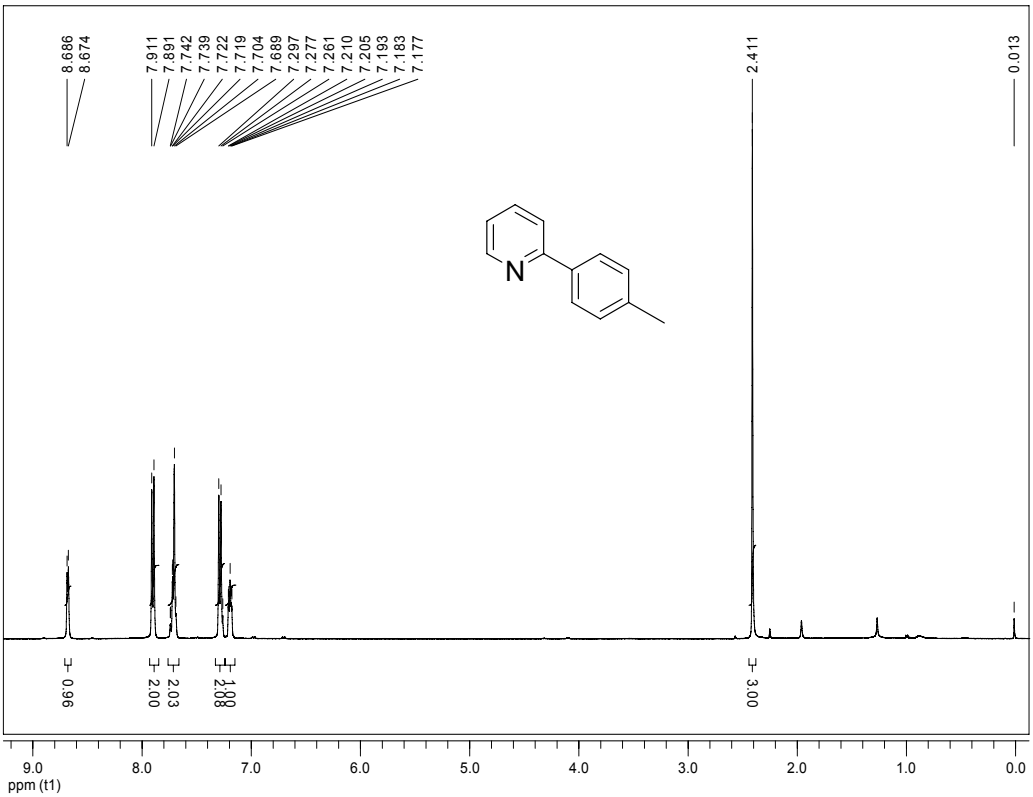

7.72
7.61
7.50
7.48
7.46
7.44
7.40
7.30
7.28
2.41
CN
1.00
1.06
3.20
1.13
2.08
Chemical Shift (ppm)
7.90
3.00
Chemical Shift (ppm)

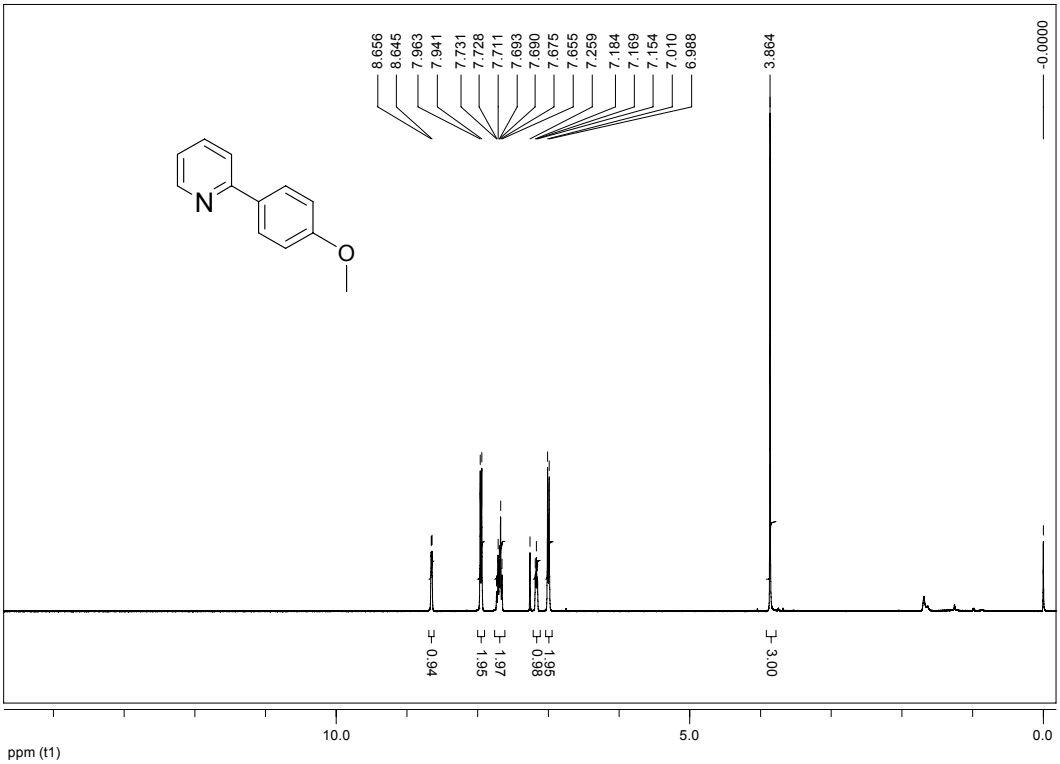

7.218
7.201
6.935
3.800
2.259
O
6.04
2.04
3.06
3.00
ppm (f1)

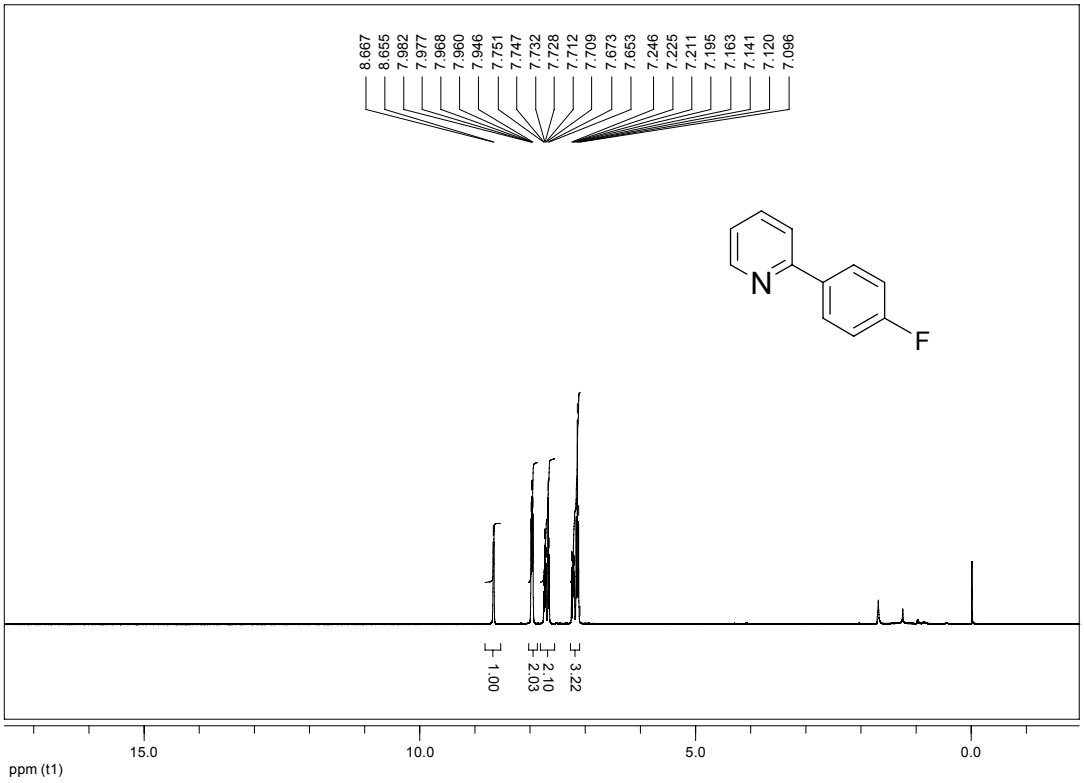

7.48
7.46
7.31
7.29
7.03
7.01
6.98
6.96
6.94
3.84
3.81
OMe
OMe
3.97
3.91
5.96
Chemical Shift (ppm)

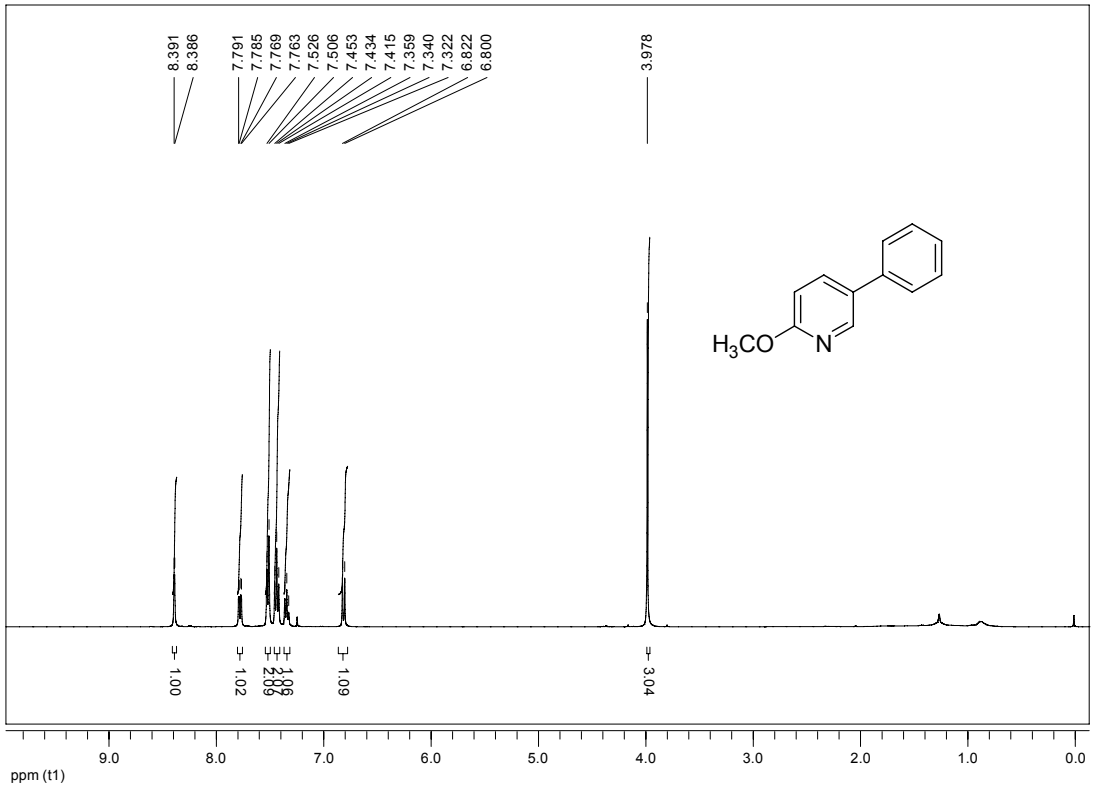

7.34
7.33
7.31
7.26
7.24
7.02
7.00
6.99
6.97
3.77
0.00
OMe
MeO
4.00
3.84
6.00
Chemical Shift (ppm)

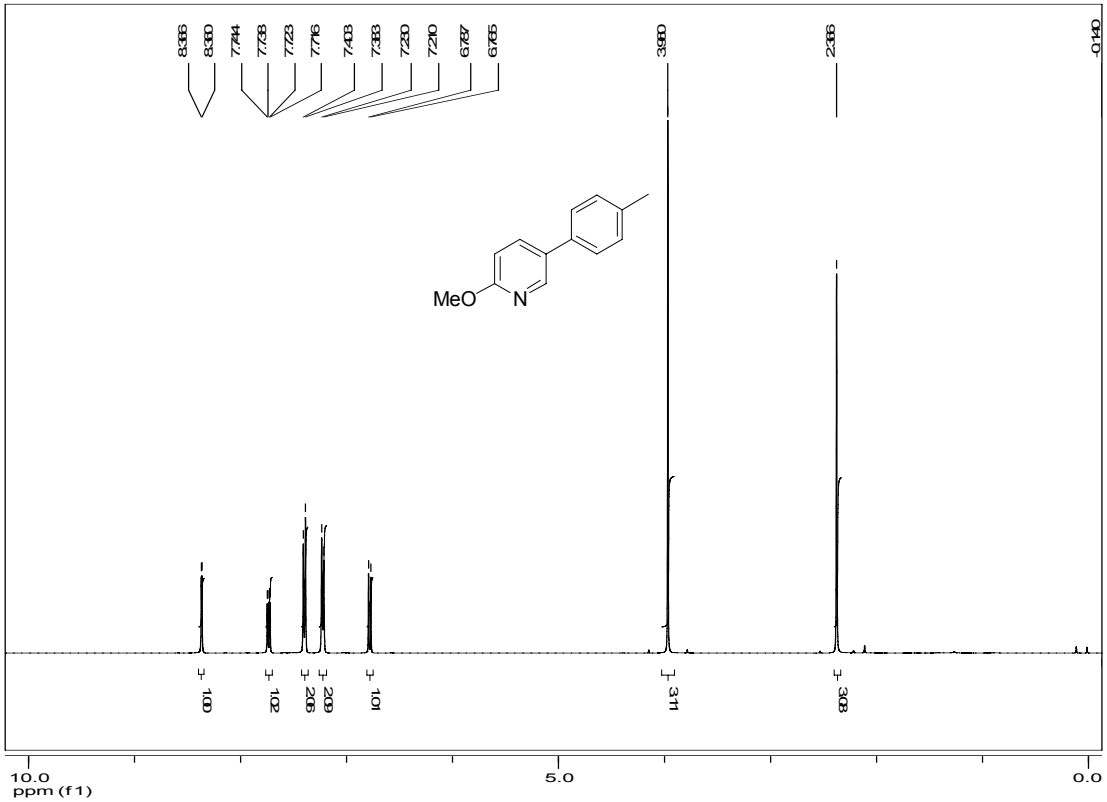

8.703
8.692
7.999
7.981
7.767
7.747
7.731
7.714
7.496
7.479
7.459
7.432
7.414
7.395
7.255
7.243
7.238
7.226
7.215
7.210
N
1.00
2.06
2.10
3.15
1.00
10.0
5.0
0.0
ppm (t1)

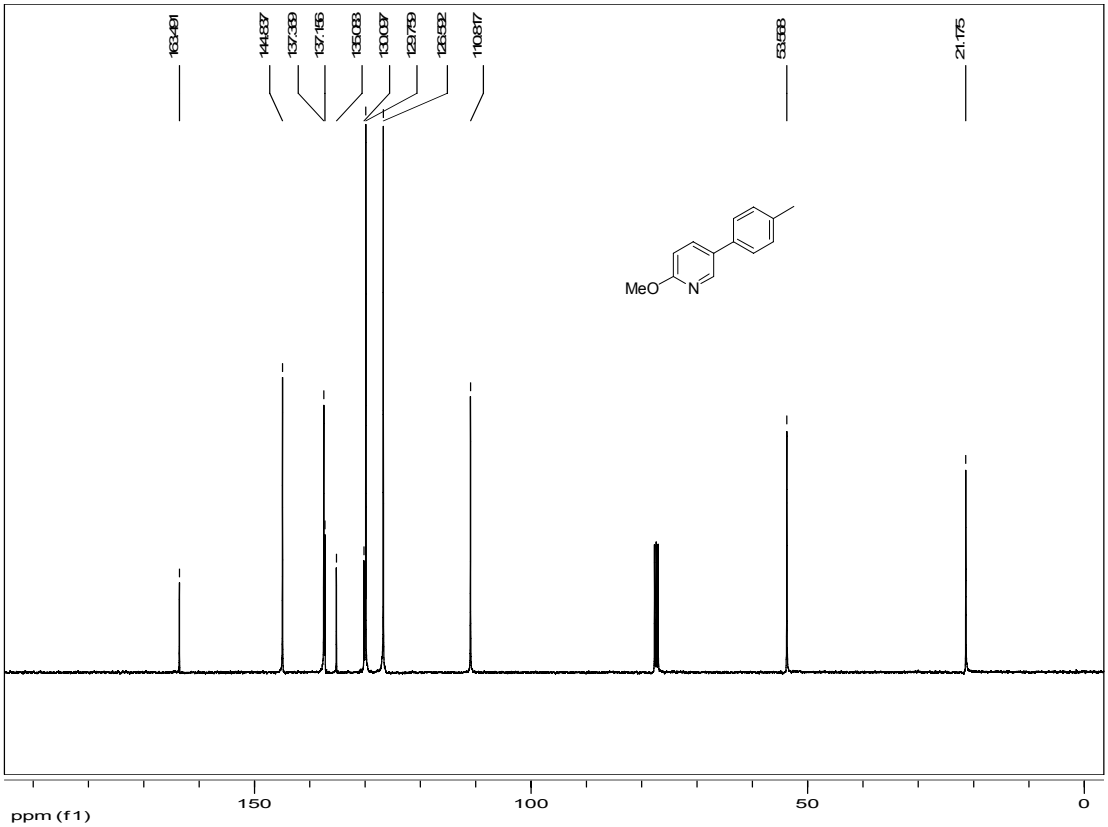

8.686
8.674
7.911
7.891
7.742
7.739
7.722
7.719
7.704
7.689
7.297
7.277
7.261
7.210
7.205
7.193
7.183
7.177
2.411
0.013
N
0.96
2.00
2.03
2.08
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

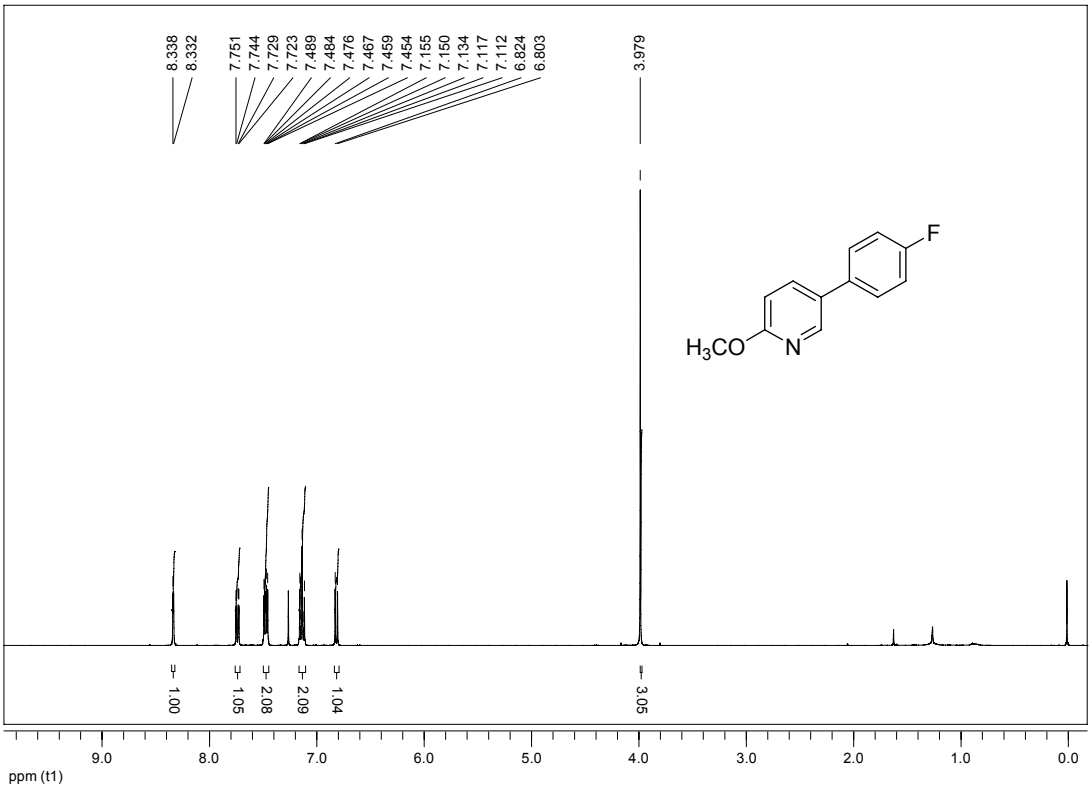

8.656
8.645
7.963
7.941
7.731
7.728
7.711
7.693
7.690
7.675
7.655
7.259
7.184
7.169
7.154
7.010
6.988
3.864
-0.0000
N
O
0.94
1.95
1.97
0.98
1.95
3.00
10.0
5.0
0.0
ppm (t1)

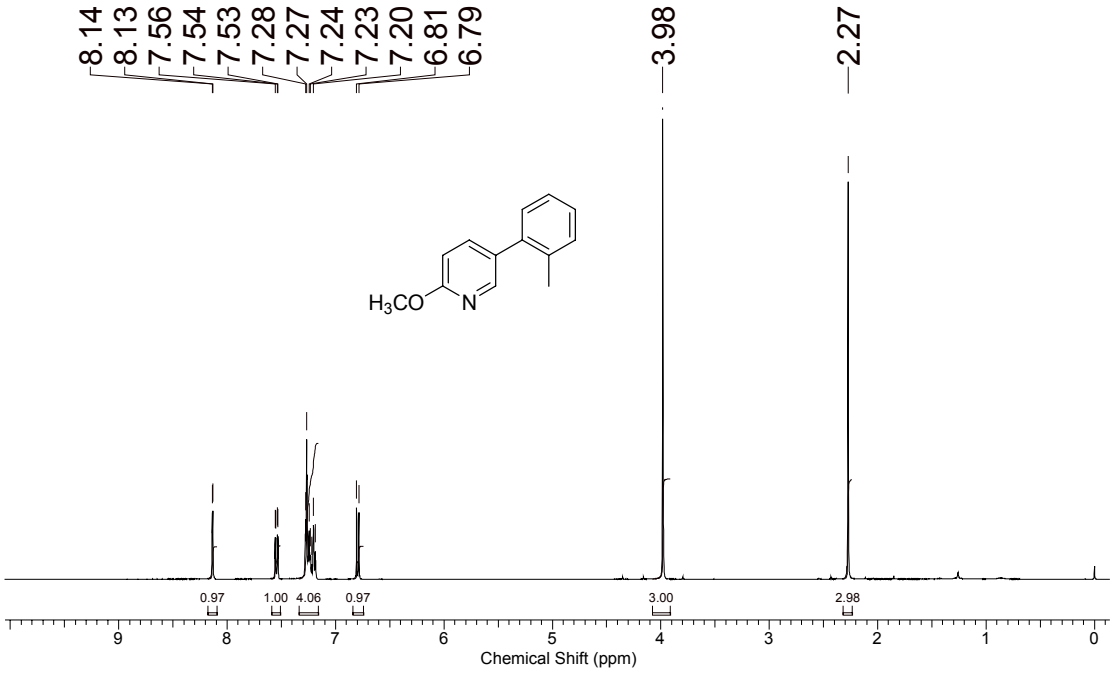

8.667
8.655
7.982
7.977
7.968
7.960
7.946
7.751
7.747
7.732
7.728
7.712
7.709
7.673
7.653
7.246
7.225
7.211
7.195
7.163
7.141
7.120
7.096
N
F
1.00
2.03
2.10
3.22
15.0
10.0
5.0
0.0
ppm (t1)

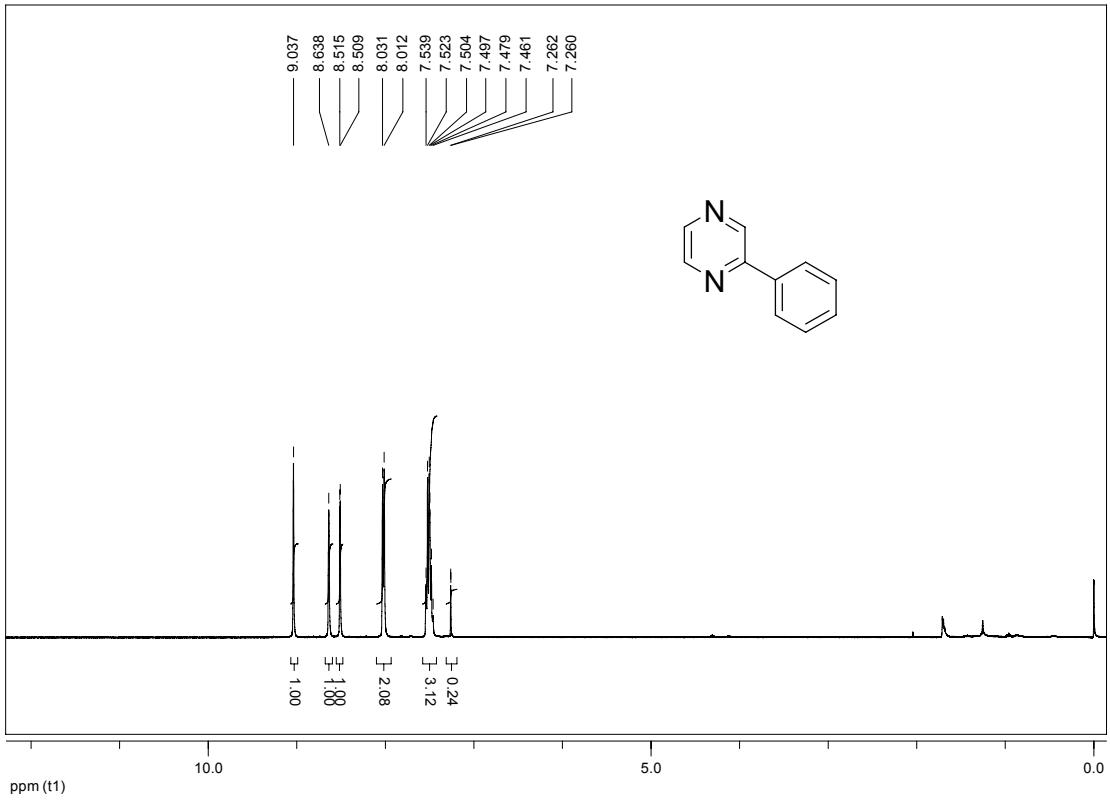

8.391
8.386
7.791
7.785
7.769
7.763
7.526
7.506
7.453
7.434
7.415
7.359
7.340
7.322
6.822
6.800
3.978
H3CO
N
1.00
1.02
1.09
3.04
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

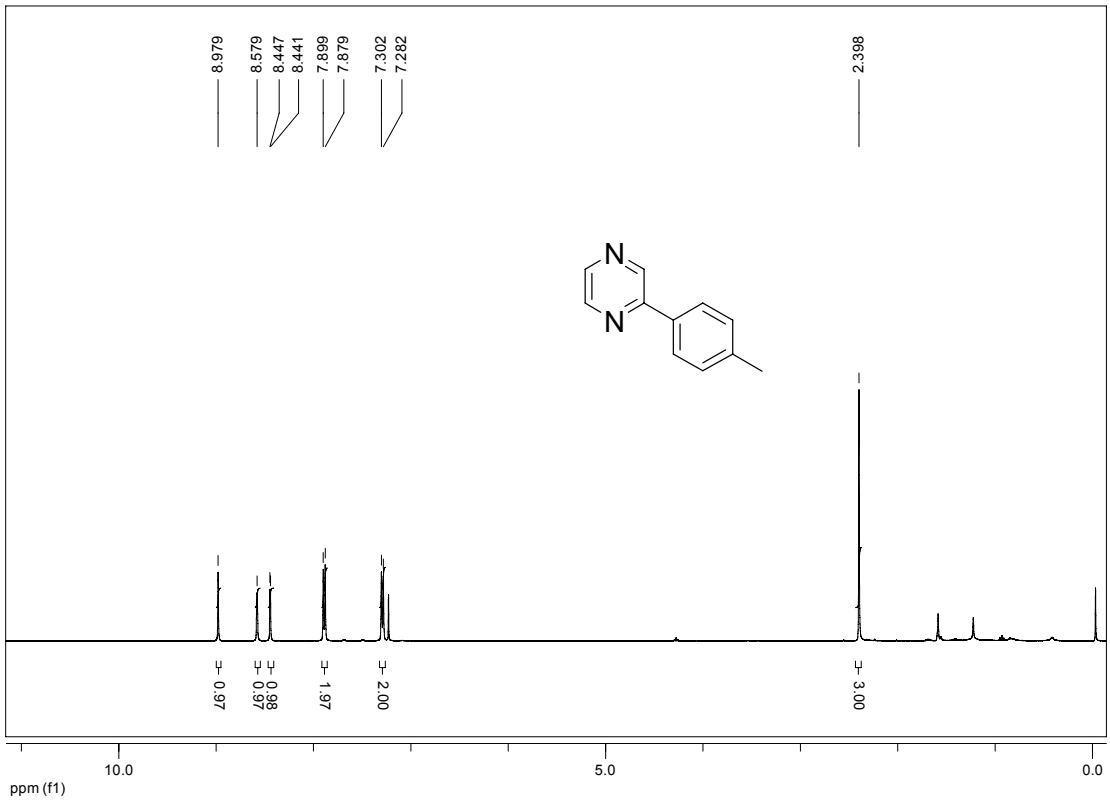

MeO
N
10.0
5.0
0.0
ppm (f1)


163.491
144.837
137.339
137.165
135.068
130.097
129.789
126.892
110.617
53.568
21.175
MeO
N
150
100
50
0
ppm (f1)


8.338
8.332
7.751
7.744
7.729
7.723
7.489
7.484
7.476
7.467
7.459
7.454
7.155
7.150
7.134
7.117
7.112
6.824
6.803
3.979
F
H3CO
N
1.00
1.05
2.08
2.09
1.04
3.05
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


8.14
8.13
7.56
7.54
7.53
7.28
7.27
7.24
7.23
7.20
6.81
6.79
3.98
2.27
H3CO
N
0.97
1.00
4.06
0.97
3.00
2.98
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


9.037
8.638
8.515
8.509
8.031
8.012
7.539
7.523
7.504
7.497
7.479
7.461
7.262
7.260
N
N
1.00
1.00
2.08
3.12
0.24
10.0
5.0
0.0
ppm (t1)


8.979
8.579
8.447
8.441
7.899
7.879
7.302
7.282
2.398
N
N
0.97
0.97
0.98
1.97
2.00
3.00
10.0
5.0
0.0
ppm (f1)