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Oxygen-promoted ligand-free palladium-catalyzed Suzuki reaction in aqueous media

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Materials and Methods

All aryl bromides and aryl boronic acids were used as received (Alfa Aesar, Avocado). All other chemicals were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a Varian Inova 400 spectrometer. Chemical shifts are reported in ppm relative to TMS. UV-vis spectroscopy measurements (300 nm-700 nm) were performed on a Beijing Rui-Li UV-2100 using quartz cells. All products were isolated by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90°C), unless otherwise noted. Compounds described in the literature were characterized by comparison of their ^{1}H NMR spectra to reported data.

Typical procedure for Suzuki-Miyaura reaction

A mixture of aryl bromide (0.5 mmol), arylboronic acid (0.75 mmol), palladium loading (0.5 mol %), K_2CO_3 (1 mmol, 138 mg) and 50% ethanol (4 mL) was stirred at 25 °C for the indicated time. The mixture was then added to brine (10 mL) and extracted four times with ethyl acetate (4 ×10 mL). The solvent was concentrated *in vacuo* and the product was isolated by short chromatography on a silica gel (200-300 mesh) column.

Control experiments under different atmosphere

Suzuki reaction performed in oxygen for example:

A mixture of aryl bromide (0.5 mmol), phenylboronic acid (0.75 mmol), $PdCl_2$ (0.5 mol %, 0.44 mg), K_2CO_3 (1 mmol) and 50% ethanol (4 mL) was stirred at 25 °C for indicated time with a balloon full of oxygen. The mixture was added to brine (10 mL) and extracted four times with ethyl acetate (4 ×10 mL), the solvent was evaporated *in vacuo* and the product isolated by column chromatography.

Tabel 1 Effects of bases on the reaction of 4-bromoanisole with phenylboronic acid

Entry	Base	Isolated Yield (%)
1	K_2CO_3	100
2	NaOH	78
3	*t*-BuOK	84
4	$K_3PO_4 \cdot 7H_2O$	83
5	Na_2CO_3	10
6	CH_3COONa	71
7	K_2CO_3	99[b]

[a] Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.75 mmol), $PdCl_2$ (0.5 mol%), base (1.0 mmol), reaction time: 30 min, 50% EtOH (4 mL), 25 °C, in air. [b] 1.5 mmol K_2CO_3 was used.

Table 2 Effects of the ratio of ethanol to water on the Suzuki reaction.

Entry	Solvent	Isolated Yield (%)
1	Pure H_2O	Trace
2	EtOH/H_2O = 1/2	37
2	EtOH/H_2O = 1/1	100
3	EtOH/H_2O = 2/1	92

Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.75 mmol), PdCl2 (0.5 mol%), K_2CO_3 (1.0 mmol), reaction time: 30 min, 25 °C, in air.

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, 2H), 7.31 (d, J = 7.2 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), ppm.

4-acetylbiphenyl[2]

^{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-phenylbenzonitrile[3]
^{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 = 7.2 Hz, 2H), 7.45 (t, J = 9.2 Hz, 1H), ppm.

4-methoxyl-2'-methylbiphenyl[4]
^{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.

4-methoxyl-3'-methylbiphenyl[4]
^{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-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.

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

2-methoxyl-2'-methylbiphenyl[6]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.40 (t, J = 8.0 Hz, 1H), 7.21 - 7.32 (m, 5H), 7.08 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H), 2.22 (s, 3H), ppm.

2-methoxyl-3'-methylbiphenyl[7]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.31-7.37 (m, 5H), 7.70 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 2.43 (s, 3H), ppm.

2-methoxyl-4'-methylbiphenyl[7]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.42 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 6.6 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.96 - 7.03 (m, 2H), 3.80 (s, 3H), 2.39 (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.

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-phenylpyridine[9]
^{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-(2-tolyl) pyridine[9]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.68 (m, 1H), 7.68-7.72 (m, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.18 - 7.28 (m, 4H), 2.36 (s, 3H), ppm.

2-(3-tolyl) pyridine[9]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.68 (d, J = 4.8 Hz, 1H), 7.83 (s, 1H), 7.70 - 7.76 (m, 3H), 7.35 (t, J = 7.6 Hz, 1H), 7.19 - 7.25 (m, 2H), 2.43 (s, 3H), ppm.

2-*p*-tolylpyridine[9]
^{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-(2-methoxylphenyl) pyridine[9]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.69 (d, J = 4.4 Hz, 1H), 7.65 - 7.80 (m, 3H), 7.37 (t, J =1.6 Hz, 1H), 7.17 (m, 1H), 7.09(t, J = 7.6 Hz, 1H), 6.98(d, J = 8.0 Hz, 1H), 3.81 (s, 3H), ppm.
2-(4-methoxyphenyl) pyridine[9]
^{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[9]
^{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.

5-(4-methyl phenyl) pyrimidine[9]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.18 (s, 1H), 8.93 (s, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 2.43 (s, 3H), ppm.

5-phenylpyrimidine[9]
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.17 (s, 1H), 8.92 (s, 2H), 7.43 - 7.59 (m, 5H), ppm.

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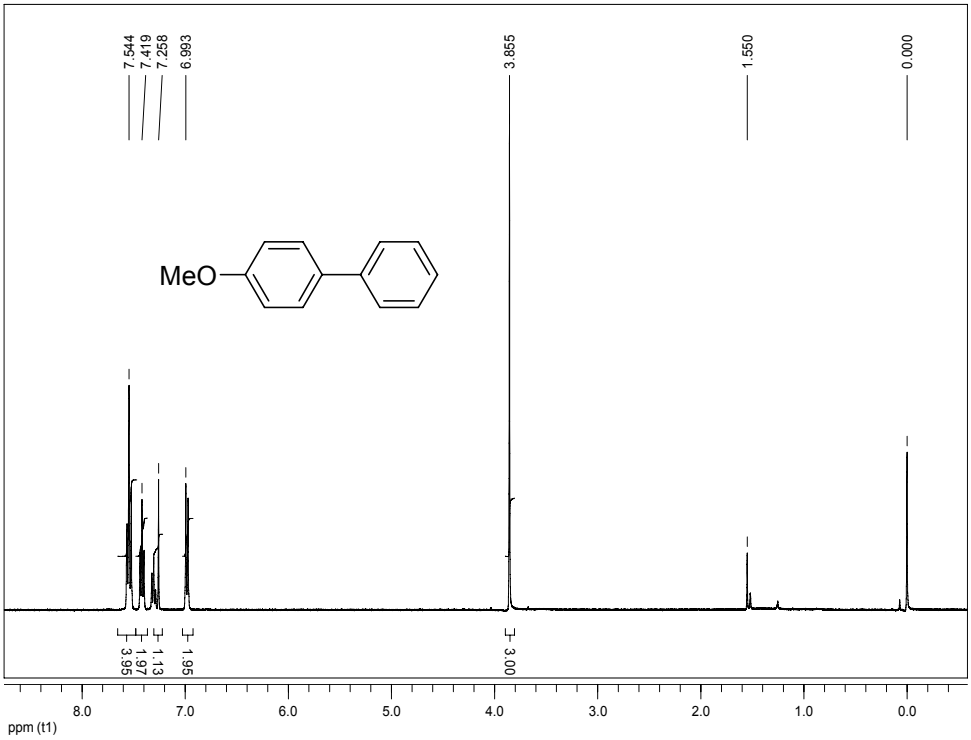
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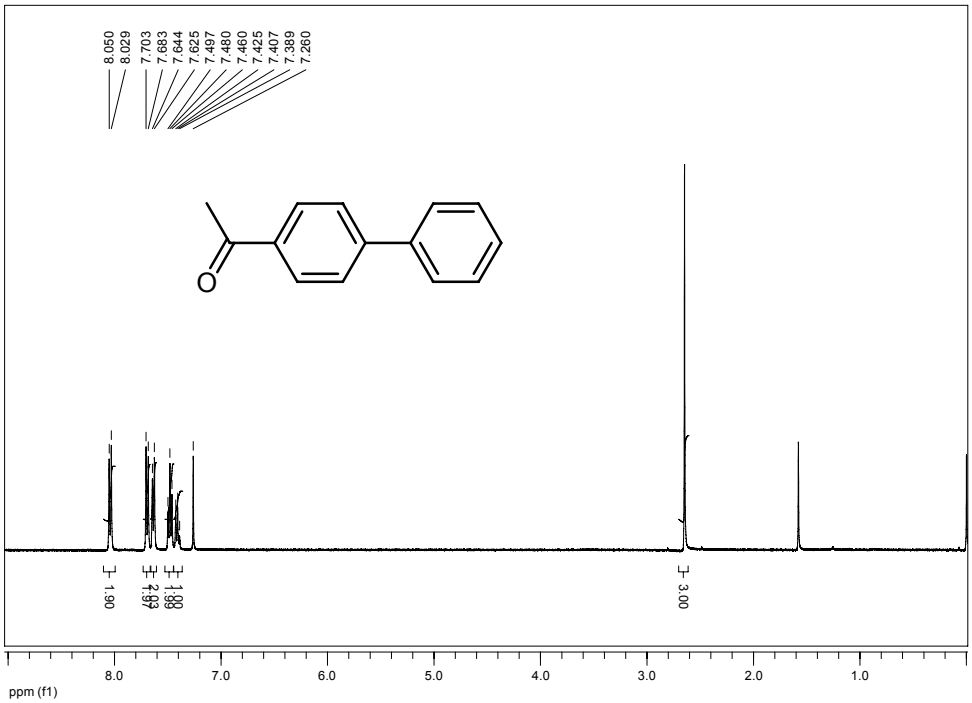
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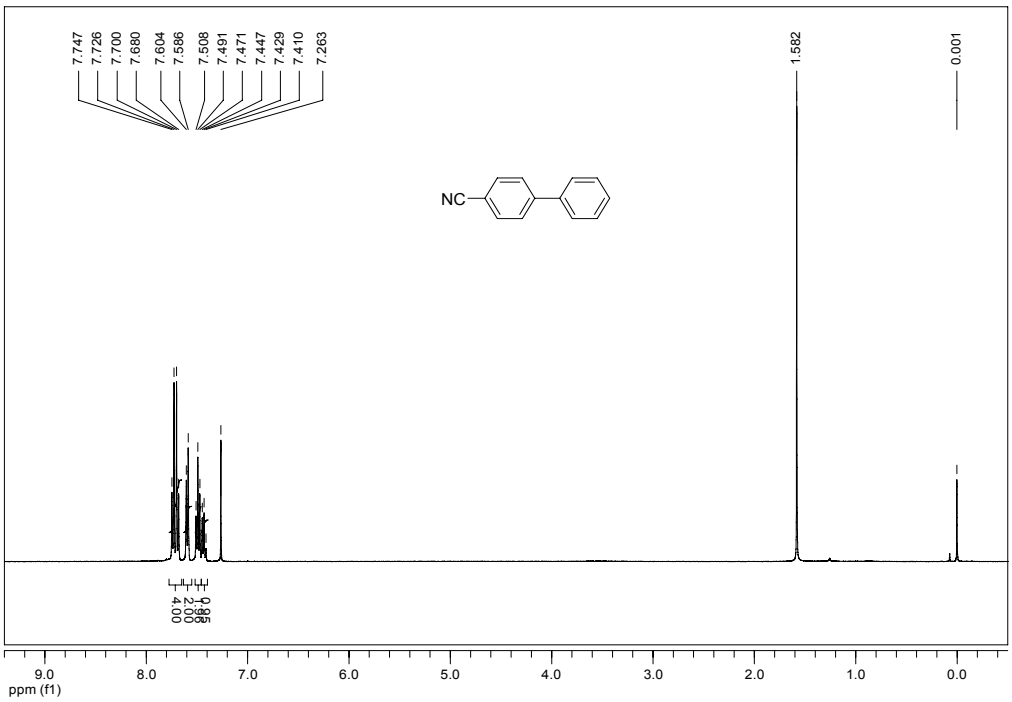
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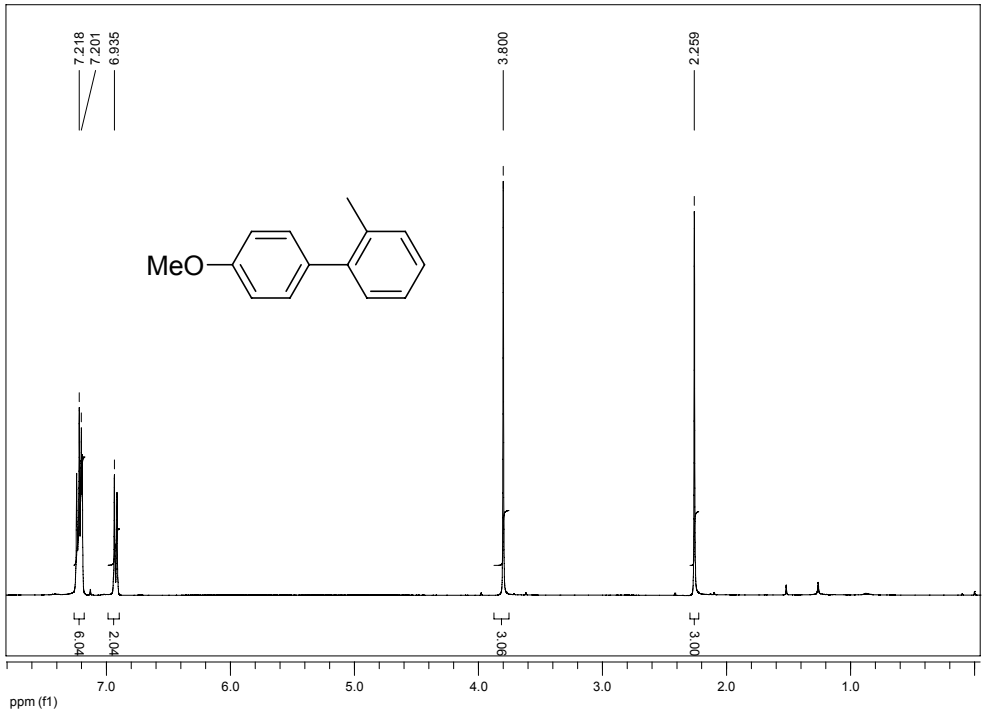
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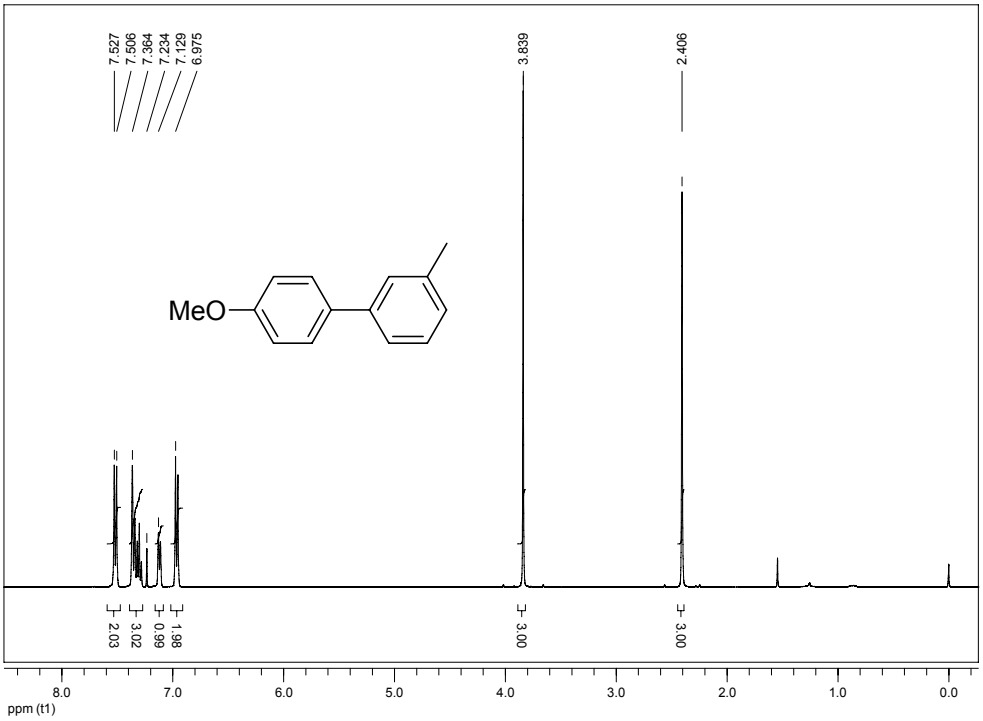
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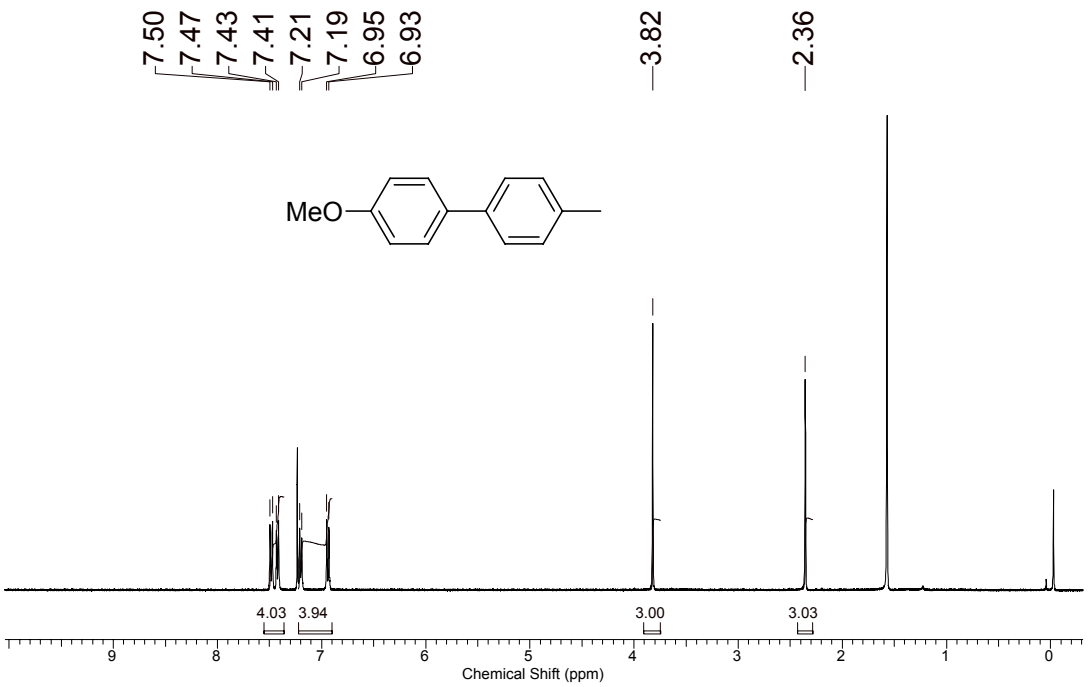
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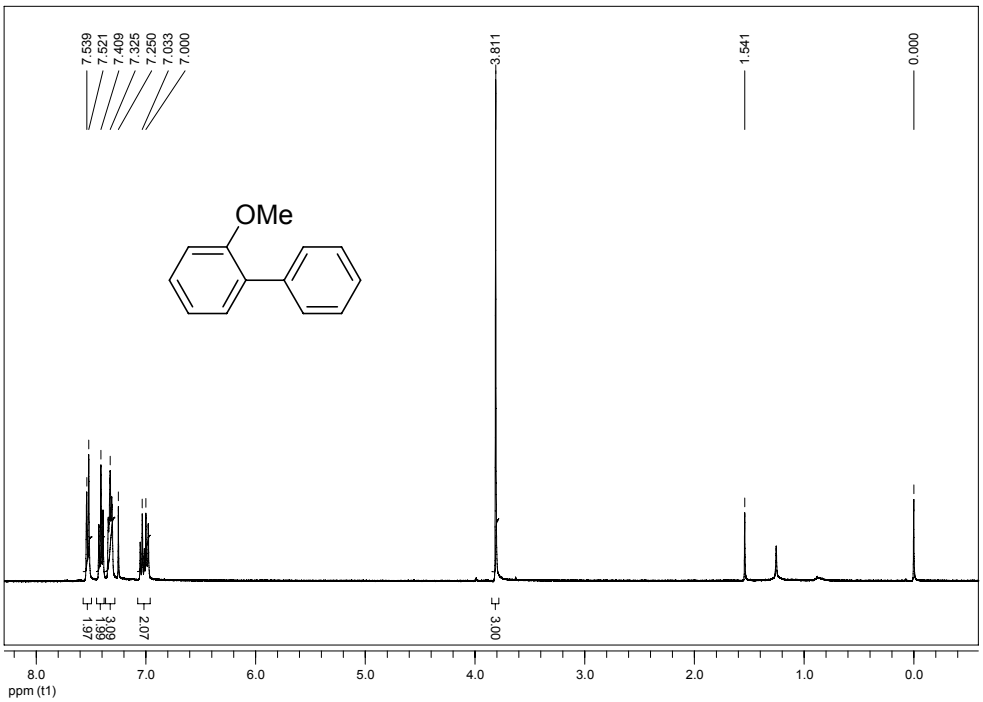
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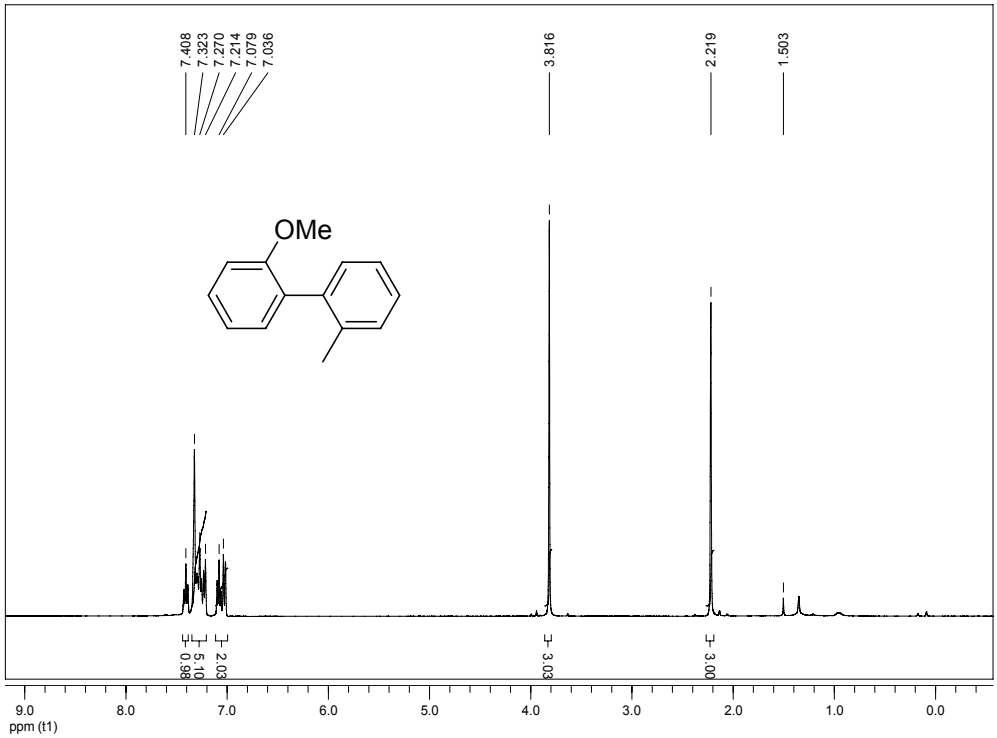
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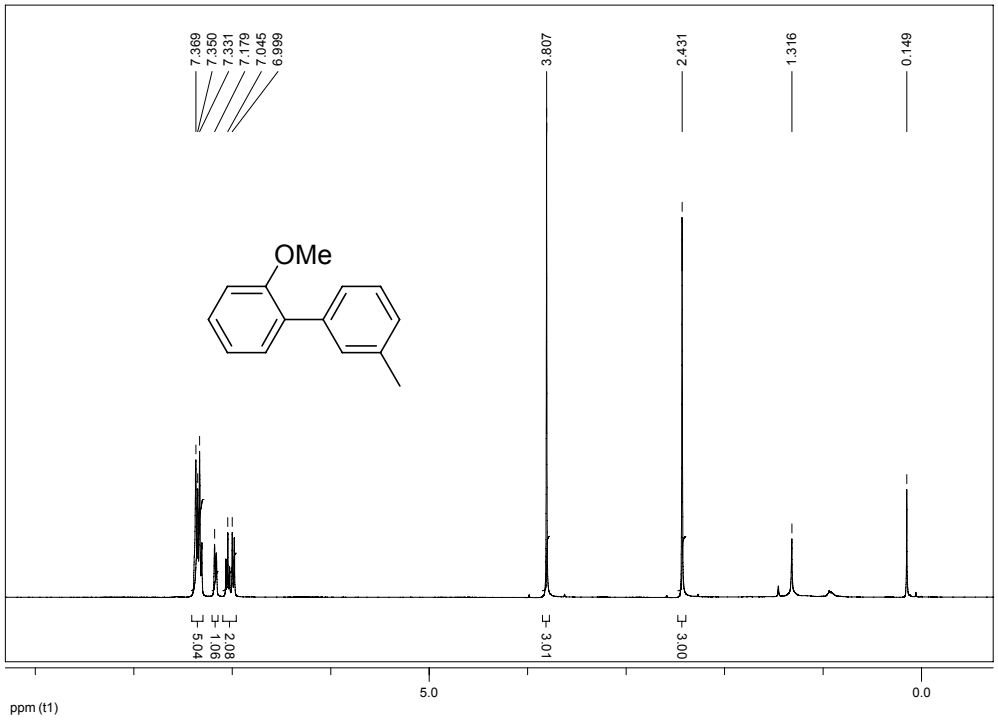
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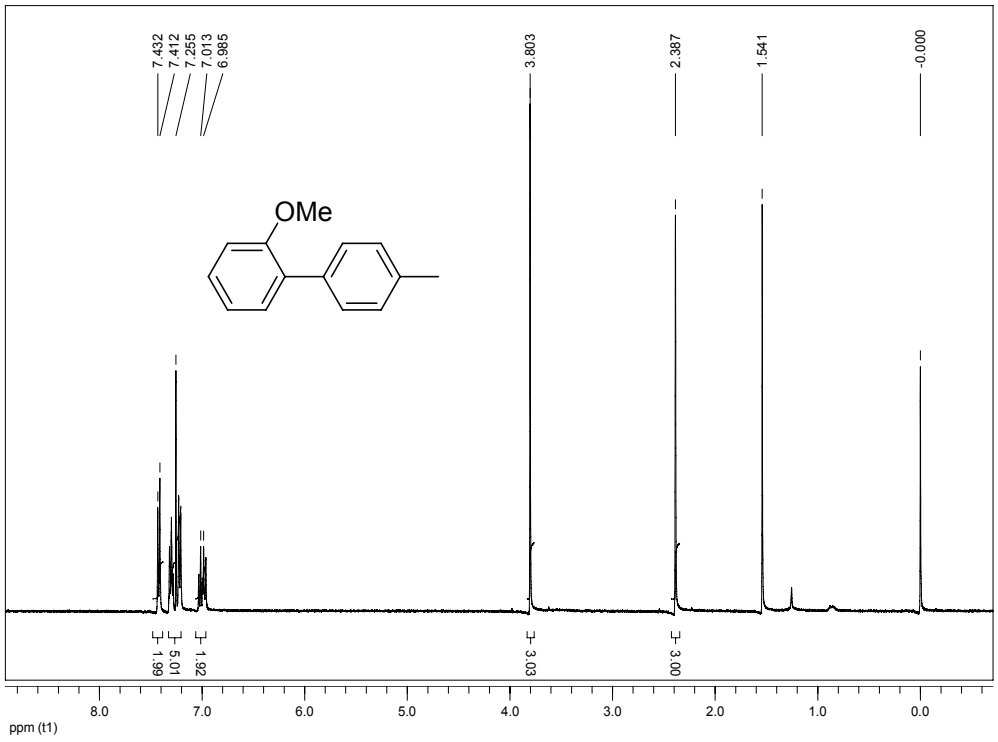
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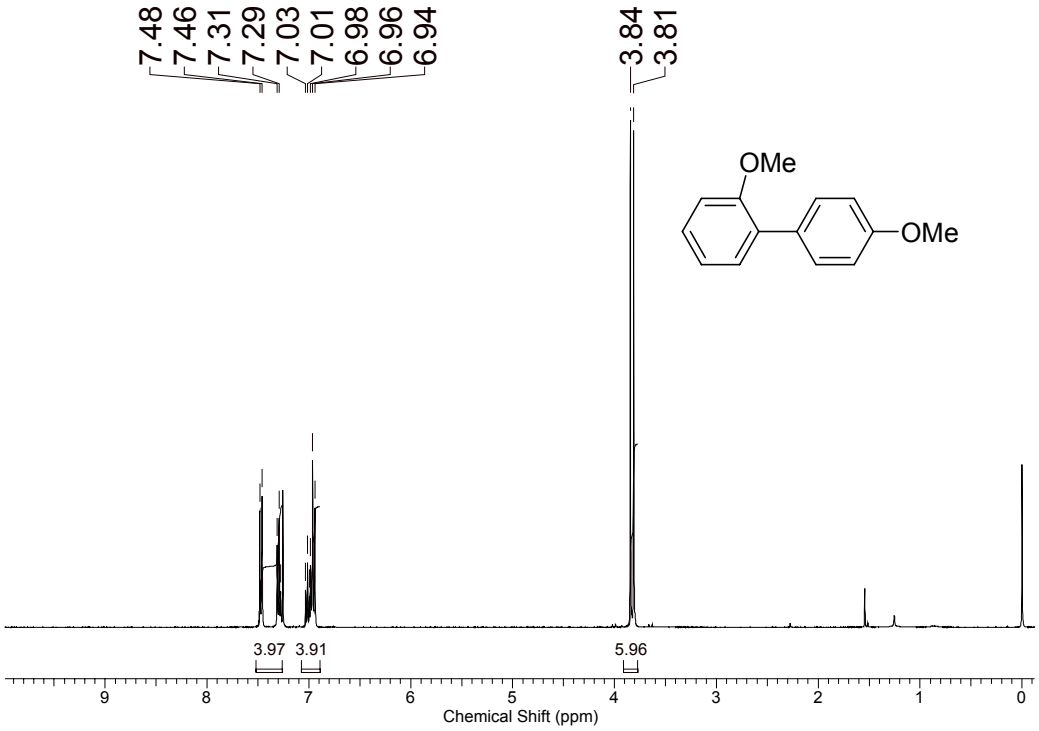
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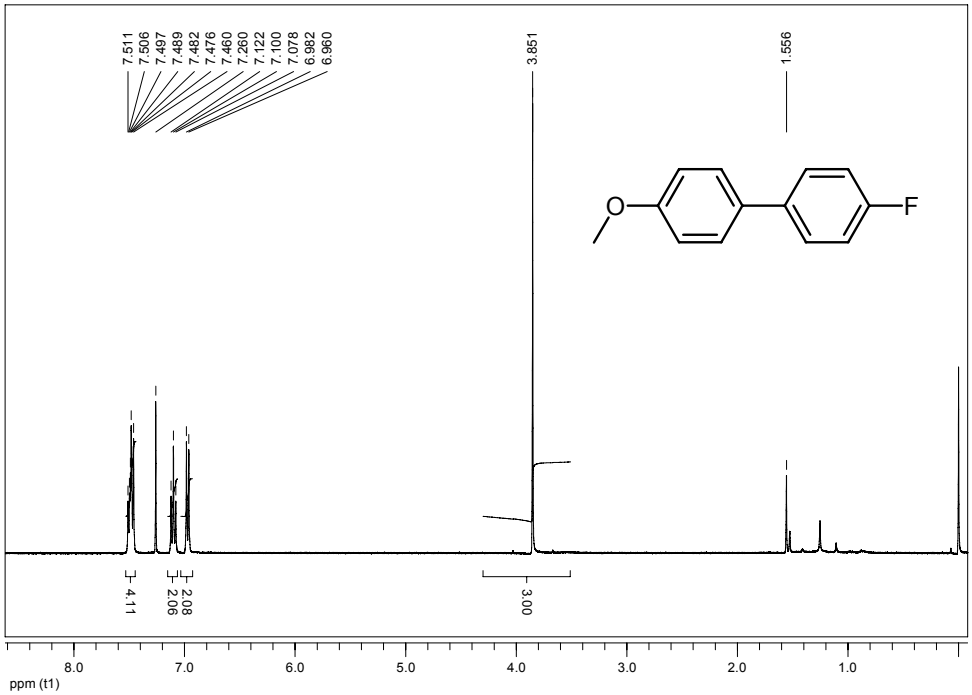
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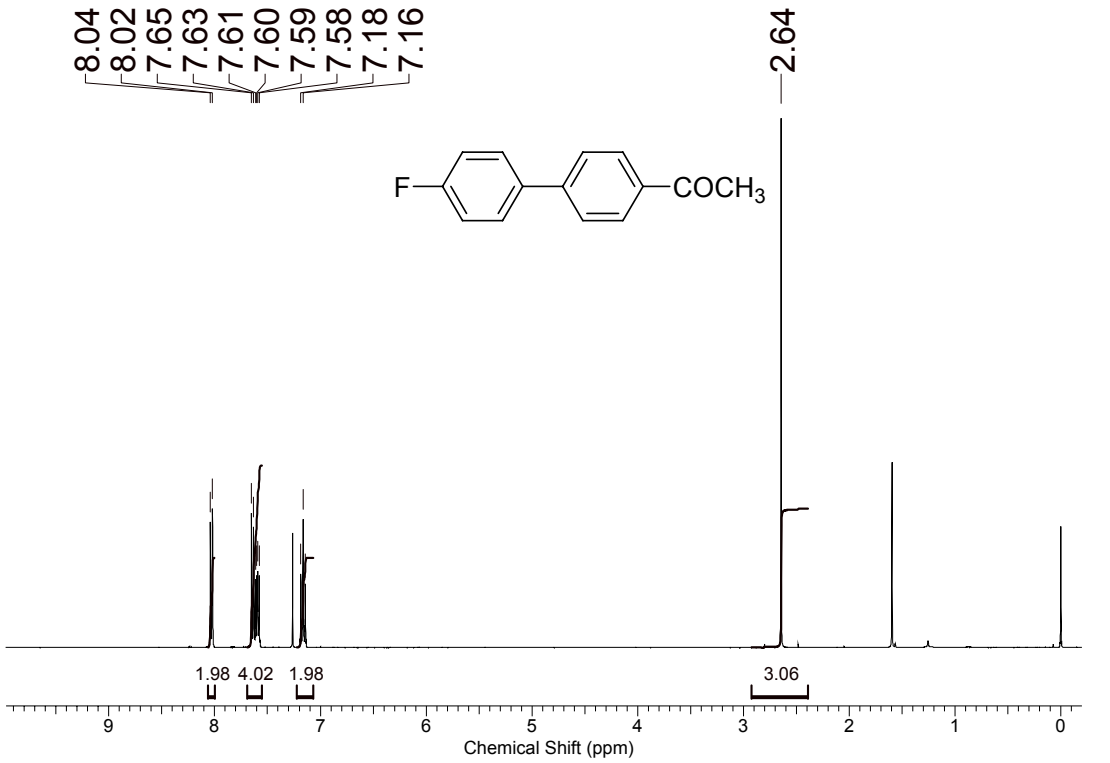
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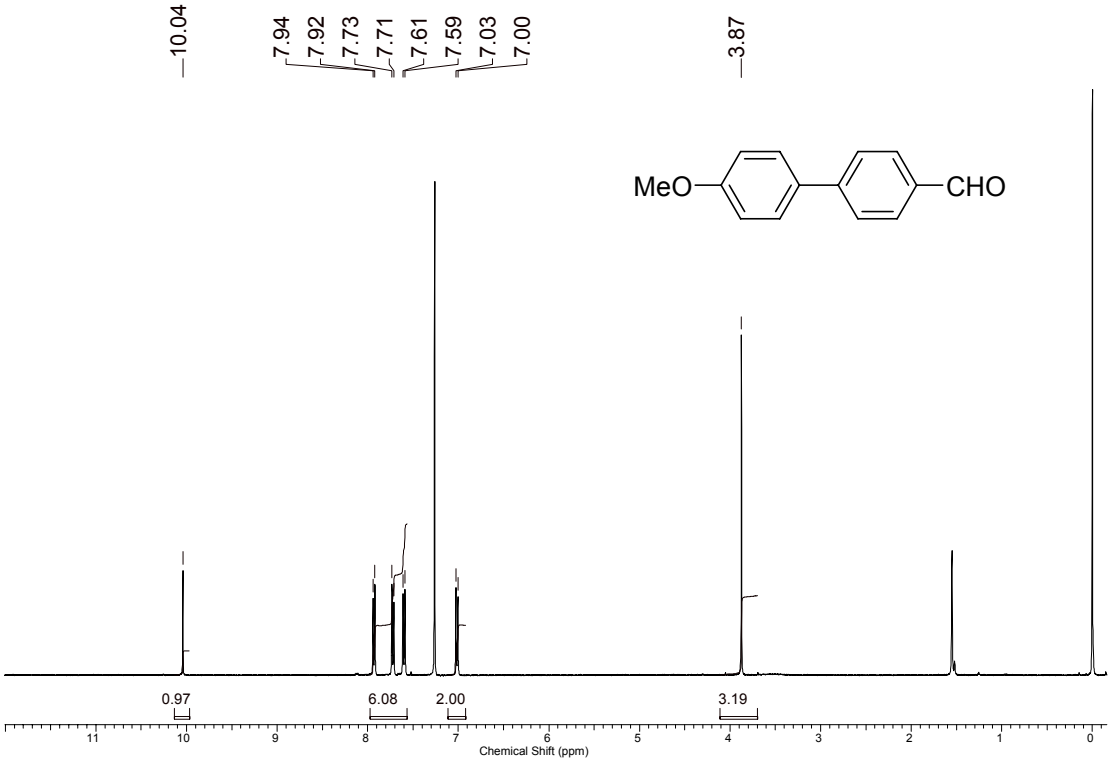
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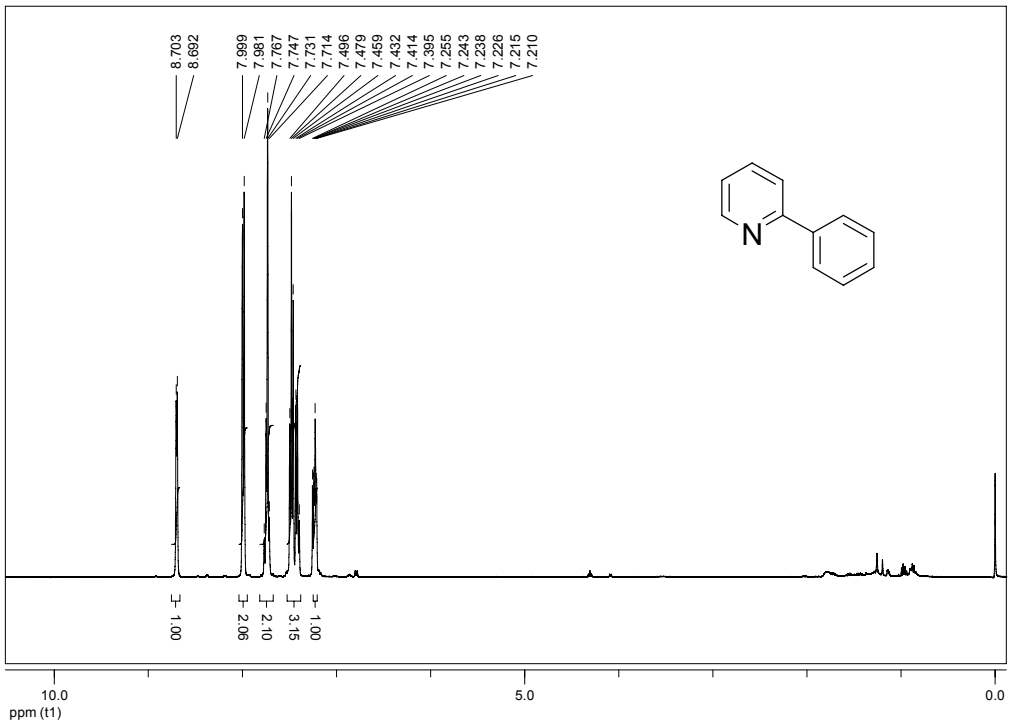
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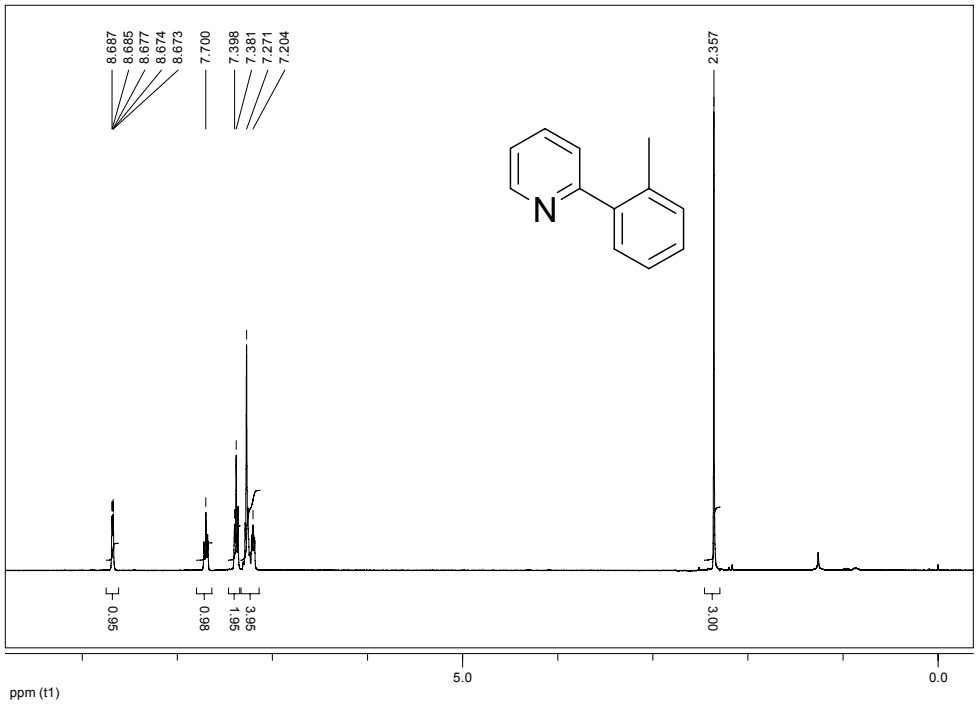
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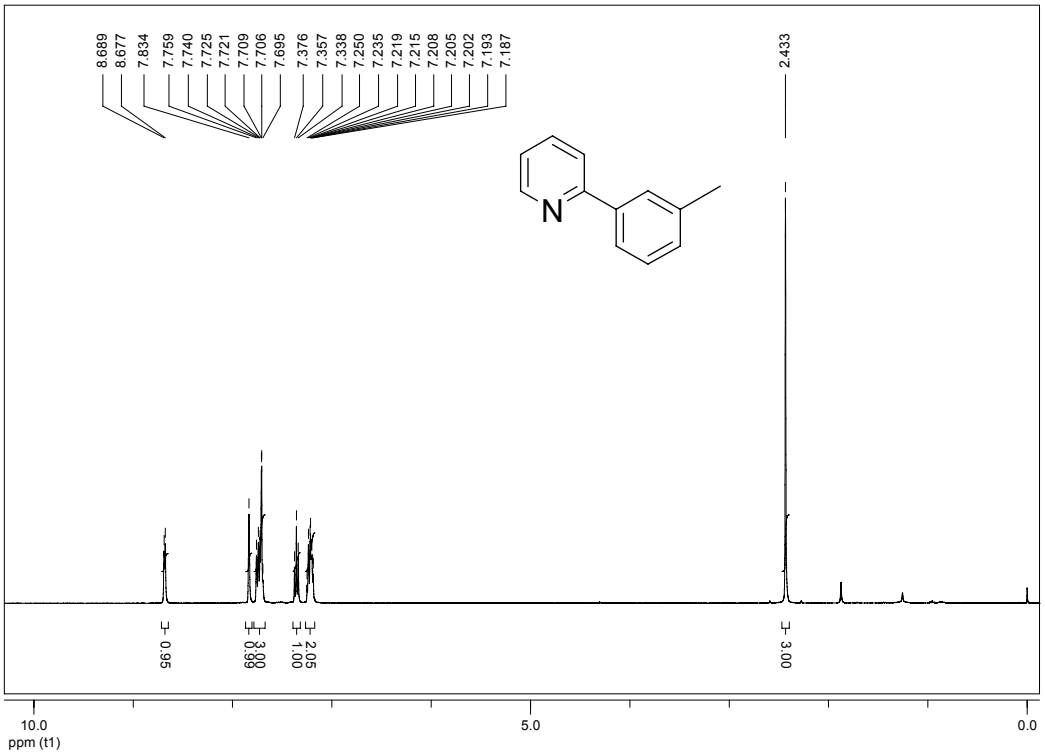
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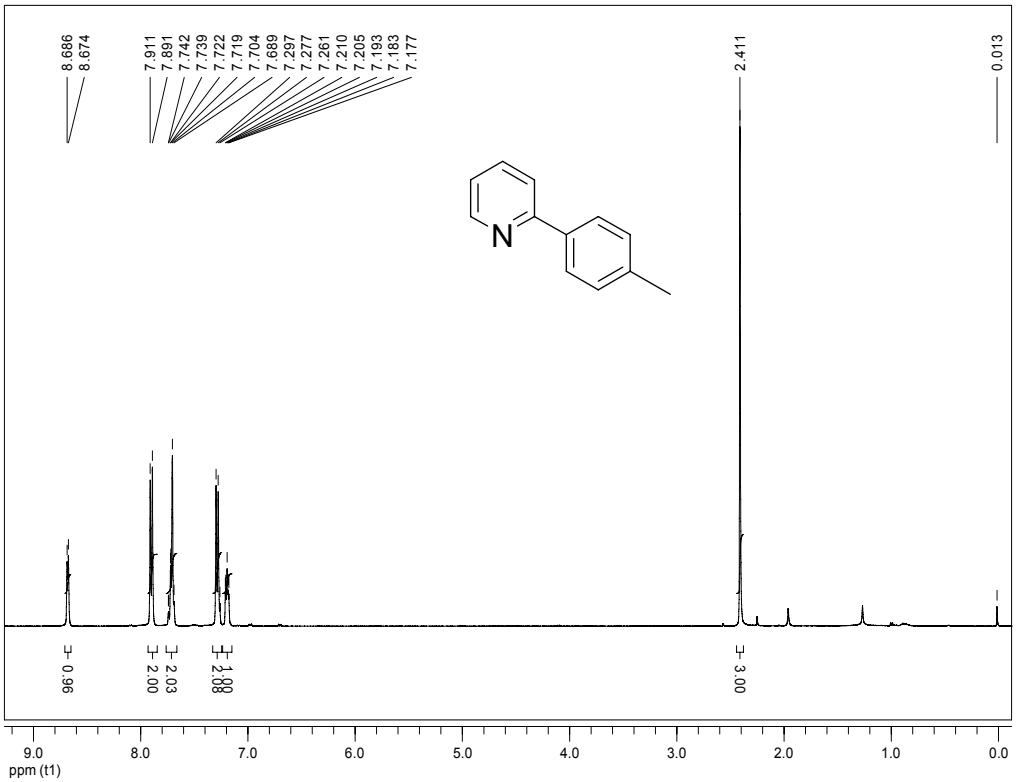
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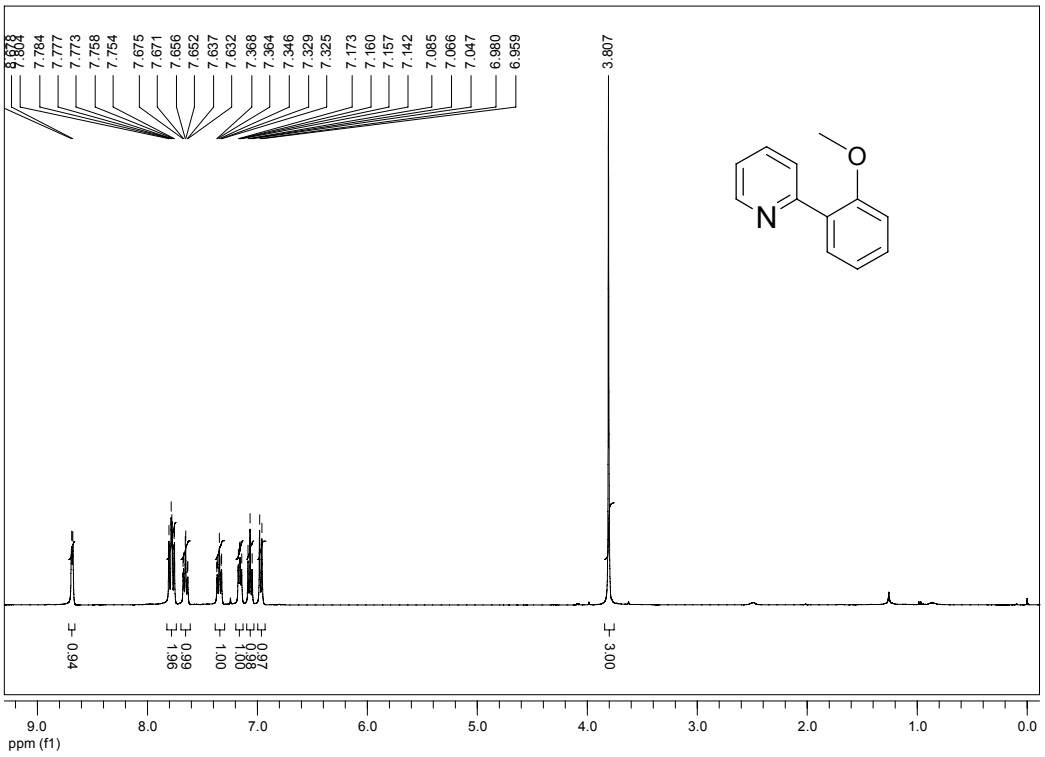
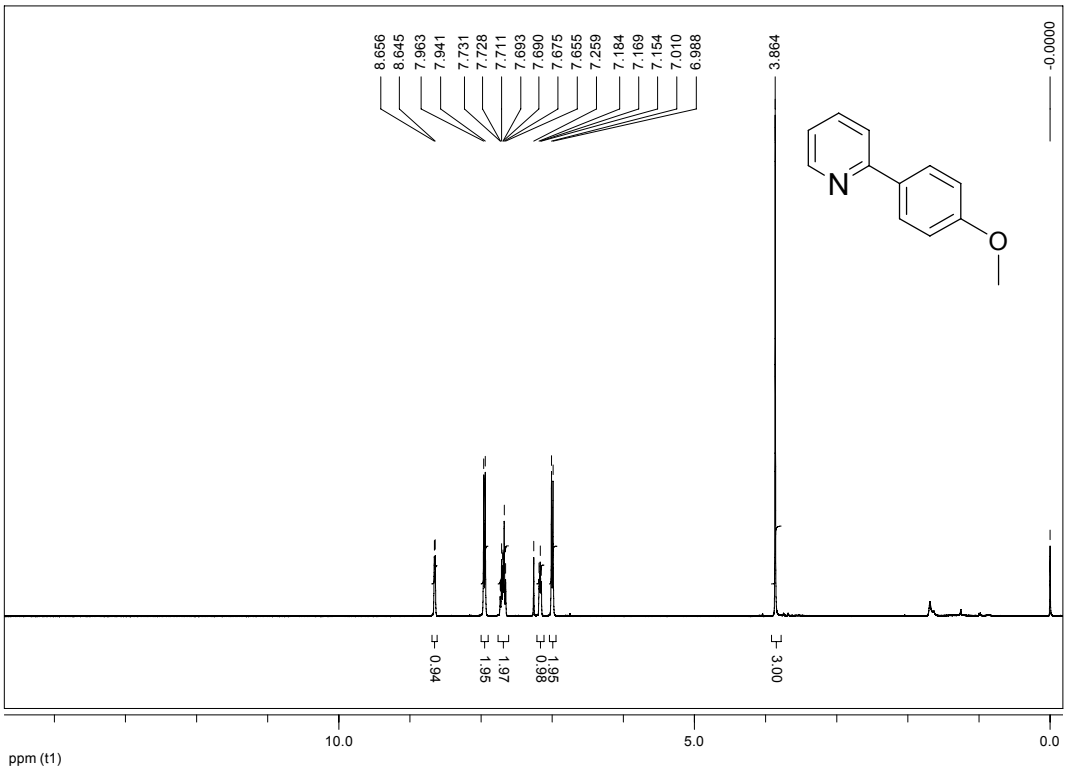
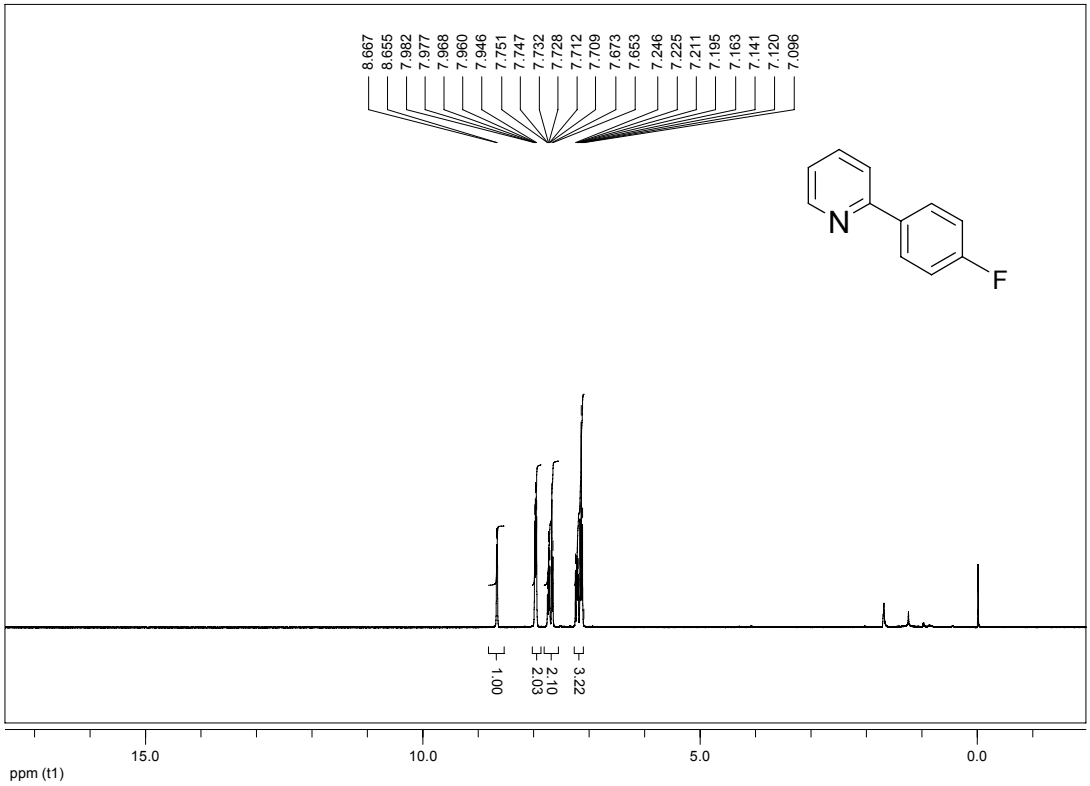
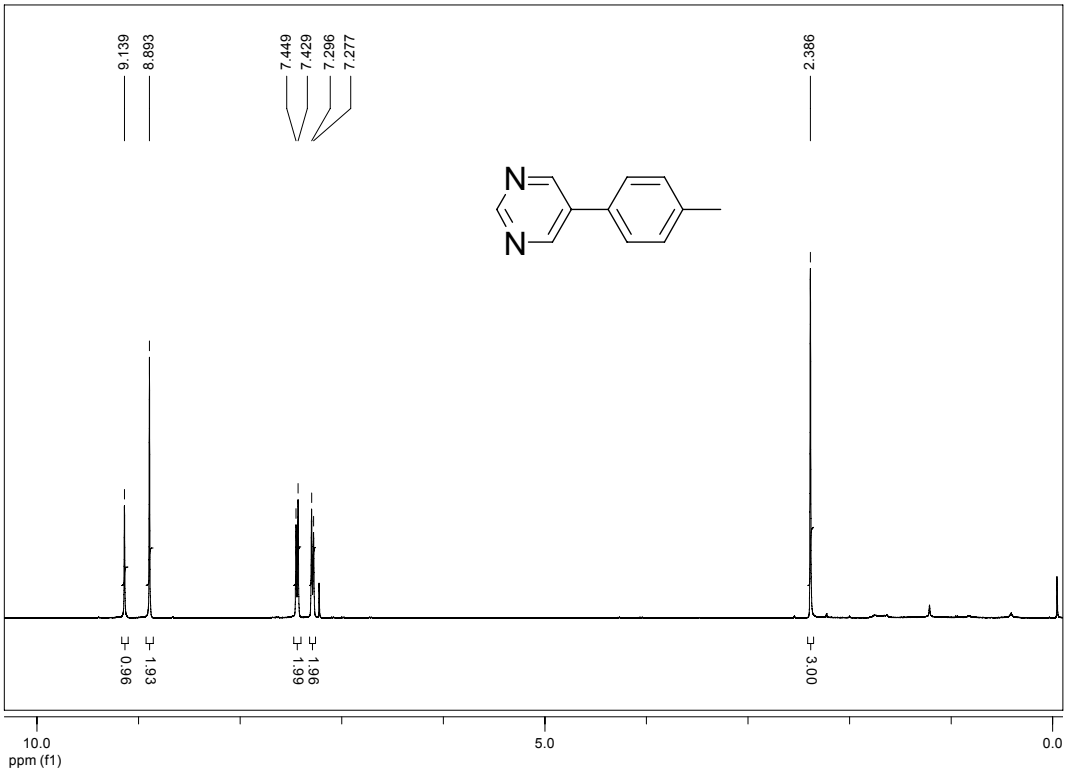
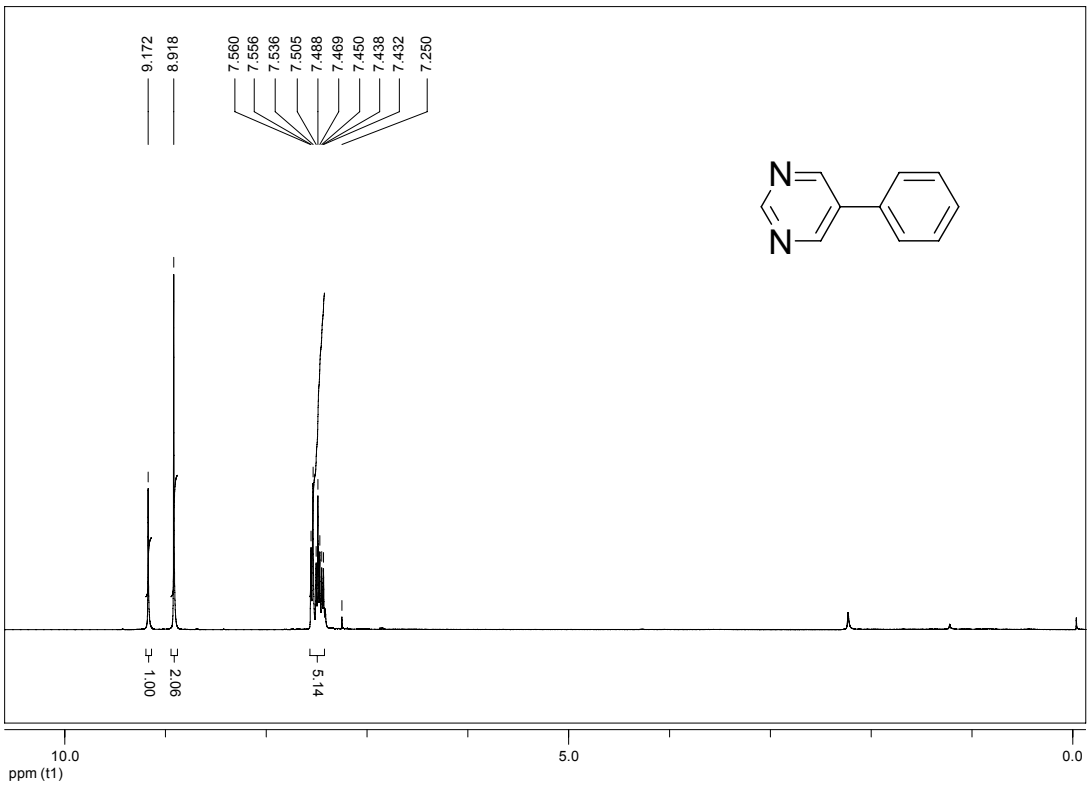

8.678
8.663
7.784
7.777
7.773
7.758
7.754
7.675
7.671
7.656
7.652
7.637
7.632
7.368
7.364
7.346
7.329
7.325
7.173
7.160
7.157
7.142
7.085
7.066
7.047
6.980
6.959
3.807
O
N
0.94
1.96
0.99
1.00
1.00
0.98
0.97
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


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
1.85
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)


9.139
8.893
7.449
7.429
7.296
7.277
2.386
N
N
0.96
1.93
1.99
1.96
3.00
10.0
5.0
0.0
ppm (f1)


9.172
8.918
7.560
7.556
7.536
7.505
7.488
7.469
7.450
7.438
7.432
7.250
N
N
1.00
2.06
5.14
10.0
5.0
0.0
ppm (t1)