Minimizing the Amount of Nitromethane in Palladium Catalyzed Cross Coupling with Aryl Halides

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Supporting Information

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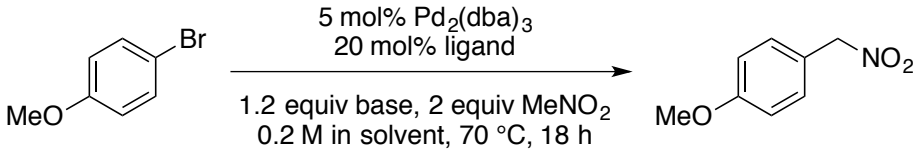
General Methods.

All commercial reagents were used as received without additional purification unless otherwise noted. Nitromethane was distilled from calcium hydride and stored at 0 °C away from light. Anhydrous 1,4-dioxane was purchased from Acros and used as received. Potassium phosphate (tribasic) was dried at 100 °C under vacuum overnight and stored in the glovebox. All purifications were performed via flash column chromatography using EM Reagents Silica Gel 60 (230-400). Analytical thin-layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 254-F plates. Visualization was accomplished with UV light and/or ceric ammonium molybdate stain. ^{1}H NMR and ^{13}C NMR chemical shifts are reported relative to the chloroform solvent resonance peak δ 7.27 for ^{1}H and δ 77.23 for ^{13}C. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, dd = doublet of doublets, td = triplet of doublets, tt = triplet of triplets, m = multiplet), coupling constants, and number of protons. Melting points are uncorrected. All yields refer to isolated yields, and product purity was determined by ^{1}H NMR spectroscopy.

Parallel Microscale Experimentation Data



96 well plate: 8 bases, 4 ligands, 3 solvents

Bases:
NaO*t*-Bu, K_3PO_4, Cs_2CO_3, K_2CO_3, Na_2CO_3, $CsHCO_3$, $KHCO_3$, $NaHCO_3$

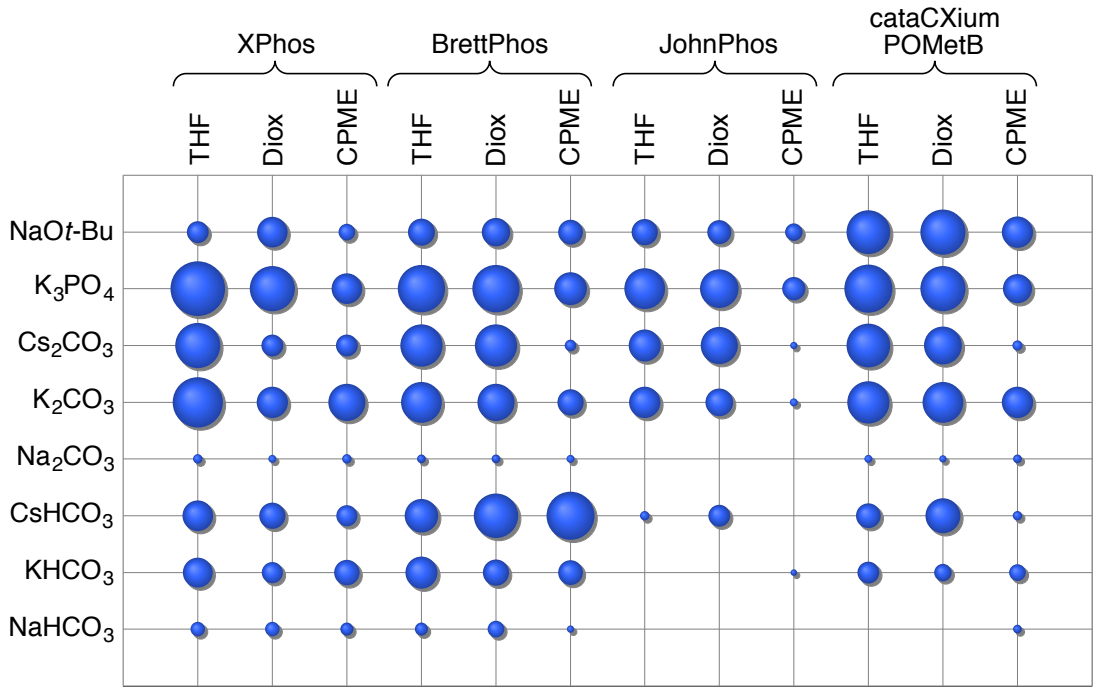
Ligands:
XPhos, BrettPhos, JohnPhos, CataCXium POMetB

Solvents:
THF, 1,4-dioxane, CPME

The ligands (4 μmol) were dosed into the 96-well reactor equipped with 1 mL vials as solutions (50 μL, 0.08 M) in 1,2-dichloroethane. Pd_2dba_3 (1.0 μmol, 50 μL of a 0.02 M solution in benzene) was then added to the vials and the resulting solutions were evacuated to dryness on a JKem-blow-down block. Base (24 μmol, 25 mg/mL slurry in THF) was then added to the ligand/catalyst mixture, and the resulting mixture was evacuated to dryness on a JKem-blow-down block. A parylene stir-bar was added to each vial. Substrate/nitromethane/solvent solutions were prepared with 4-bromoanisole (0.2 M, 20 μmol/reaction) and nitromethane (0.4 M, 40 μmol/reaction) in the requisite solvent and then dosed in the reaction vials (100 μL reaction volume). The reactor block was sealed, removed from the glovebox and heated at 70 ºC for 18 h on an Alligator tumble stirrer (500 rpm). After cooling to ambient temperature, the reactions were quenched *via* dilution with a solution of internal standard in MeCN (2 μmol biphenyl, 0.002M, 500 μL), and the contents were stirred. Into a separate 96-well plate LC block (Analytical Sales and Services, part # 17P687) was added 700 μL of MeCN and then 25 μL aliquots of the diluted reaction mixtures. The 96-well plate LC block was then sealed with a polypropylene 1 mL cap mat (Analytical Sales and Services, part # 96057). The

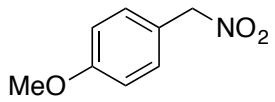
reaction mixtures were analyzed using an Agilent Technologies 1200 series HPLC with a 96-well plate auto-sampler. Assay conditions: Supelco Ascentis Express C18 100 mm x 4.6 mm or ZORBAX Eclipse XDB-C8, 4.6 x 50 mm, 1.8 µm. MeCN with H_2O + 0.1 % H_3PO_4. 1.8 mL/min; 10 % in MeCN to 95 % MeCN in 6 min, hold for 2 min. Post time 2 min. Column at 40 °C; 210 nm.

Bubble chart of the results: Bubble size corresponds to Product:Internal Standard ratio as determined by LC. Note: BrettPhos, $CsHCO_3$, CPME was incorrectly dosed (excess SM and $MeNO_2$) leading to an inaccurately high P/IS value.



Top results based on P/IS ratios.

Ligand	Base	Solvent	P/IS
Xphos	K_3PO_4	THF	5.854
Xphos	K_2CO_3	THF	4.998
cataCXiumPOMetB	K_3PO_4	THF	4.567
BrettPhos	K_3PO_4	THF	4.519
BrettPhos	K_3PO_4	Diox	4.412
Xphos	Cs_2CO_3	THF	4.062
cataCXiumPOMetB	K_3PO_4	Diox	4.050
Xphos	K_3PO_4	Diox	4.047
cataCXiumPOMetB	NaOtBu	Diox	4.015



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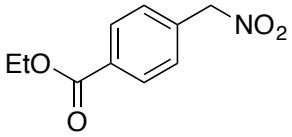

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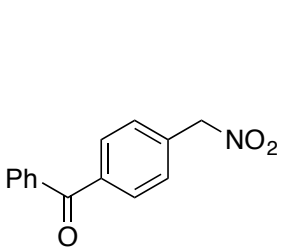

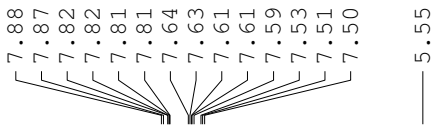

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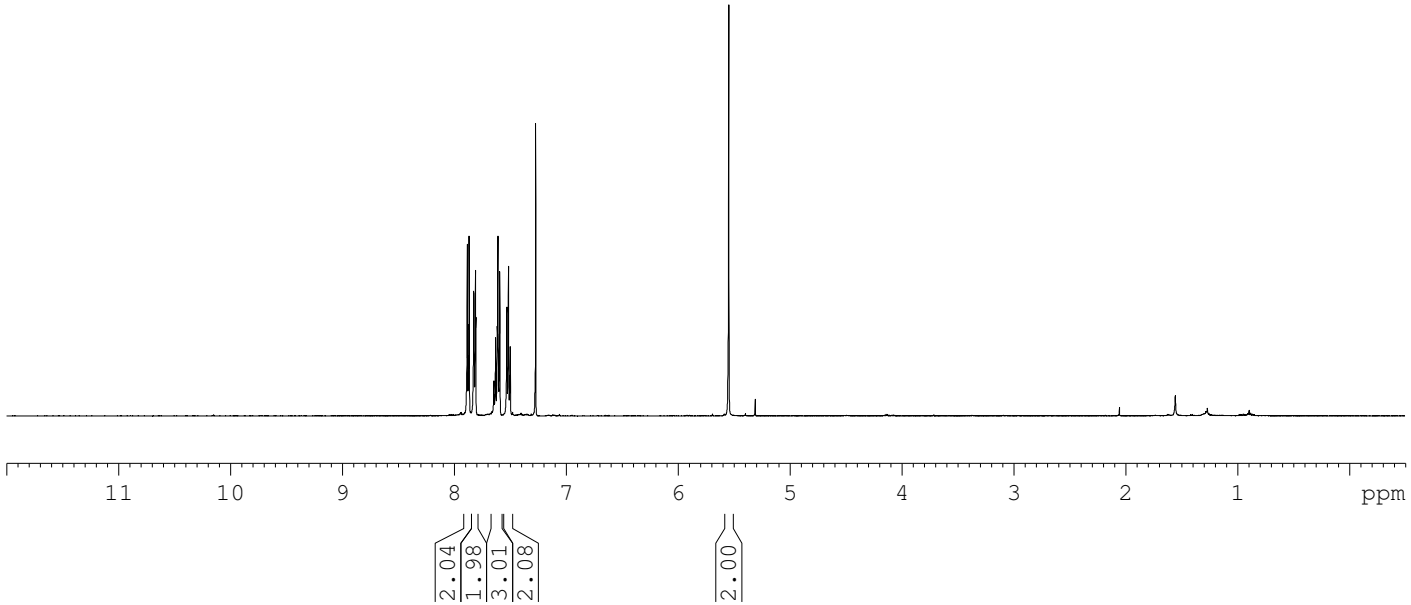

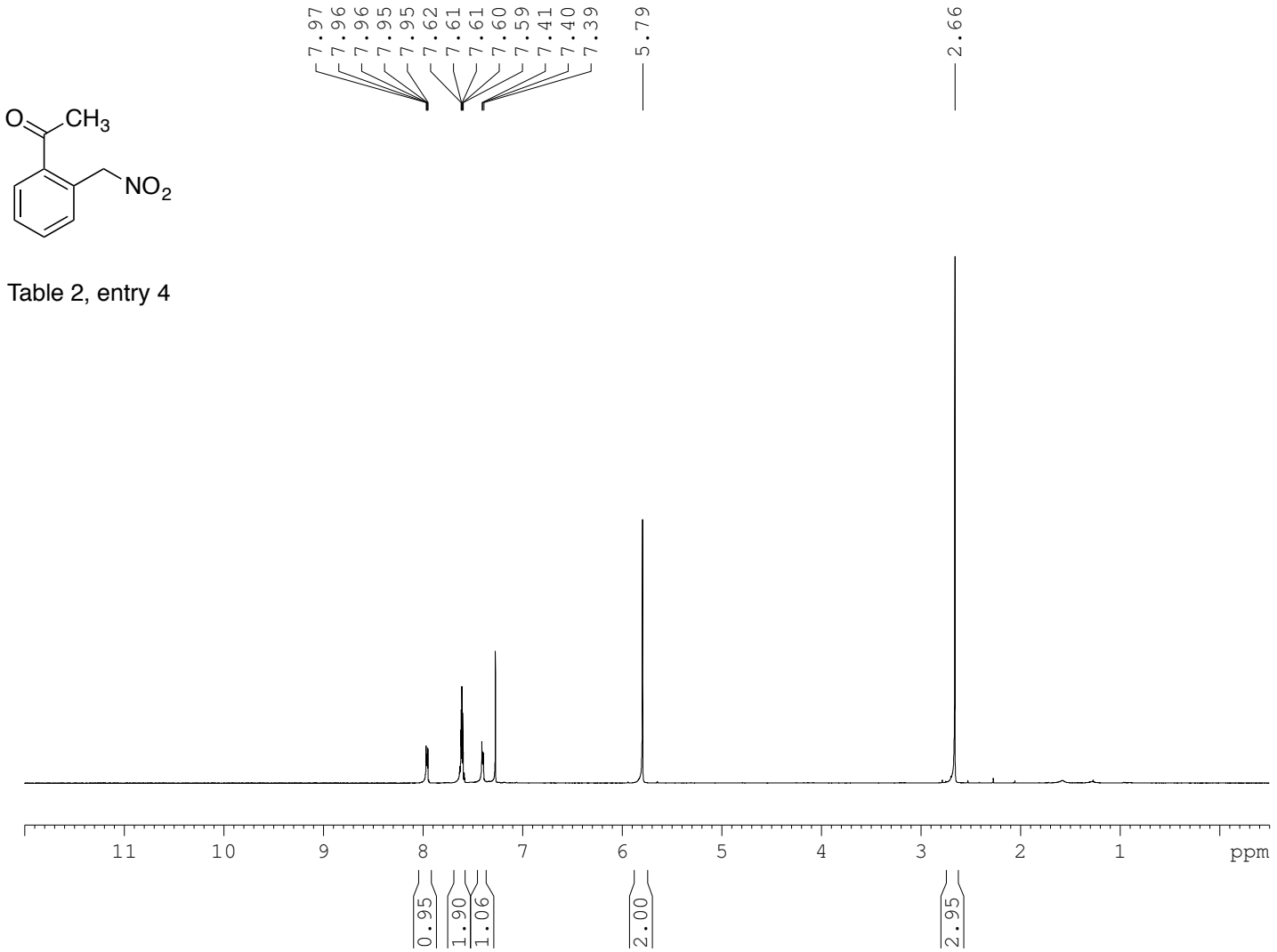

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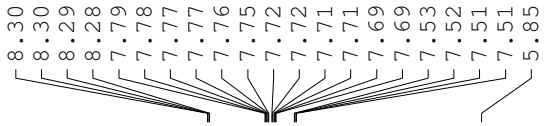

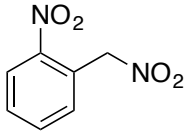

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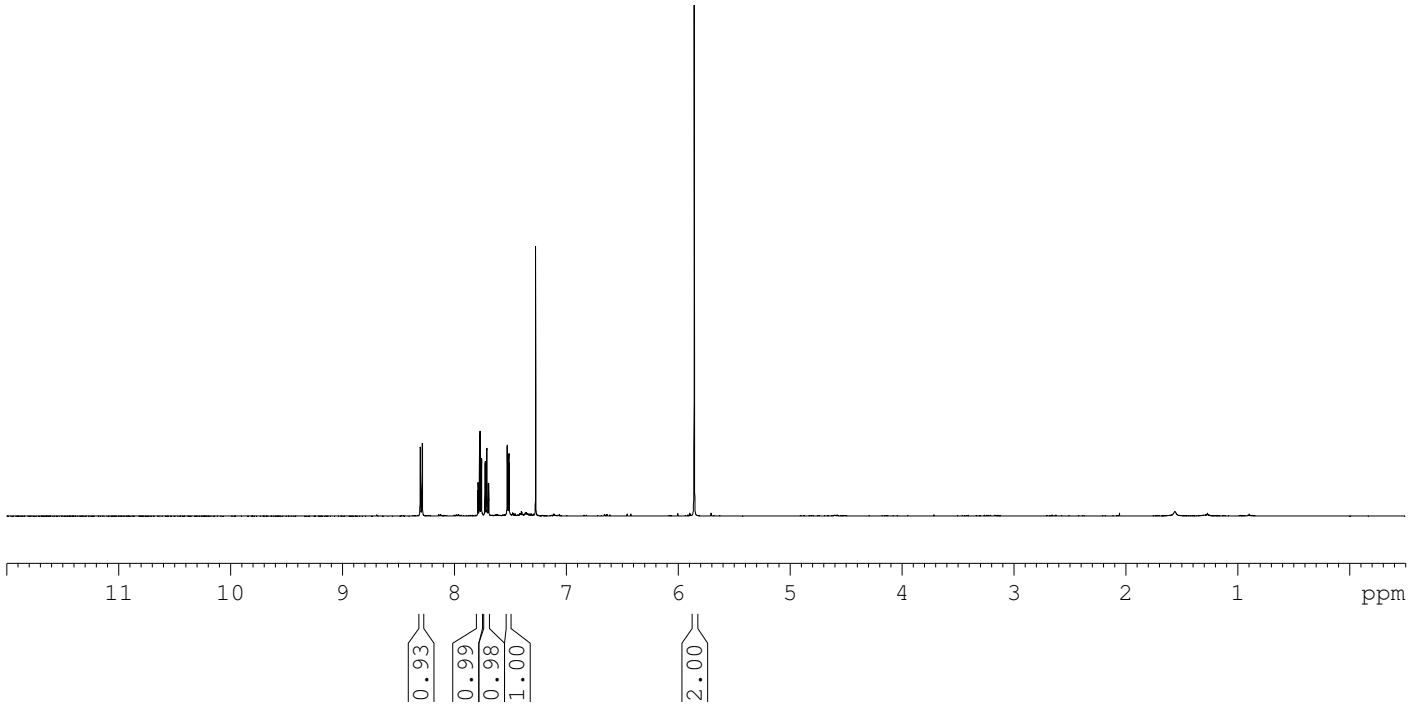

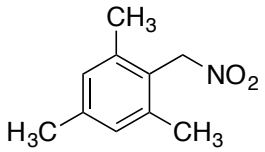

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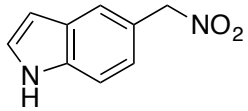

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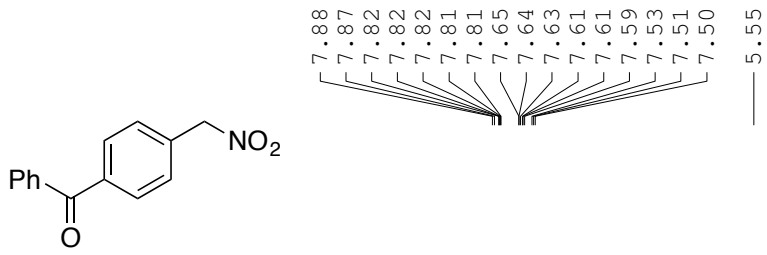

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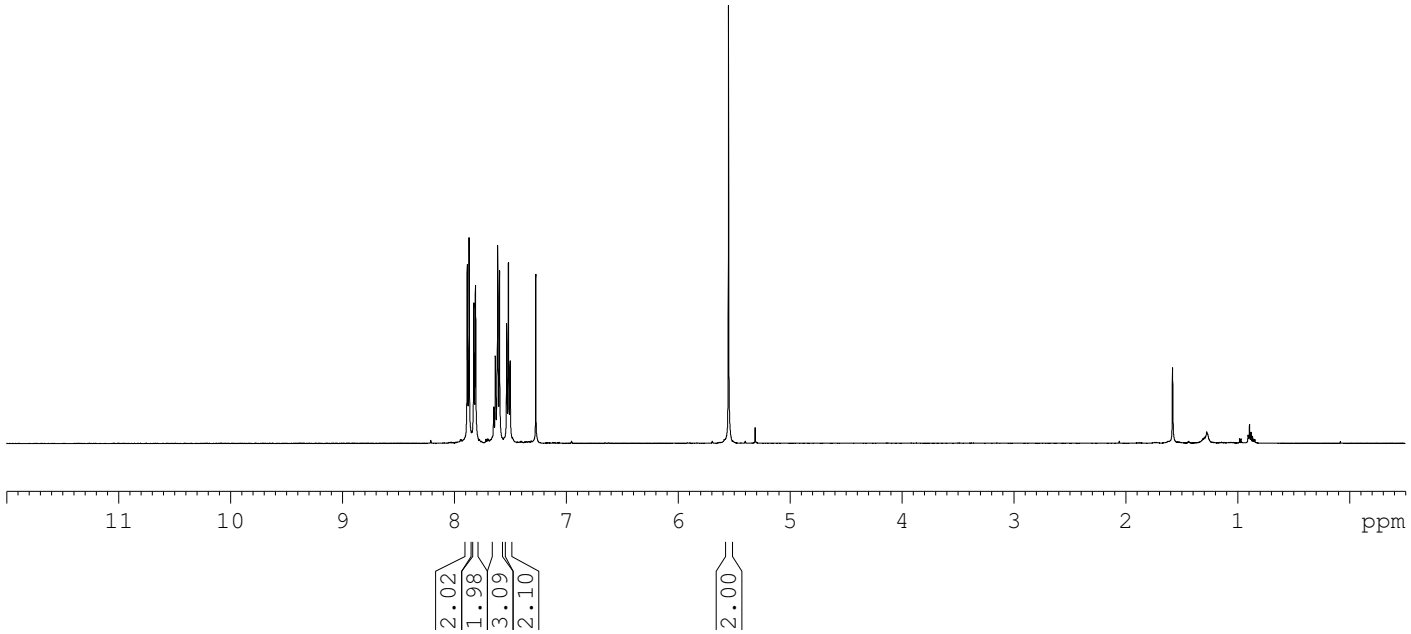

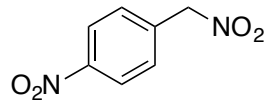

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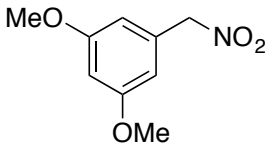

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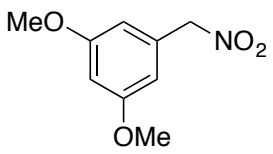

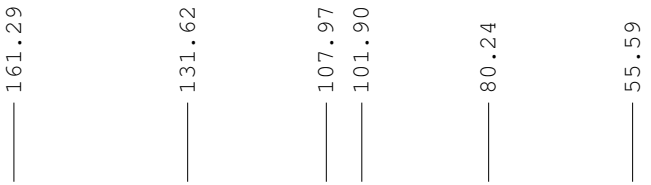

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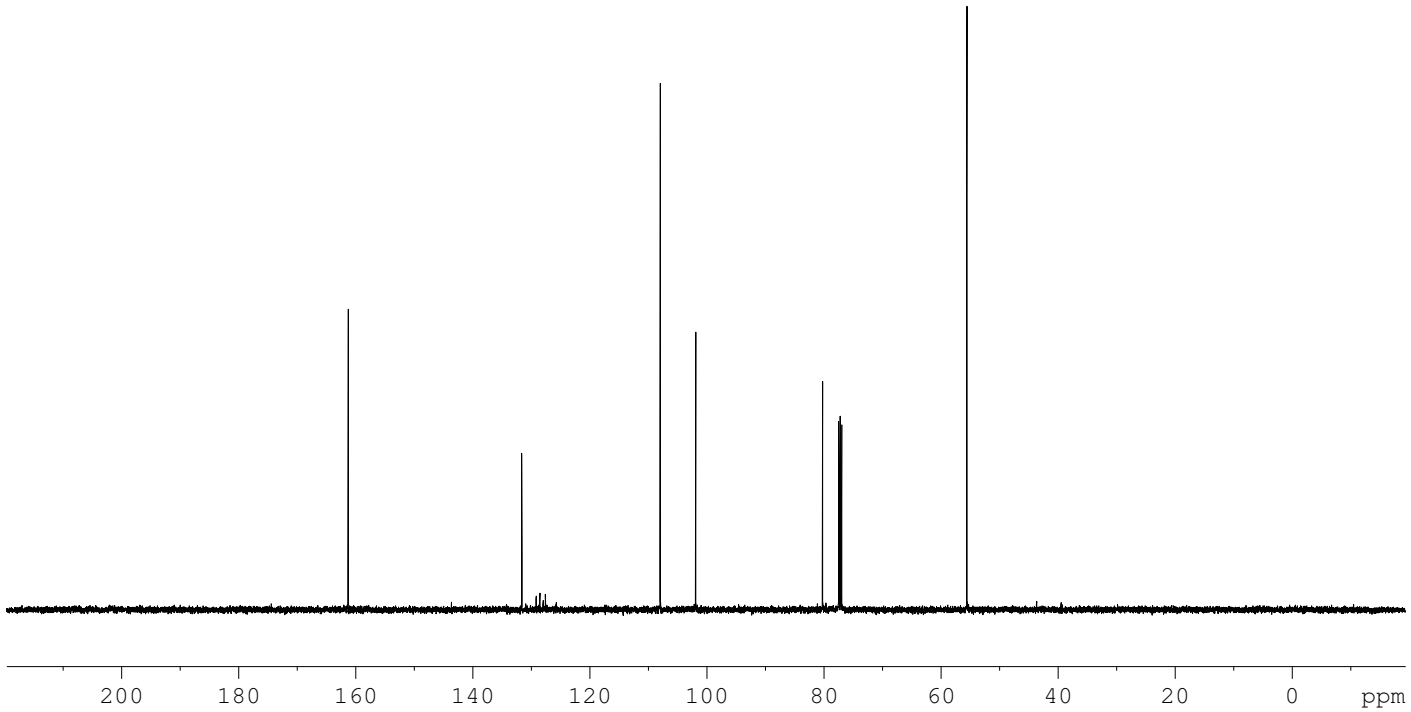

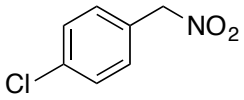

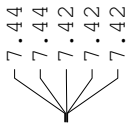

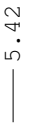

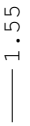

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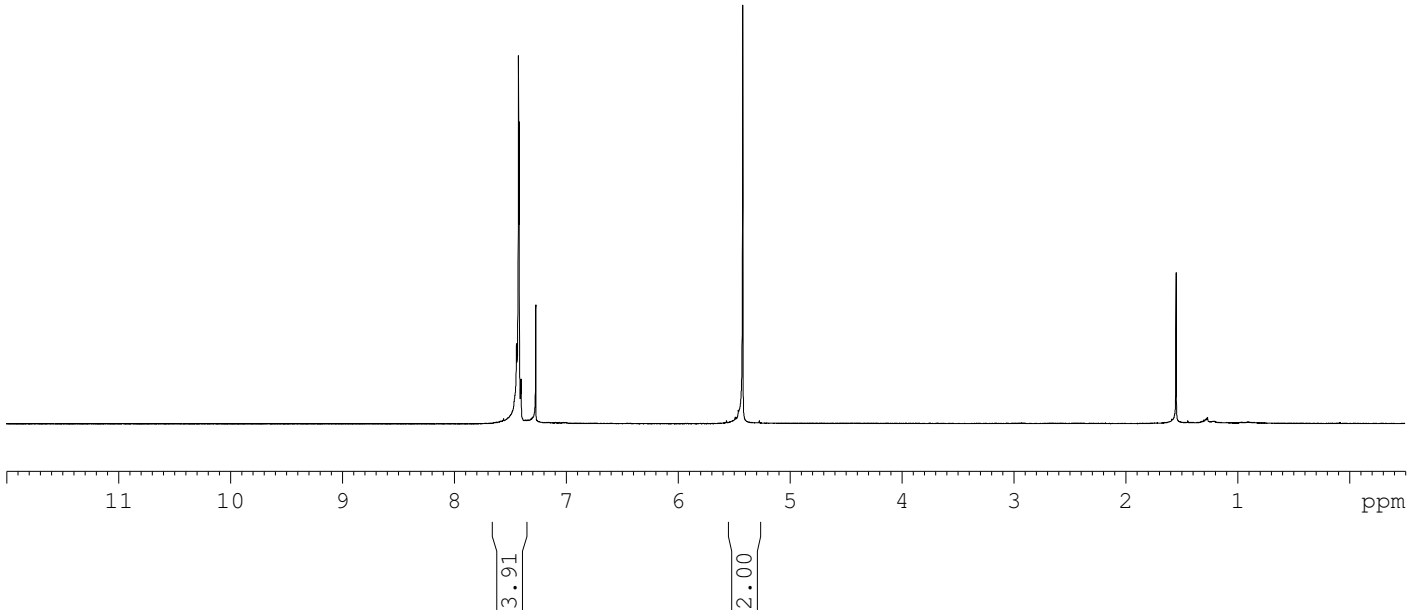

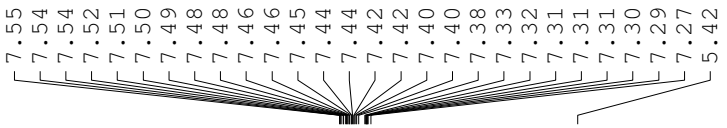

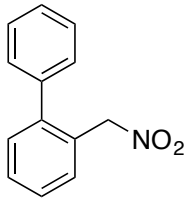

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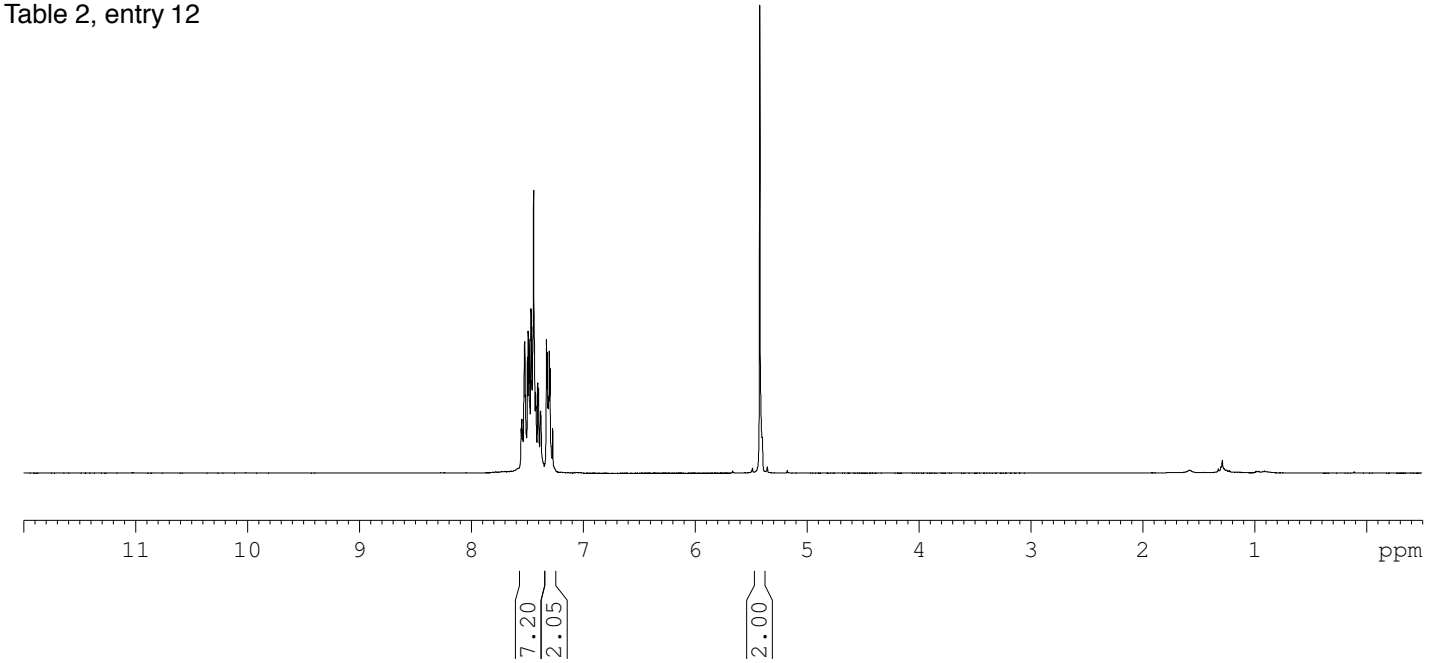

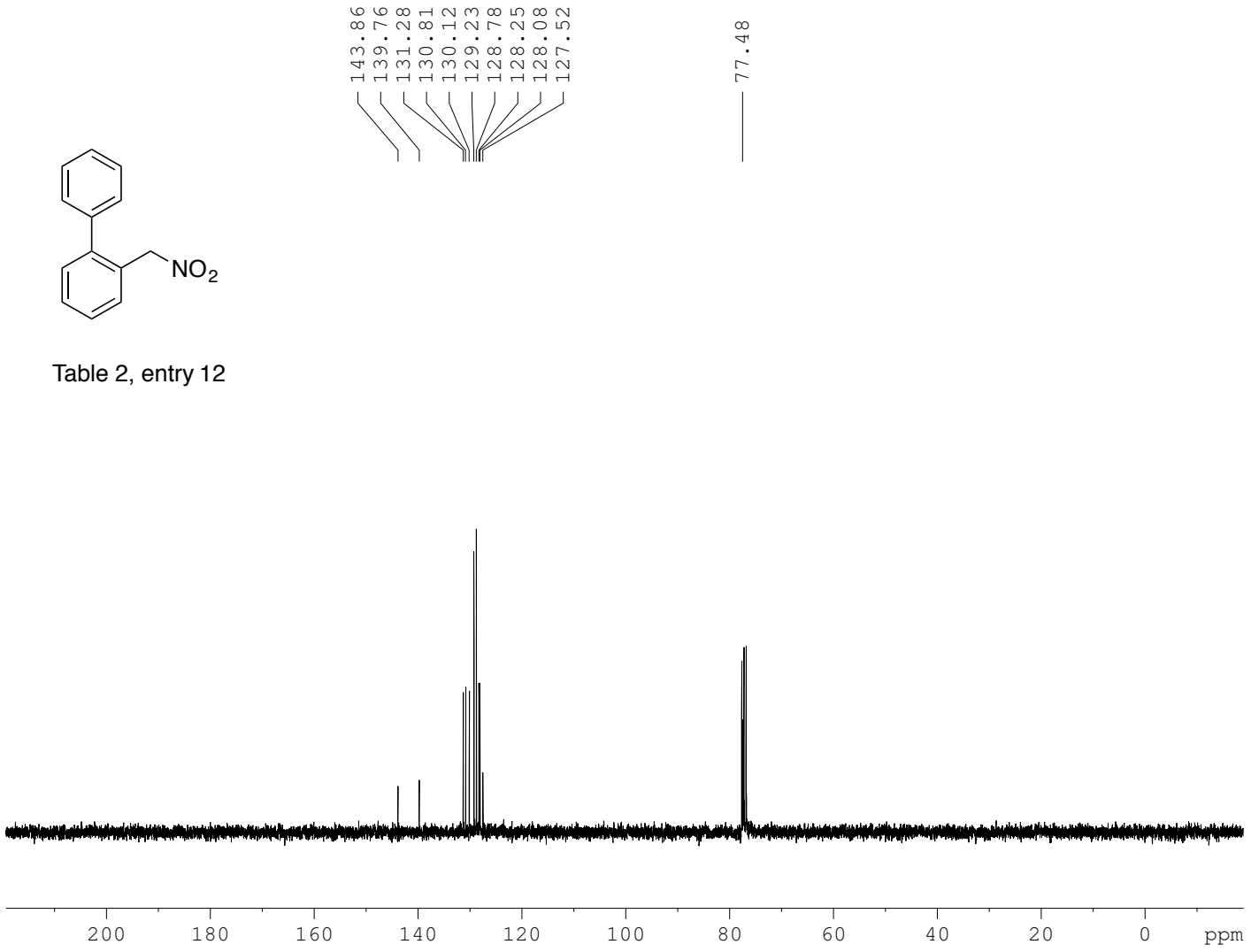

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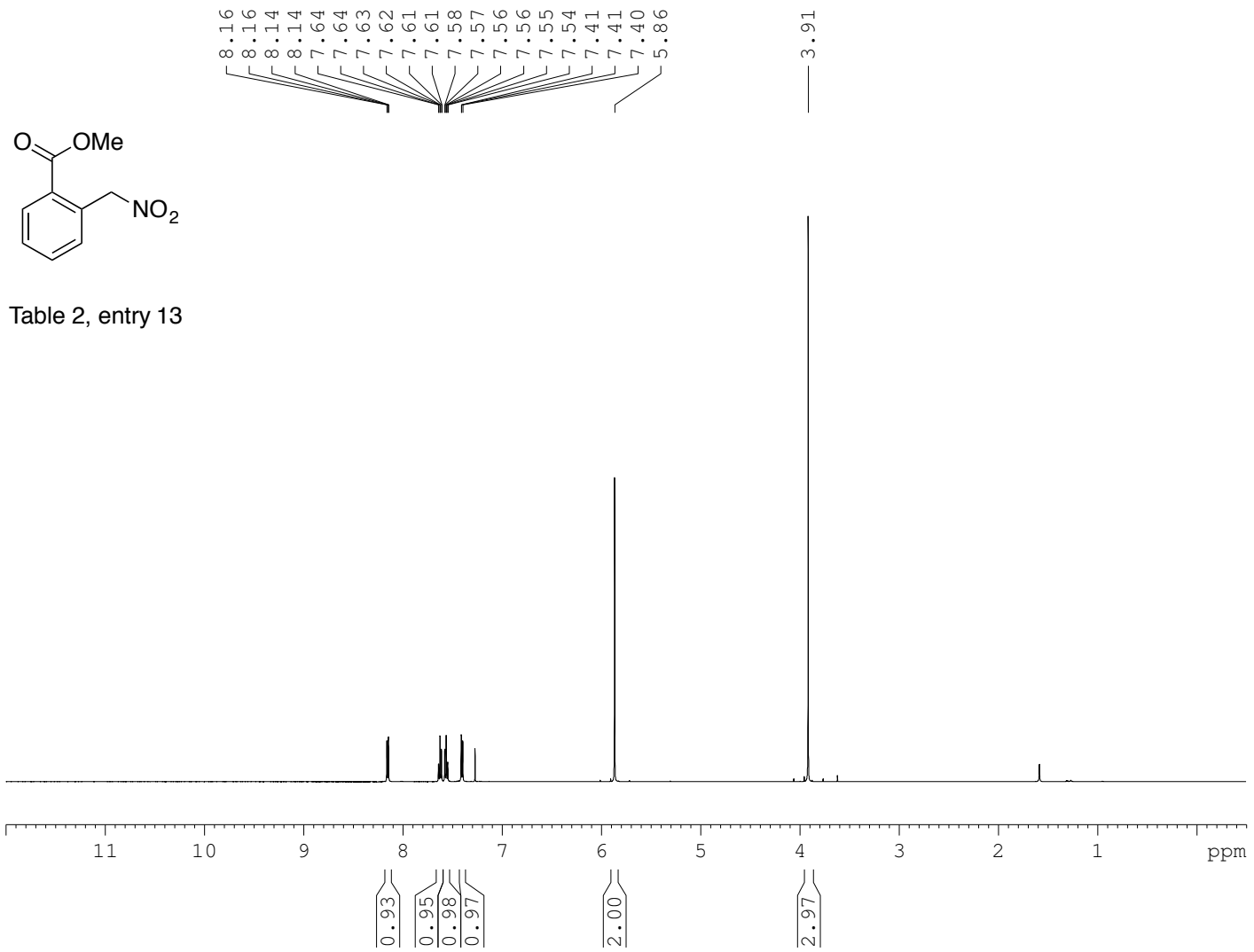

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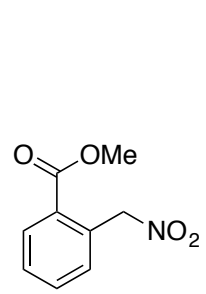

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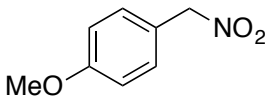

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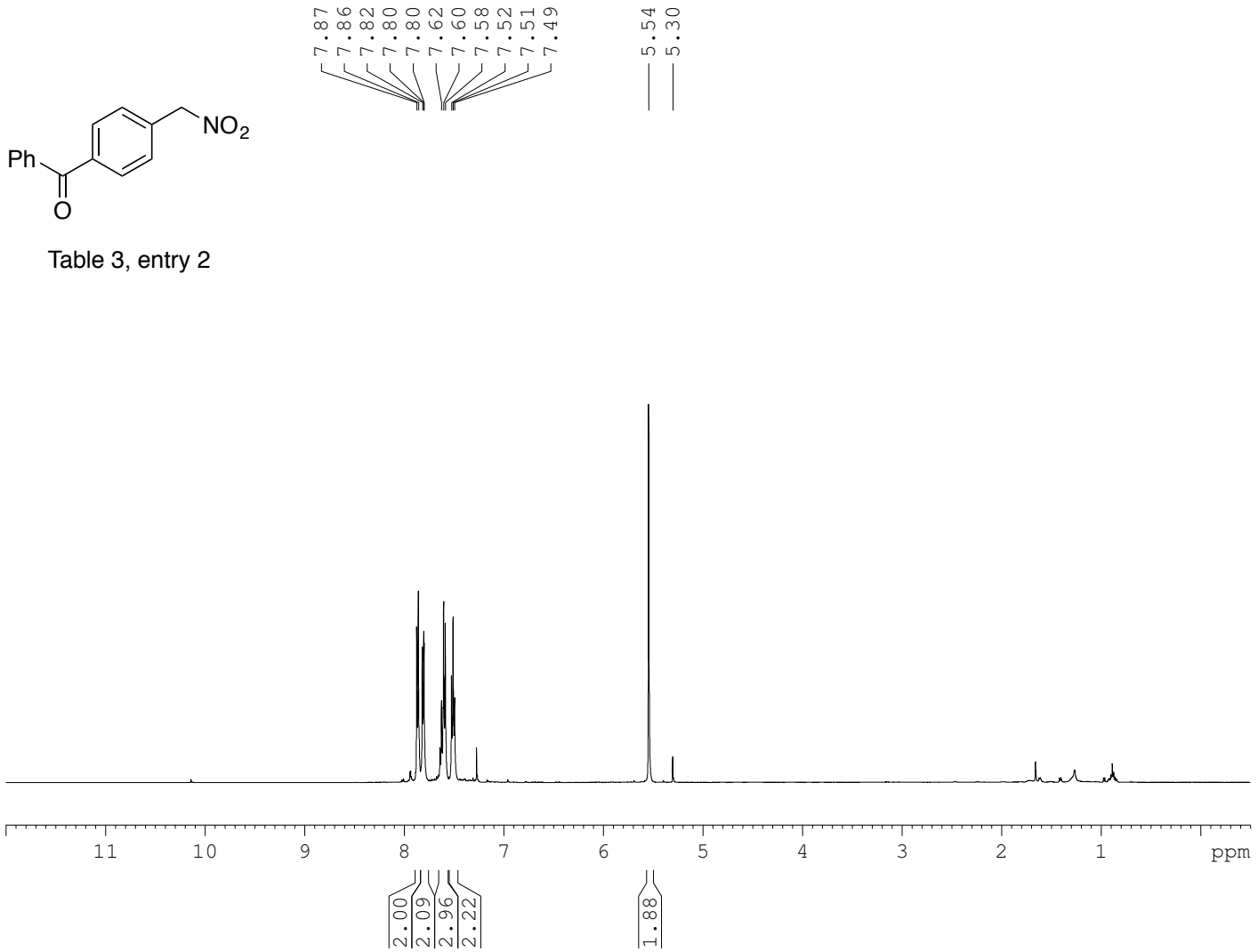

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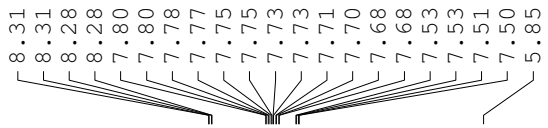

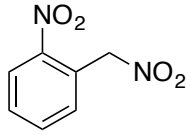

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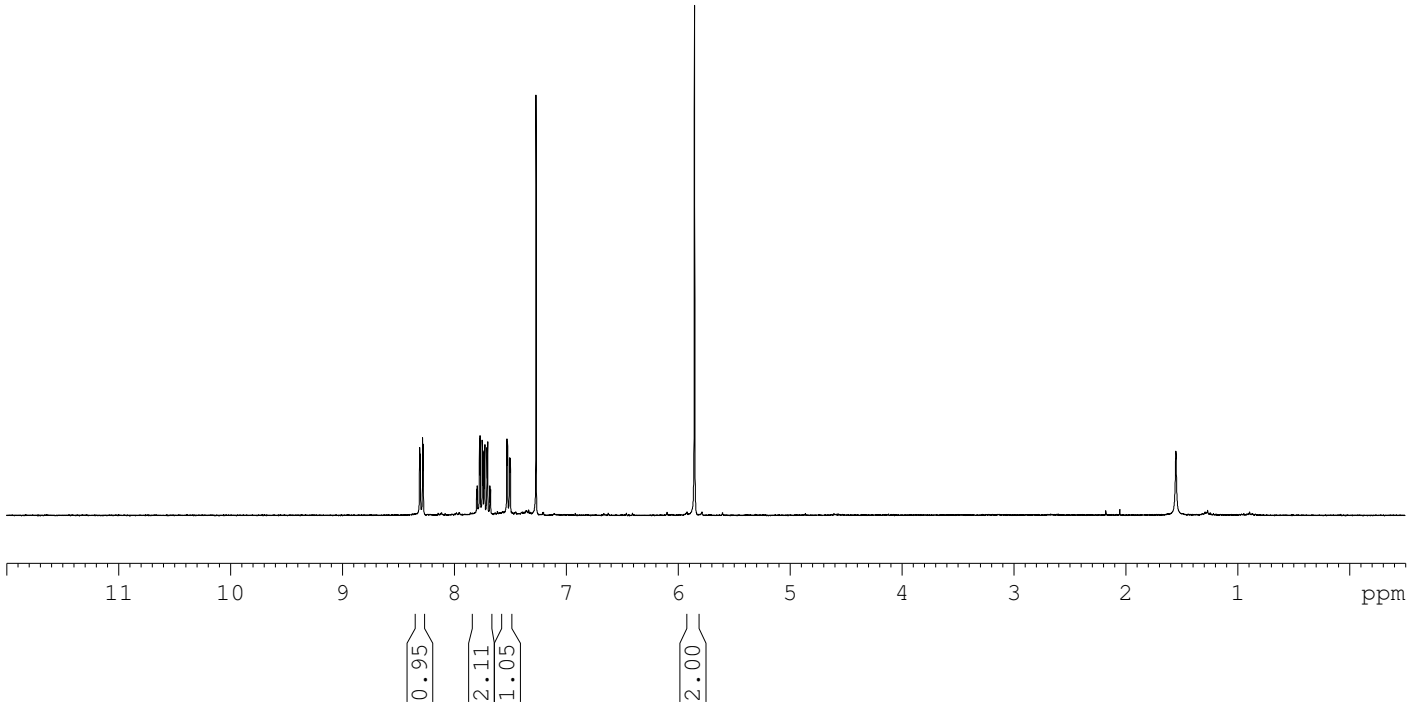

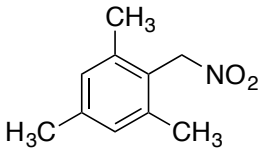

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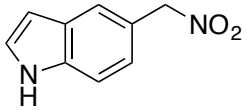

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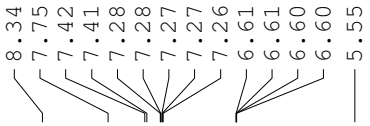

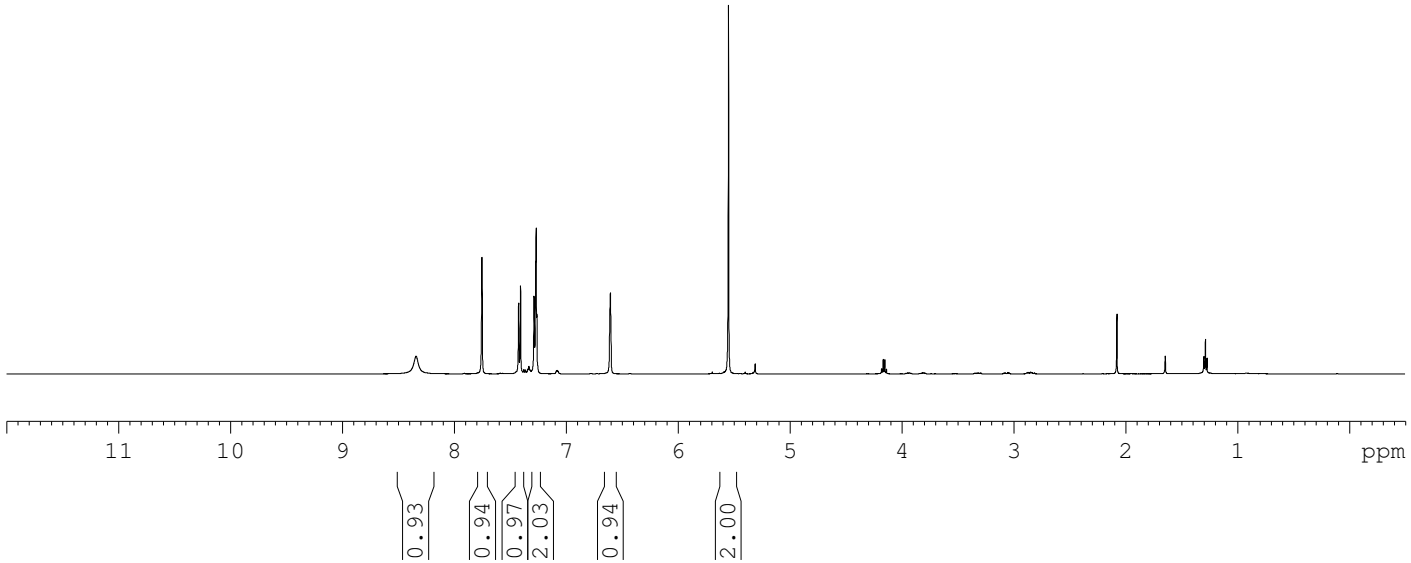

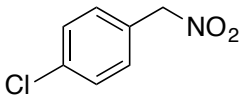

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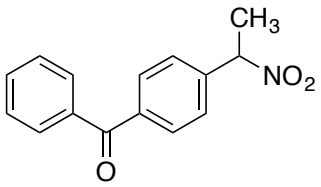
CH3
NO2
O

Scheme 3

7.85
7.83
7.81
7.80
7.79
7.63
7.62
7.60
7.60
7.59
7.58
7.52
7.50
7.49
5.73
5.71
5.70
5.69
1.96
1.95
11
10
9
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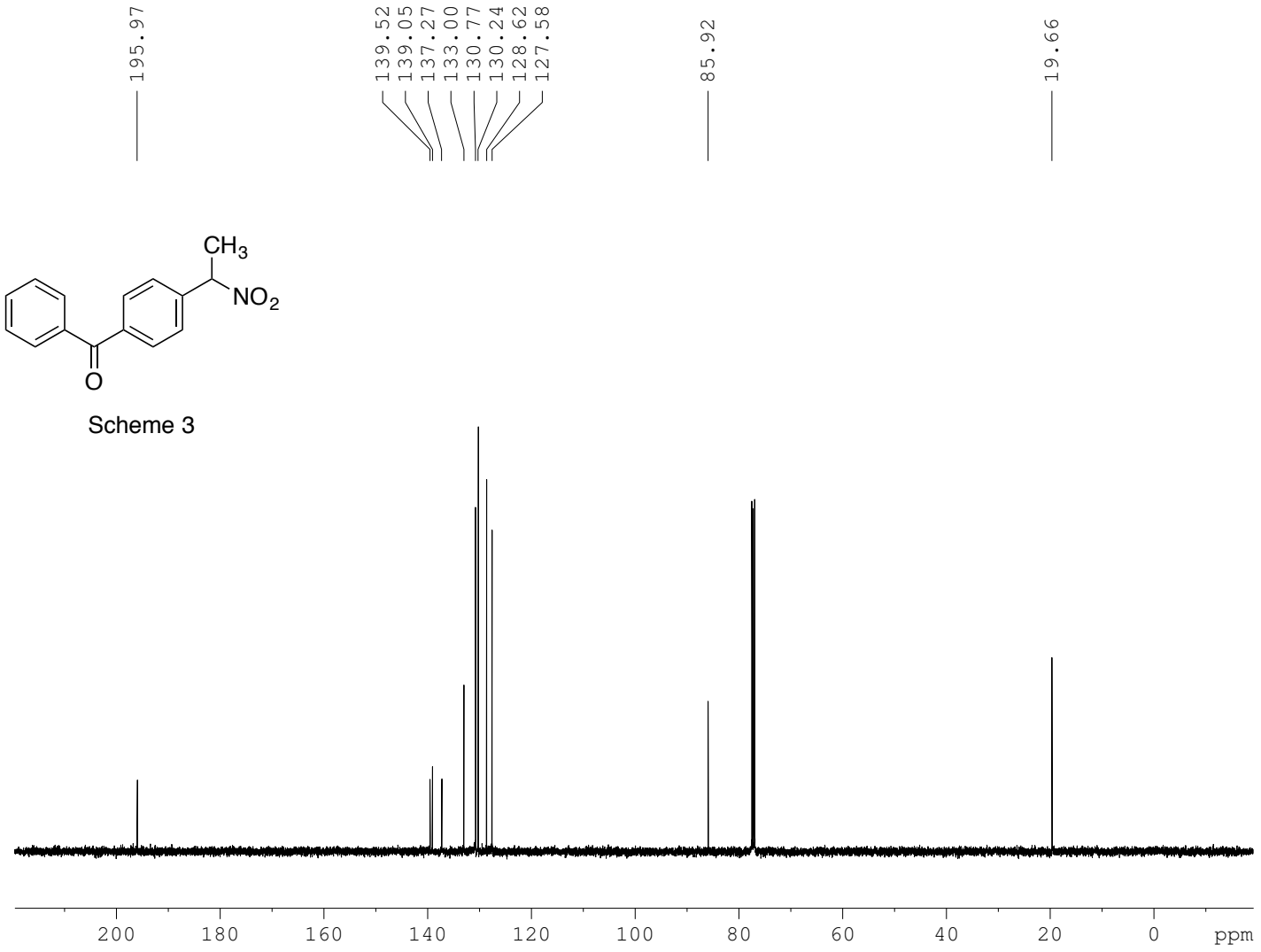
2.01
3.06
2.06
1.00
3.12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139.52
139.05
137.27
133.00
130.77
130.24
128.62
127.58
85.92
19.66
CH3
NO2
O
200
180
160
140
120
100
80
60
40
20
0
ppm

Scheme 3