

The Importance of Off-Cycle Species in the Acid-Catalysed Aza-Piancatelli Rearrangement

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General Remarks. Furan-2-yl(phenyl)methanol was prepared according to literature precedent of a similar transformation by reacting furfural with phenylmagnesium bromide.¹ Dysprosium (III) trifluoromethanesulfonate (Dy(OTf)₃) was used as received from Strem Chemicals, Inc.. All other materials were obtained from conventional suppliers and used as received. Flash chromatography was carried out using Sorbtech silica gel 60A (230x400 mesh). Thin-layer chromatography (TLC) was performed on Sorbtech precoated silica gel plates and was visualized by irradiation with UV light or staining with potassium permanganate solution.

Kinetic studies monitored by in-situ FTIR were conducted with a in situ FT-IR fitted with a Diamond ATR probe. Reaction temperatures were controlled using an internal temperature

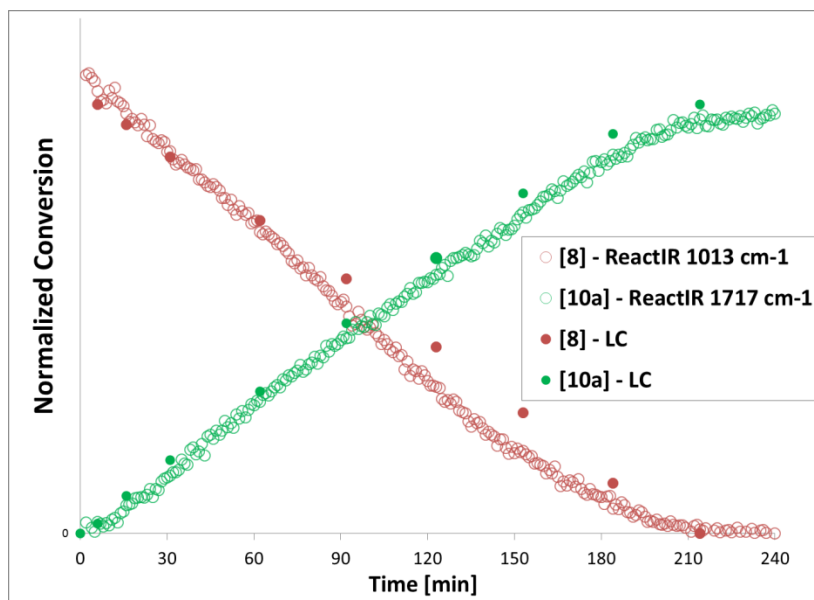
modulator. 2-Methoxynaphthalene was used as an internal standard in some experiments as specified, and had no effect on the reaction, as confirmed by monitoring reactions via ReactIR and HPLC-MS both with and in the absence of the standard.

^1H NMR spectra were recorded on an NMR spectrometer (at 400, 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 MHz). Data for ^{13}C NMR spectra are reported as follows: shift (δ ppm), multiplicity and coupling constant (Hz). IR spectra were recorded on by ATR-FT-IR and are reported in terms of frequency of absorption (cm^{-1}).

Validation of FTIR for Reaction Analysis. Validation of FTIR as a suitable technique for in-situ reaction analysis was performed through reaction sampling and HPLC-MS analysis of reaction conversion and product formation as a function of time. The reaction was sampled by withdrawal of approximately 5 microliter aliquots of the reaction solution and diluted with methanol at room temperature. Samples were analyzed by HPLC-MS immediately. HPLC-MS analysis was conducted with an Agilent Eclipse XDB C18, 3.5 μm , 3.0 x 75 mm column. Reactions under standard conditions used the below conditions for separation, except for the competition experiments (see appropriate section).

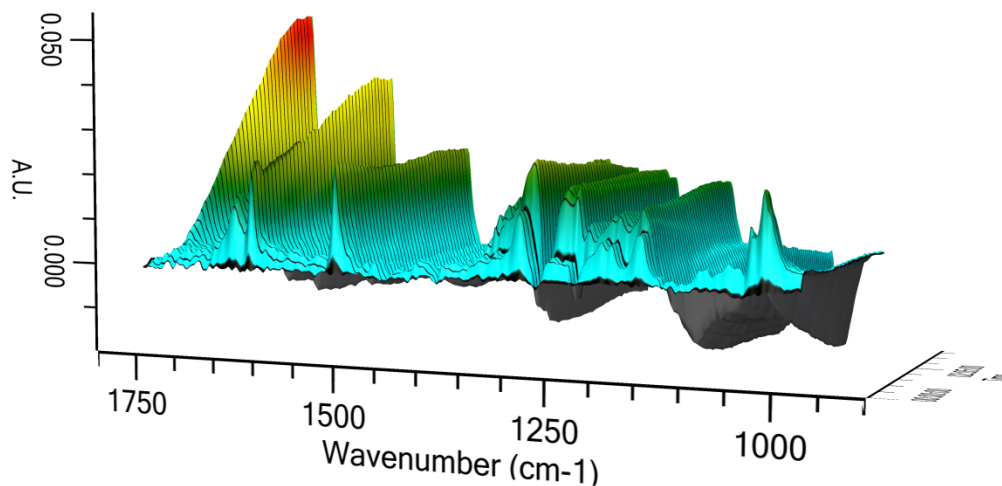
A= Water, 0.05% TFA
B= Acetonitrile, 0.05% TFA
Start 38% B
20 min 100% B
Flow rate 0.400 mL/min

Tandem Reaction Monitoring by ReactIR and HPLC-MS

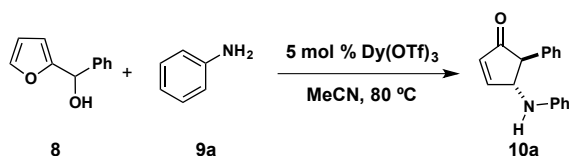


Analysis of the reaction conversion time course by FTIR and sampling methods were in agreement.

Sample FTIR Spectra of Dy(OTf)₃ - Catalyzed Zero-Order Reaction



General Procedure for Kinetic Experiments

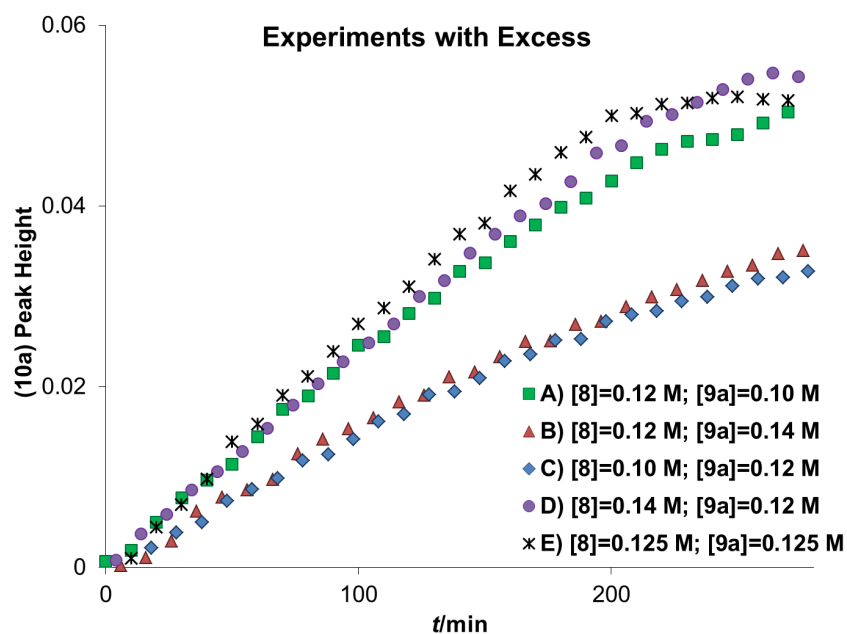


To a 10 mL vial with PTFE-silicon septum and open screw-cap was added 2 mL of acetonitrile. The vial was placed in a pre-heated oil-bath at 80 °C and allowed to equilibrate. After taking a background scan in hot solvent, furan-2-yl(phenyl)methanol **8** (44.0 mg, 0.250 mmol, 0.125 M) and aniline **9a** (23.0 mg, 0.250 mmol, 0.125 M) were added to the pre-equilibrated acetonitrile. After a stable FTIR signal was observed, Dy(OTf)₃ (7.6 mg, 0.013 mmol, 5 mol %) catalyst was added. Reaction progress was monitored by FTIR using two peaks: 1013 cm⁻¹ for the consumption of furylcarbinol **8**, and 1715 cm⁻¹ for the appearance of cyclopentenone **10a**.

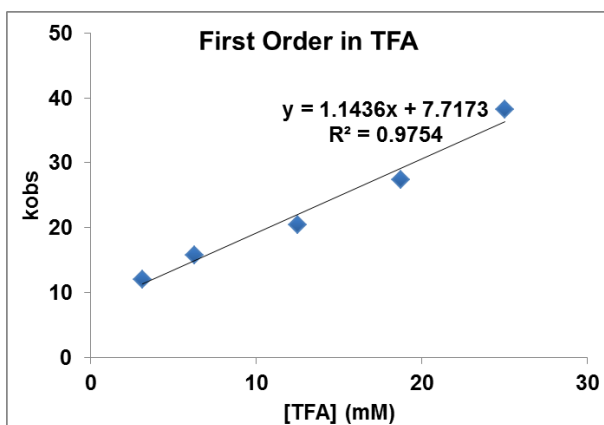
Experiments with Same Excess. As an internal standard, 20 μL of a 0.58 M stock solution of 2-methoxynaphthalene was used in each reaction. On the ReactIR, a background scan was taken in 65 °C acetonitrile and 2-methoxynaphthalene. Stock solutions of furylcarbinol **8** and aniline **9a** were injected, followed by subsequent addition of solid Dy(OTf)₃. All experiments in same excess used the same concentration of Dy(OTf)₃ (0.00625 M) and a total reaction volume of 2 mL. The following table summarizes the molarities and excesses of furylcarbinol **8** to aniline **9a**.

Experiment	[8] ₀ / M	[9a] ₀ / M	[9a]-[8] / M
Same excess [8]	0.12	0.10	- 0.02
Same excess [8]	0.14	0.12	- 0.02
Same excess [9a]	0.10	0.12	0.02
Same excess [9a]	0.12	0.14	0.02

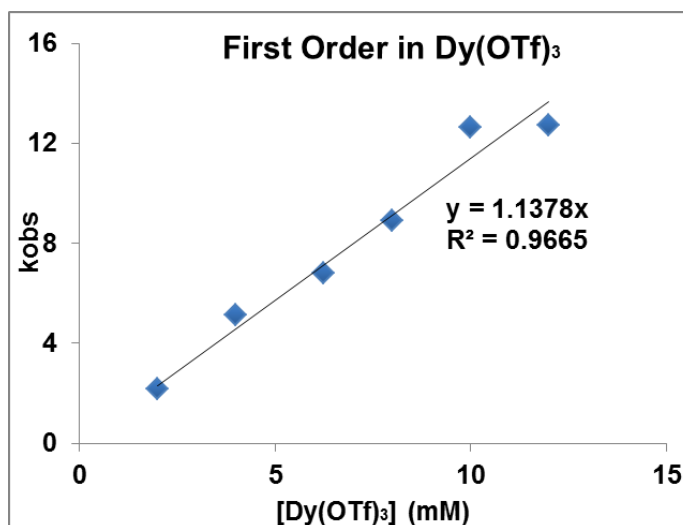
The subsequent reaction solutions were analyzed by HPLC to check conversion of furylcarbinol **8** to the cyclopentenone **10a**. The formation of cyclopentenone **10a**, as monitored by ReactIR, is graphed without normalization below.



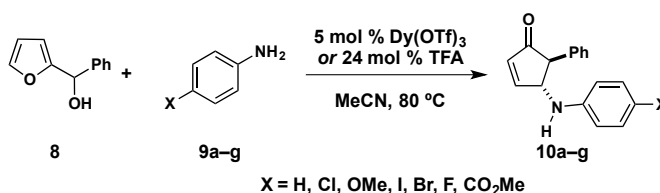
Order in Trifluoroacetic Acid Catalyst. Stock solutions of **8**, **9a**, and trifluoroacetic acid (TFA) in acetonitrile were prepared and used within two days. Reactions were 0.125 M in **8** and **9a** and were run at 65 °C. Concentrations of TFA were as follows: 3.125, 6.25, 12.5, 18.75, 25, and 30 mM. To a pre-heated vial of acetonitrile, the stock solutions of furylcarbinol **8** and aniline **9a** were added. When a steady signal was reached on the FTIR, an appropriate portion of the TFA stock solution was injected. The slope of the initial rate of formation of **9a** in each reaction was used in finding the order in TFA. The positive and linear fit implies that the Piancatelli reaction is first order in TFA. *Note:* these are not absolute rate (k) constants, but relative k values.



Order in Dy(OTf)₃ Catalyst. Stock solutions of **8** and **9a** in acetonitrile were prepared and used within two days. Reactions were 0.125 M in **8** and **9a** and were run at 65 °C. Concentrations of Dy(OTf)₃ were as follows: 2, 4, 6.25, 8, 10, and 12 mM. To a pre-heated vial of acetonitrile, the stock solutions of furylcarbinol **8** and aniline **9a** were added. When a steady signal was reached on the FTIR, the appropriate amount of Dy(OTf)₃ was added as a solid. The slope of the initial rate of formation of **9a** in each reaction was used in finding the order in Dy(OTf)₃. The positive and linear fit implies that the Piancatelli reaction is first order in Dy(OTf)₃. *Note:* these are not absolute rate (k) constants, but relative k values.

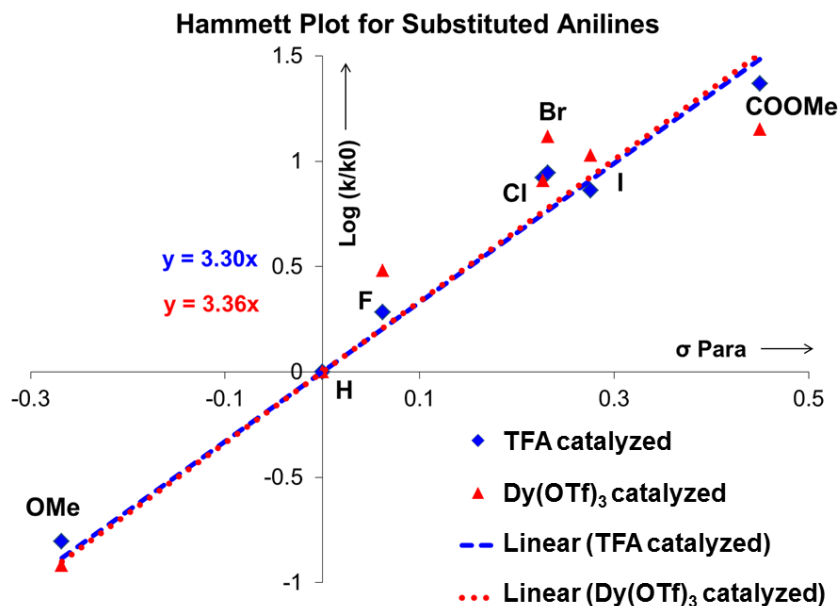


Linear Free Energy Relationships

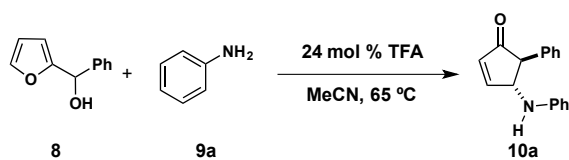


A stock solution of **8** in acetonitrile was prepared and used within two days. Reactions were 0.125 M in **8** and the substituted aniline **9a-g** and were run at 80 °C on a 2 mL scale. To a pre-heated vial of acetonitrile, the stock solutions of furylcarbinol **8** and the substituted aniline **9a-g** were added. When a steady signal was reached on the FTIR, Dy(OTf)₃ (7.6 mg, 0.013 mmol, 5 mol % relative to furylcarbinol) was added as a solid. For the TFA-catalyzed experiments, 0.02 mL of a 0.3 M TFA stock solution was used to provide a 2 mL reaction solution that was 30 mM in TFA (24 mol % relative to furylcarbinol **8**). The slopes of initial rate

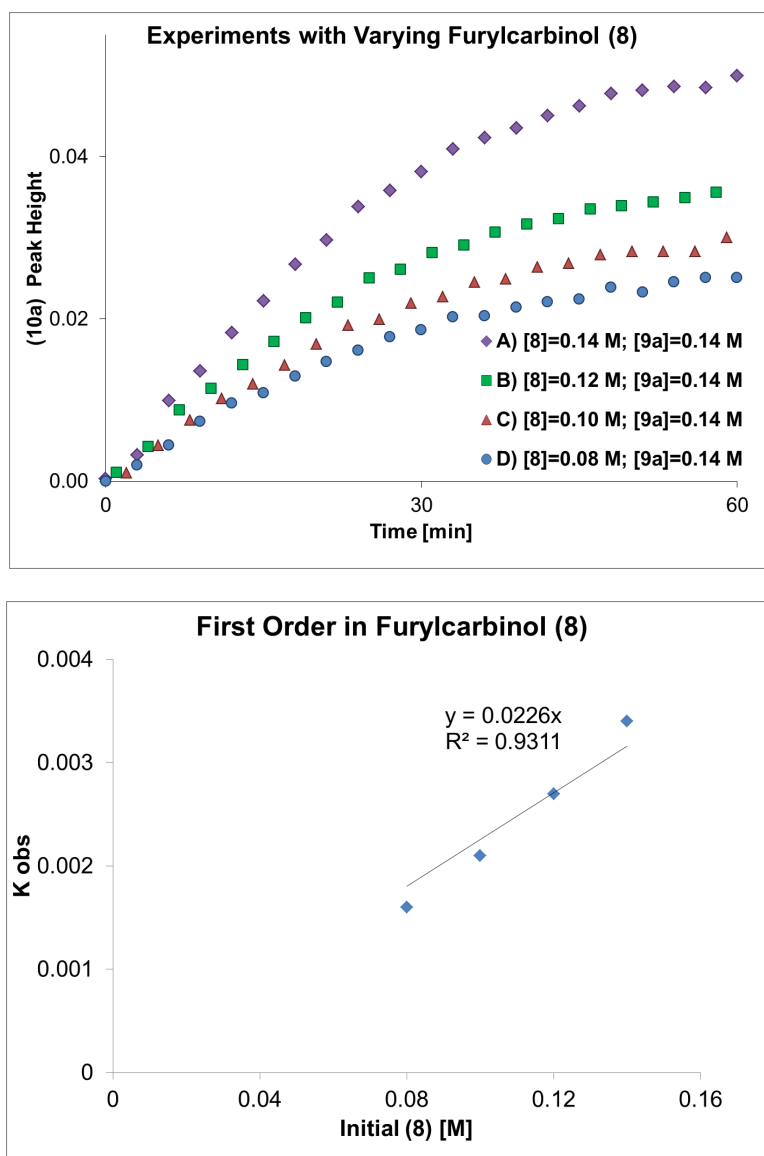
of formation of **10a-g** in individual reactions were used in graphing the Hammett Plots. *Note:* these are not absolute rate (k) constants, but relative k values.



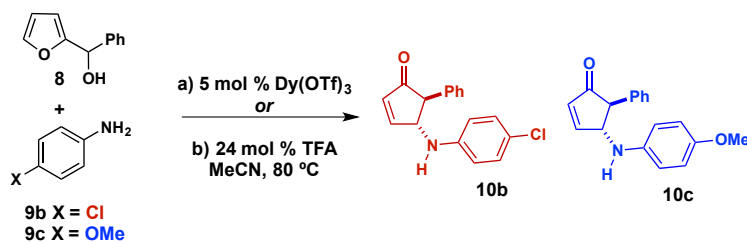
Order in Furylcarbinol **8**, TFA Catalyzed



Stock solutions of **8** and **9a** in acetonitrile were prepared and used within two days. Reactions were 0.125 M in **8** and **9a** and were run at 65 °C on a 2 mL scale. To a pre-heated vial of acetonitrile, the stock solutions of furylcarbinol **8** and aniline **9a** were added. When a steady signal was reached on the FTIR, 0.02 mL of a 0.3 M TFA stock solution was used to provide a 2 mL reaction solution that was 30 mM in TFA (24 mol % relative to aniline **9a**). The slope of the initial rate of formation of **10a** in each reaction was used in finding order in furylcarbinol. *Note:* these are not absolute rate (k) constants, but relative k values.



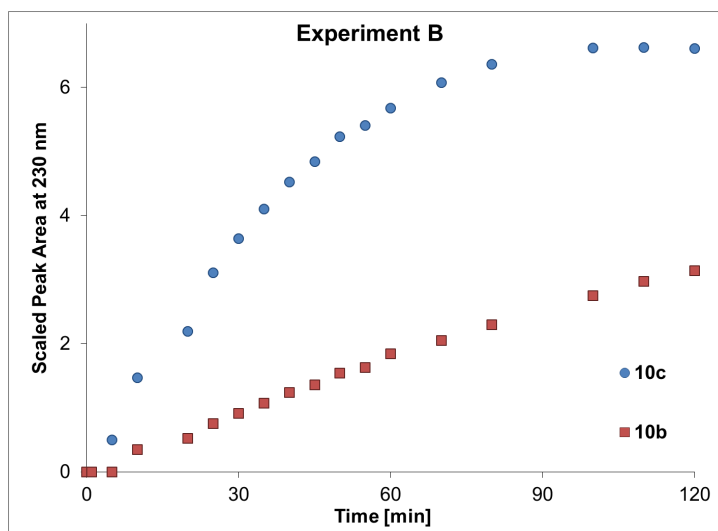
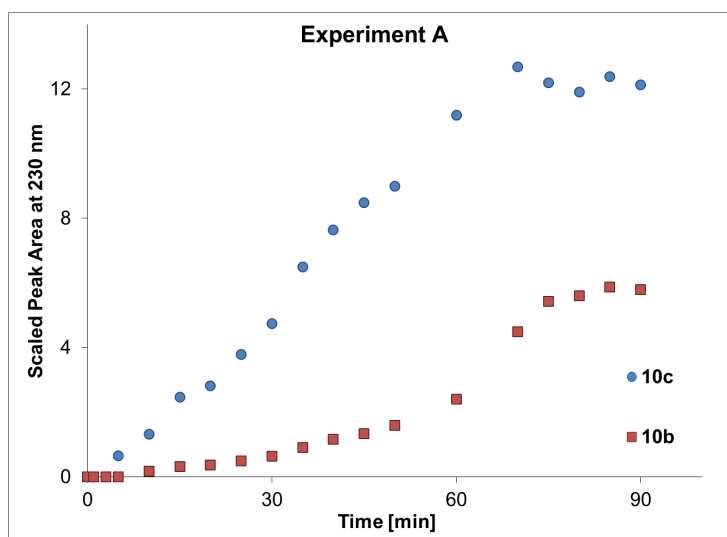
Competition Experiments

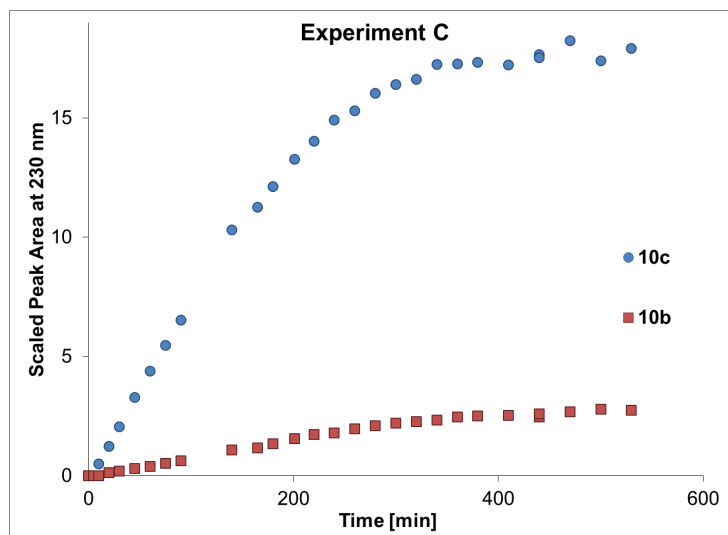


Competition experiments were conducted at 80 °C with 4-chloroaniline **9b** and 4-methoxyaniline **9c** to make cyclopentenones **10b** and **10c**, respectively. As a standard, 0.1 mL of a 0.101 M stock solution of 2-methoxynaphthalene for every 1 mL reaction solution was used. A

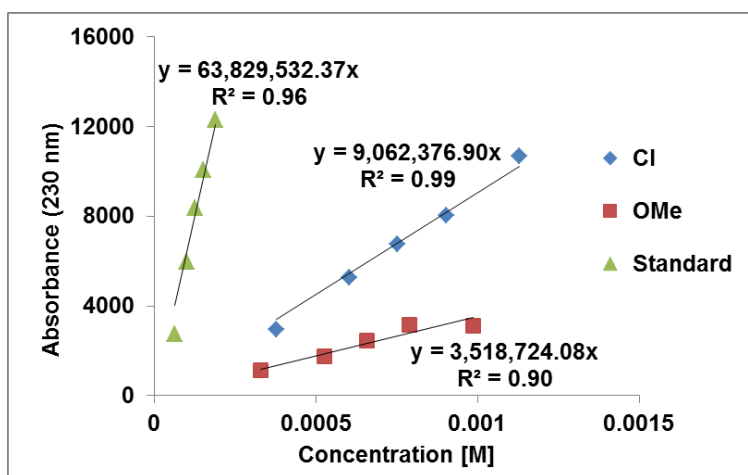
3 mL solution of acetonitrile and 2-methoxynaphthalene was preheated to 80 °C. Furylcarbinol **8** was added by dissolution from a tared syringe, followed by solid aniline **9b** or **9c**. A sample was taken at this point for analysis of initial conditions. Either Dy(OTf)₃ (5 mol % relative to furylcarbinol **8**) or TFA (24 mol % relative to furylcarbinol **8**) was added. The reactions were sampled by taking approximately 5 µL aliquots and dilution with approximately 1 mL of methanol and immediately analyzed by HPLC-MS.

Experiment	Catalyst	[8] ₀ / M	[9b] ₀ / M	[9c] ₀ / M	Catalyst / M
A	Dy(OTf) ₃	0.125	0.0625	0.0625	0.0063
B	TFA	0.125	0.0625	0.0625	0.030
C	Dy(OTf) ₃	0.125	0.125	0.125	0.0063





A calibration curve was created between the two cyclopentenone products **10b** and **10c** and the standard, 2-methoxynaphthalene, to determine the selectivity for either product over time. Each cyclopentenone was synthesized by the standard procedure² and purified by flash column chromatography (1:6 to 1:4 EtOAc:hexanes). Relative UV absorptivities at 230 nm with 8 μ L injections were analyzed by HPLC-MS for the following calibration curves:



The column conditions were as follows:

A= Water, 0.05% TFA

B= Acetonitrile, 0.05% TFA

Start 10%B

6.5 min 45%B

18 min 65%B

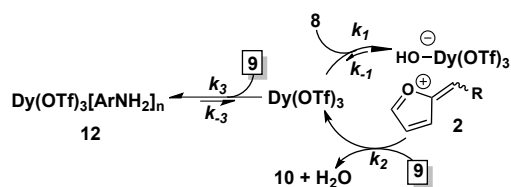
20 min 100%B

Flow rate 0.400 mL/min

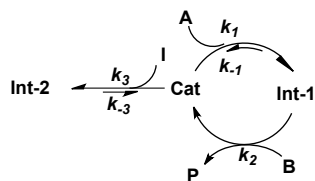
Agilent Eclipse XDB C18, 3.5 μ m, 3.0 x 75 mm column

Derivation of Steady State Rate Law

The proposed mechanism based on the competitive inhibition model follows the scheme:



Or drawn in general:



Assumptions:

Mass balance for the catalyst is given by

$$1) [\text{cat}_{\text{tot}}] = [\text{cat}_0] = [\text{cat}] + [\text{Int1}] + [\text{Int2}]$$

By using steady state approximations,

$$2a) \frac{d[\text{cat}]}{dt} \approx 0 \approx -k_1 [\text{cat}][\text{A}] + k_{-1} [\text{Int1}] + k_2 [\text{B}][\text{Int1}] - k_3 [\text{I}][\text{cat}] + k_{-3} [\text{Int2}]$$

$$2b) \frac{d[\text{Int1}]}{dt} \approx 0 \approx k_1 [\text{cat}][\text{A}] - k_{-1} [\text{Int1}] - k_2 [\text{Int1}][\text{B}]$$

$$2c) \frac{d[\text{Int2}]}{dt} \approx 0 \approx k_3 [\text{cat}][\text{I}] - k_{-3} [\text{Int2}]$$

Rate of product formation:

$$\frac{d[\text{P}]}{dt} = k_2 [\text{Int1}][\text{B}]$$

Define $[\text{cat}]$ in terms of $[\text{Int1}]$ by using 2b):

$$k_1 [\text{cat}][\text{A}] = k_{-1} [\text{Int1}] + k_2 [\text{Int1}][\text{B}]$$

$$[\text{cat}] = \frac{k_{-1}[\text{Int1}] + k_2[\text{Int1}][\text{B}]}{k_1[\text{A}]} = \frac{(k_{-1} + k_2[\text{B}])[\text{Int1}]}{k_1[\text{A}]}$$

Substitute [cat] into 2c)

$$0 = k_3[\text{I}] \left(\frac{(k_{-1} + k_2[\text{B}])[\text{Int1}]}{k_1[\text{A}]} \right) - k_{-3}[\text{Int2}]$$

$$[\text{Int2}] = \frac{k_3(k_{-1} + k_2[\text{B}])[\text{Int1}][\text{I}]}{k_{-3}k_1[\text{A}]}$$

Substitute [Int2] into [cat_{tot}]:

$$[\text{cat}_{\text{tot}}] = \frac{(k_{-1} + k_2[\text{B}])[\text{Int1}]}{k_1[\text{A}]} + [\text{Int1}] + \frac{k_3[\text{Int1}][\text{I}](k_{-1} + k_2[\text{B}])}{k_{-3}k_1[\text{A}]}$$

$$[\text{cat}_{\text{tot}}] = [\text{Int1}] \left(\frac{(k_{-1} + k_2[\text{B}])}{k_1[\text{A}]} \right) + [\text{Int1}] + [\text{Int1}] \left(\frac{k_3[\text{I}](k_{-1} + k_2[\text{B}])}{k_{-3}k_1[\text{A}]} \right)$$

$$[\text{cat}_{\text{tot}}] = [\text{Int1}] \frac{k_{-3}(k_{-1} + k_2[\text{B}]) + k_{-3}k_1[\text{A}] + k_3[\text{I}](k_{-1} + k_2[\text{B}])}{k_{-3}k_1[\text{A}]}$$

$$[\text{Int1}] = \frac{[\text{cat}_{\text{tot}}]k_{-3}k_1[\text{A}]}{k_{-3}(k_{-1} + k_2[\text{B}]) + k_{-3}k_1[\text{A}] + k_3[\text{I}](k_{-1} + k_2[\text{B}])}$$

Therefore, rate of product formation is:

$$\frac{d[\text{B}]}{dt} = k_2[\text{B}][\text{Int1}] = \frac{k_1k_2k_{-3}[\text{A}][\text{B}][\text{cat}_{\text{tot}}]}{k_{-3}(k_{-1} + k_2[\text{B}]) + k_{-3}k_1[\text{A}] + k_3[\text{I}](k_{-1} + k_2[\text{B}])}$$

If I = B,

$$\frac{d[\text{P}]}{dt} = \frac{k_1k_2k_{-3}[\text{A}][\text{B}][\text{cat}_{\text{tot}}]}{k_{-3}(k_{-1} + k_2[\text{B}] + k_1[\text{A}]) + k_3(k_1[\text{B}] + k_2[\text{B}]^2)}$$

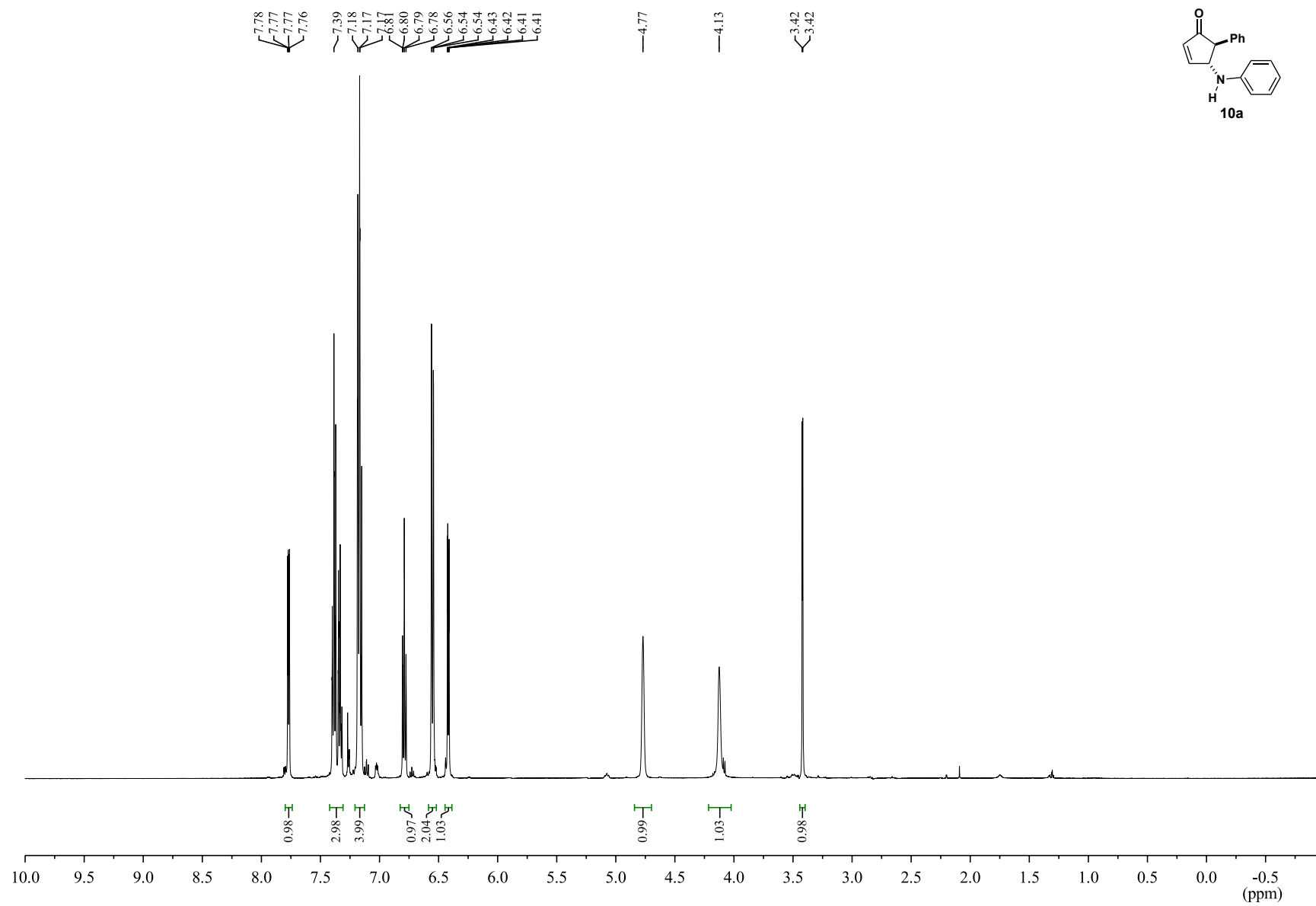
If we assume the terms k_3 and k_2 are the most important (largest magnitude) this reduces to:

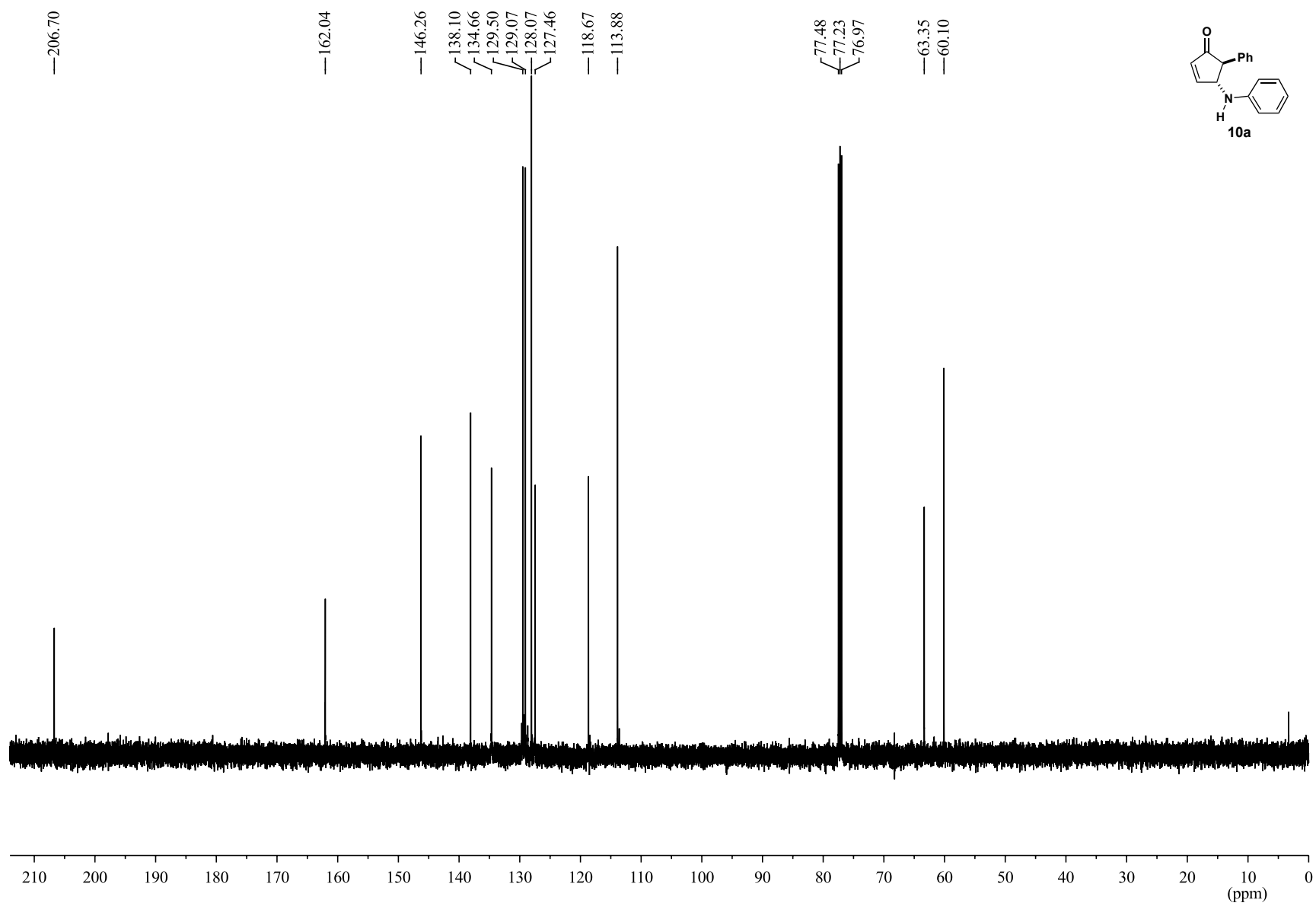
$$\frac{d[\text{P}]}{dt} = \frac{k_1k_{-3}[\text{A}][\text{cat}_{\text{tot}}]}{k_3[\text{B}]}$$

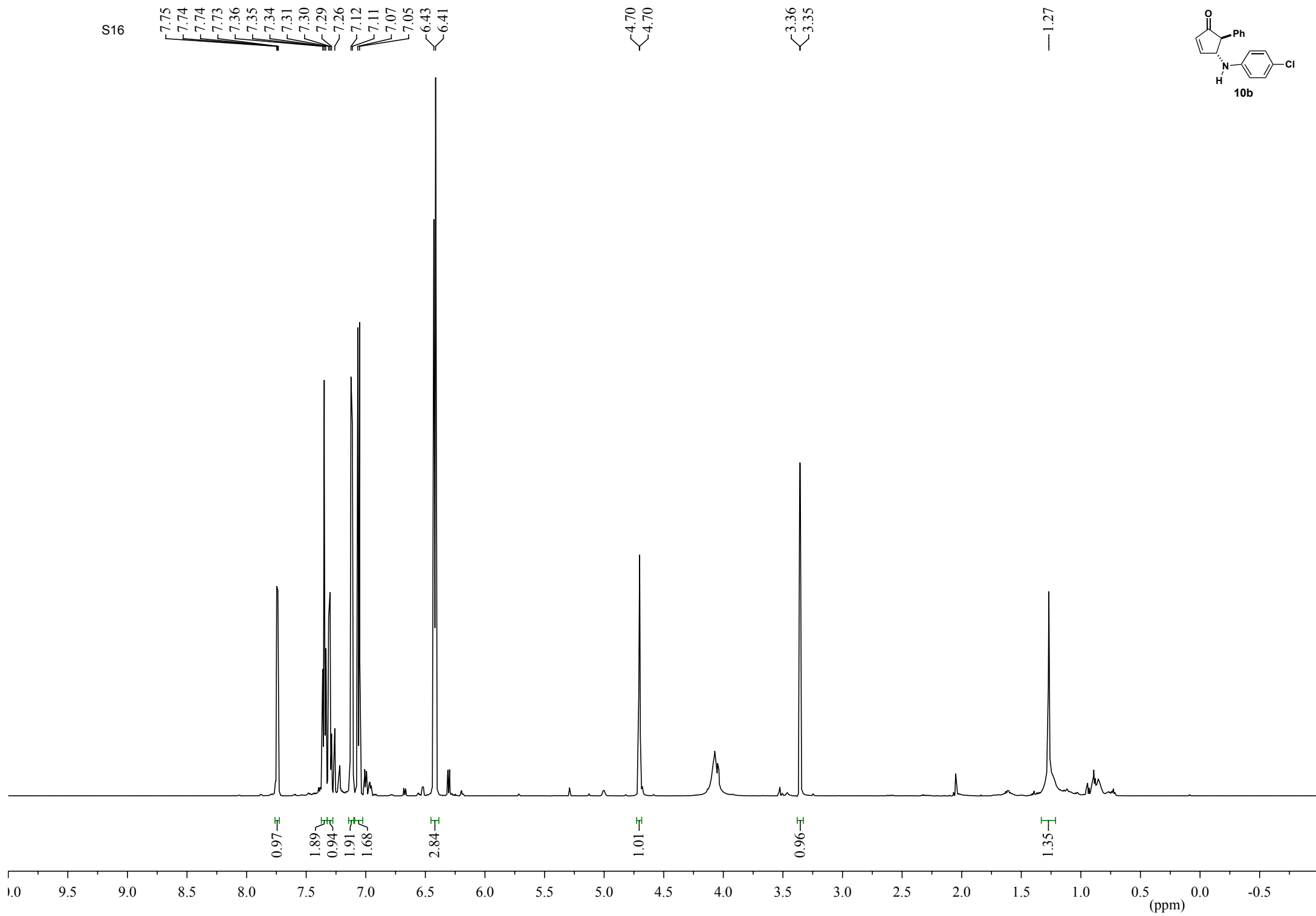
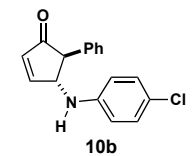
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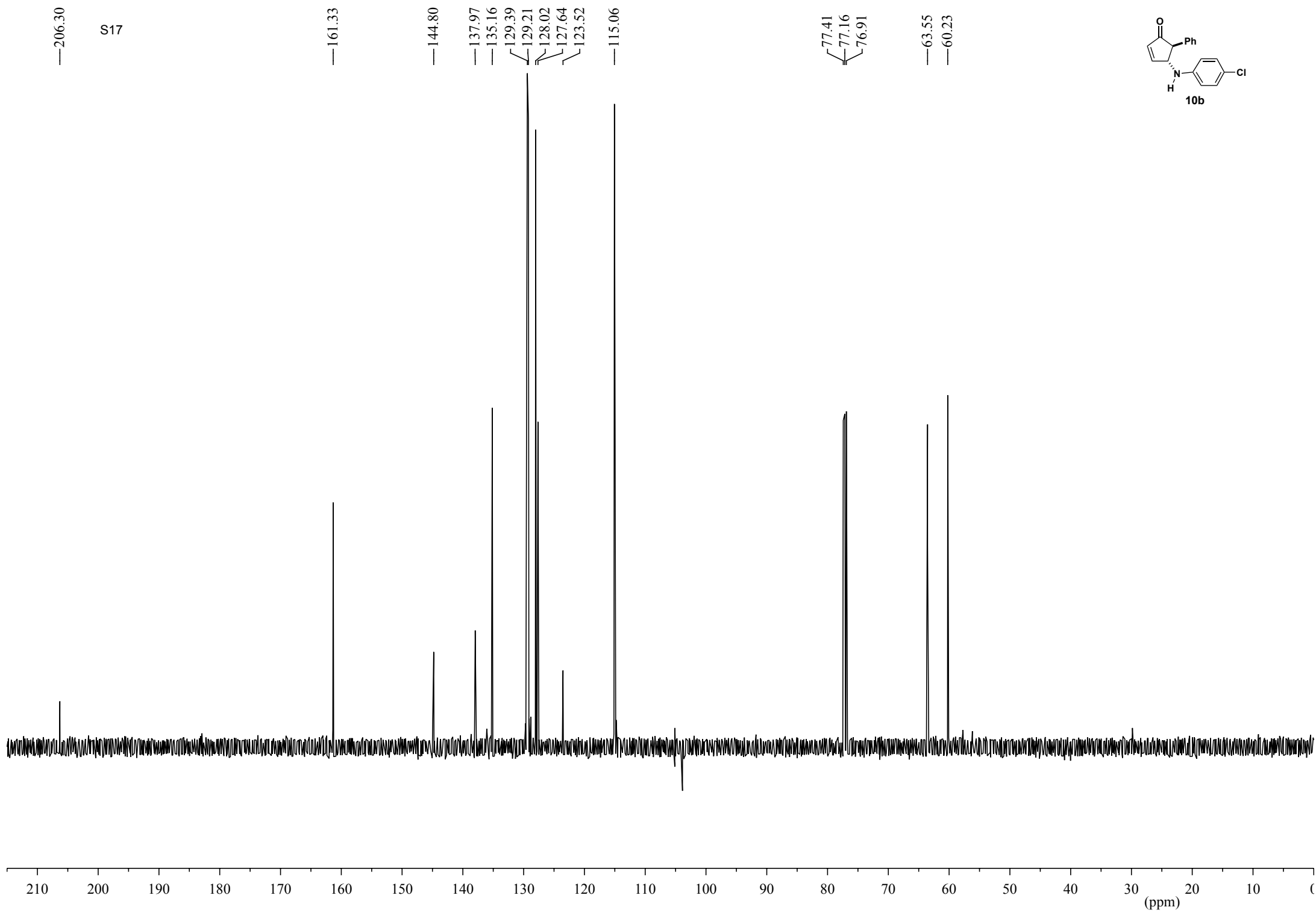
[1] Csakÿ, A.G.; Mba, M.; Plumet, J. *Synlett* **2003**, *13*, 2092–2094.

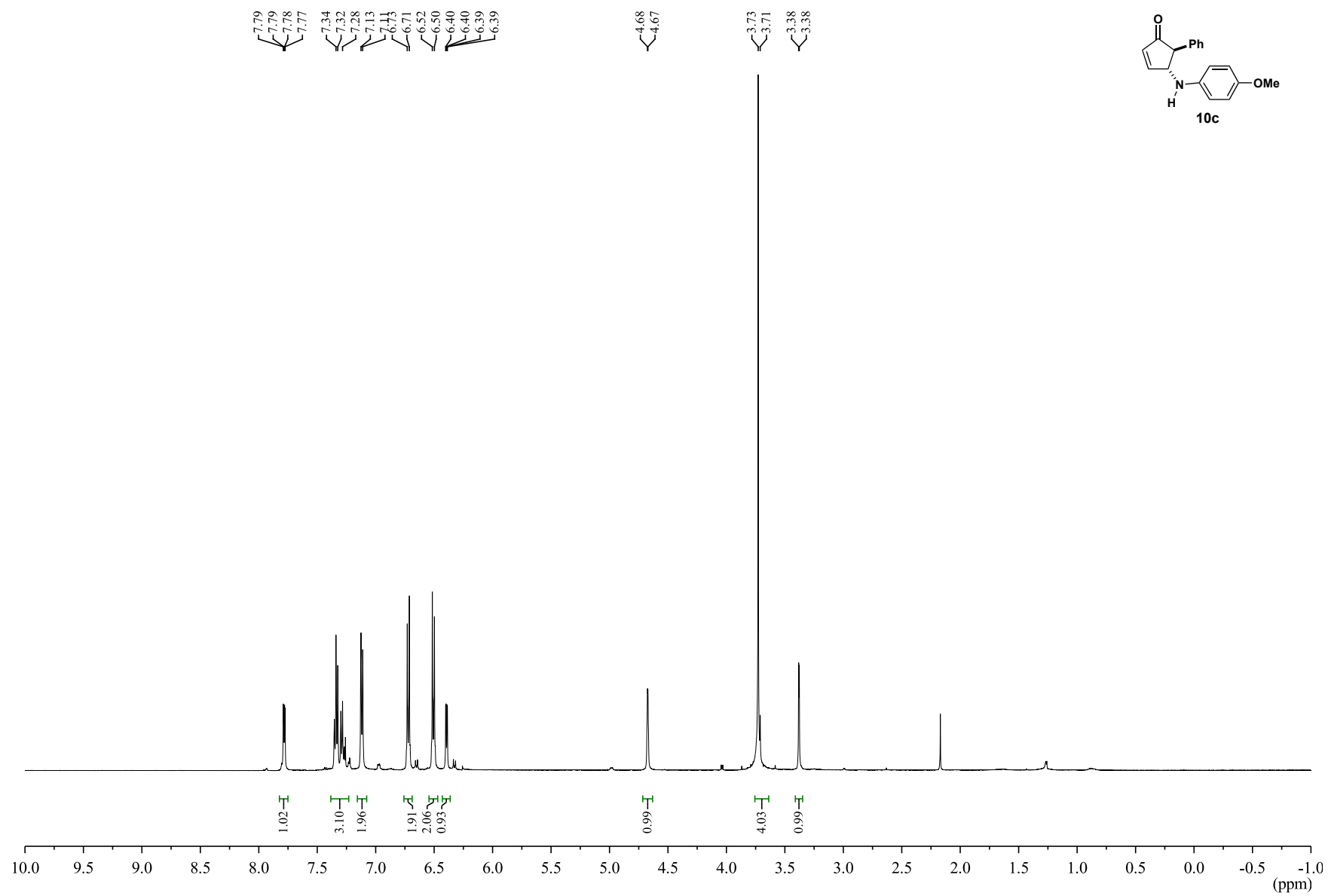
[2] Veits, G. K.; Wenz, D. R.; Read de Alaniz, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 9484–9487.

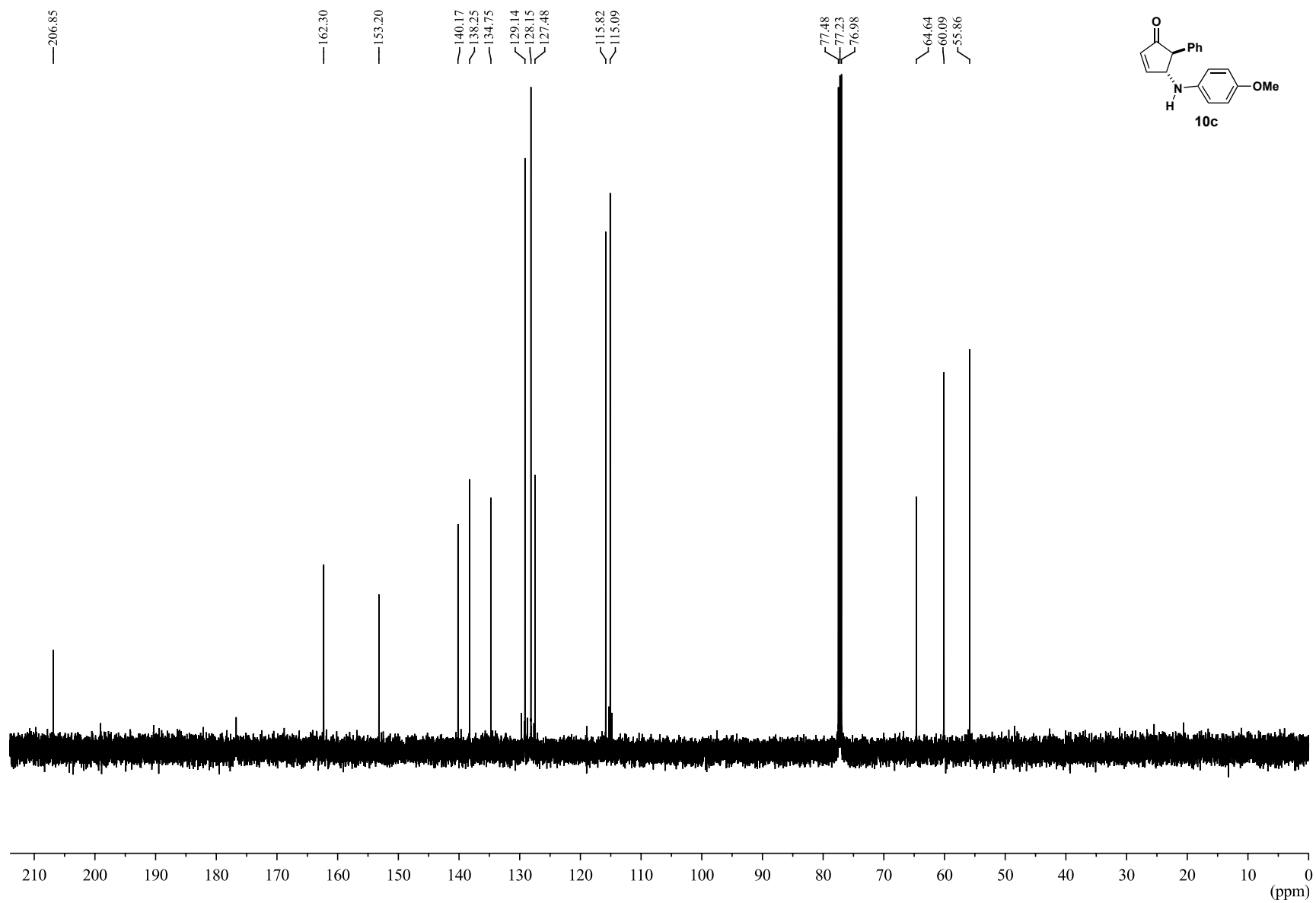


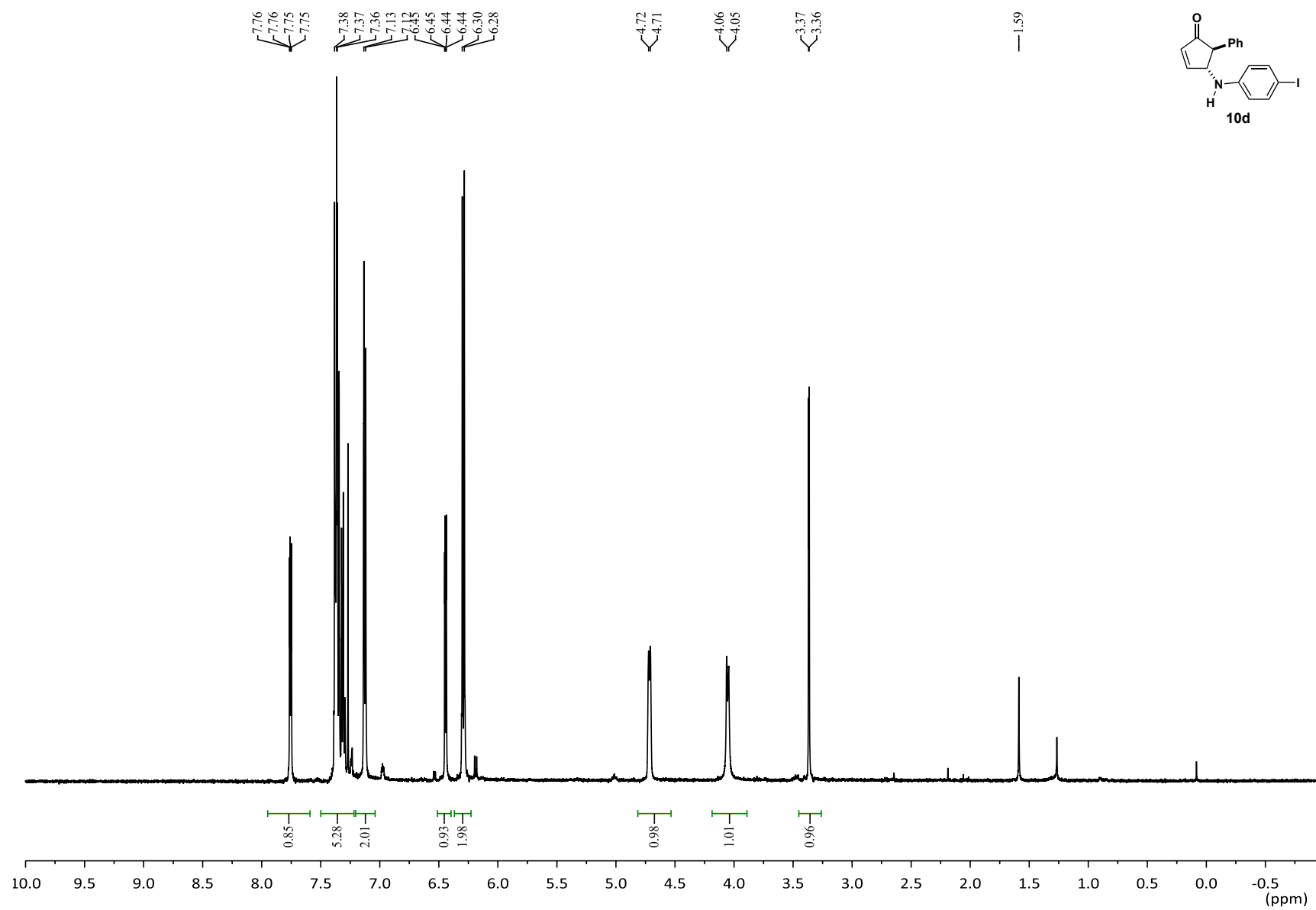


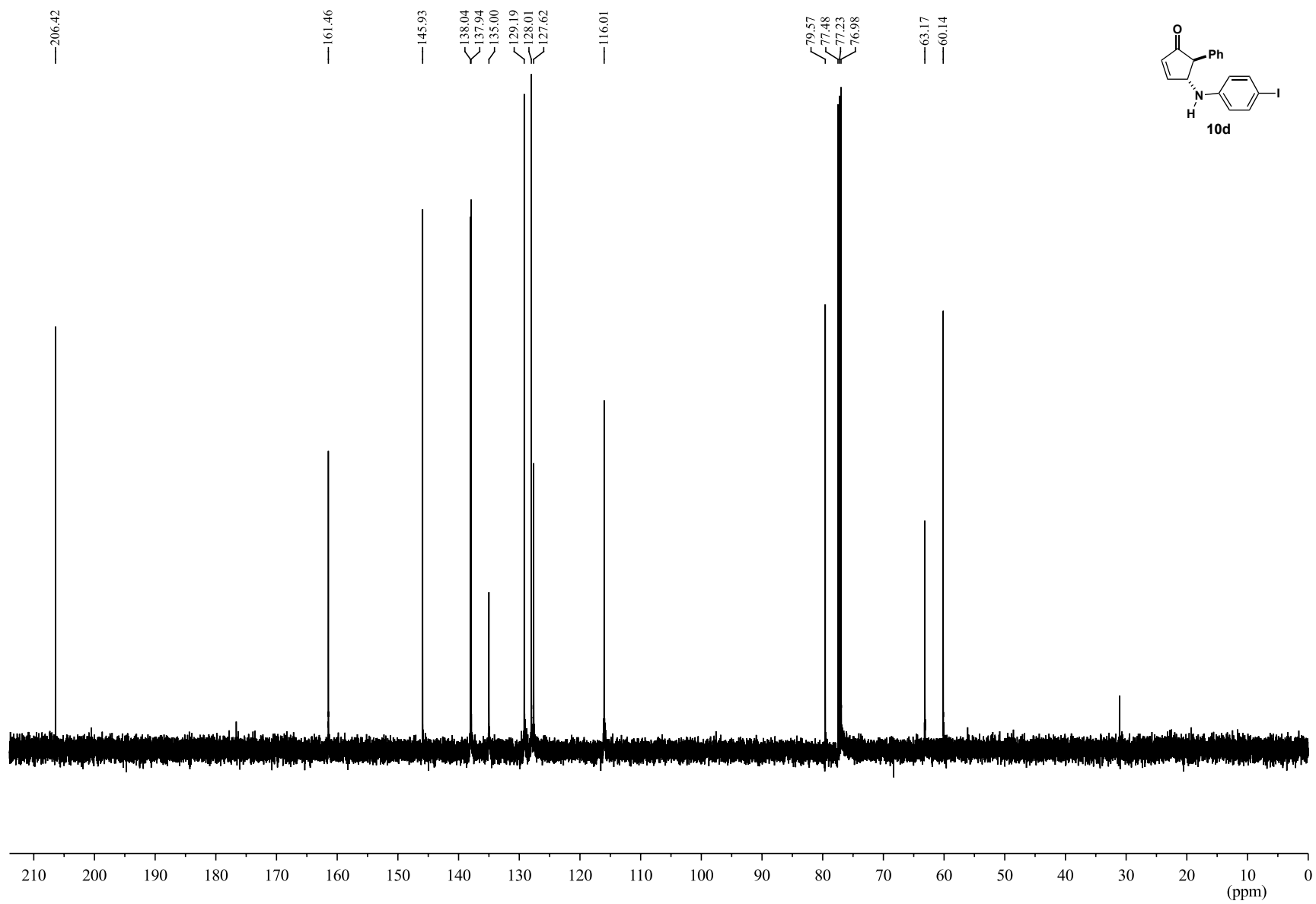


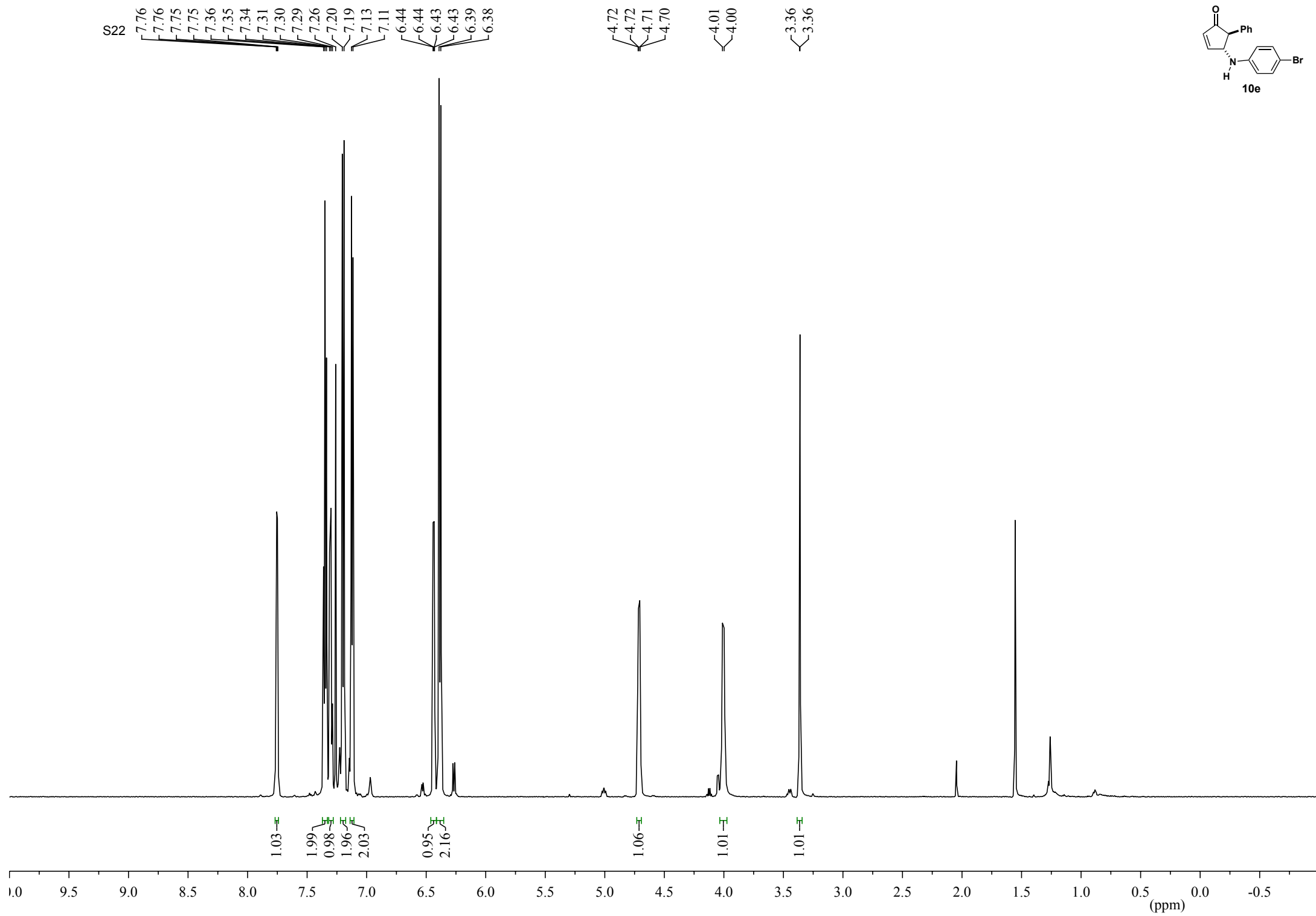
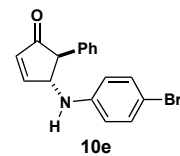


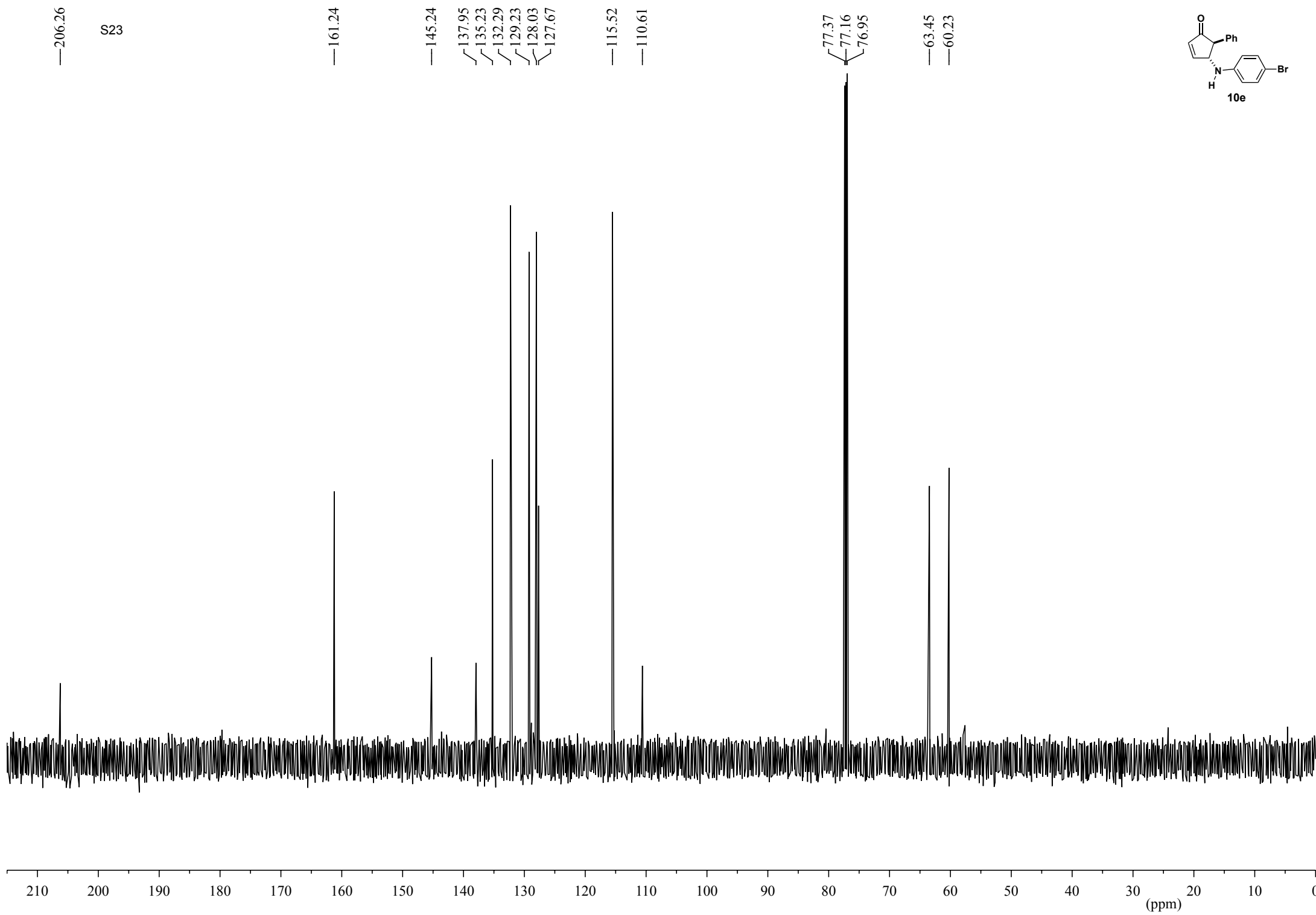
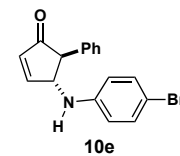












S24

