

Allylic Oxidations Catalyzed by Dirhodium Caprolactamate via Aqueous *tert*-Butyl Hydroperoxide: The Role of the *tert*-Butylperoxy Radical

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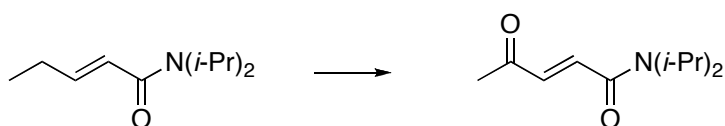
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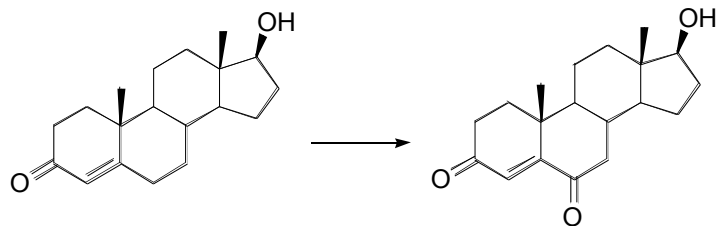
General Methods

HPLC grade solvents were used for extraction and purification. Unless otherwise indicated, all reactions were run under atmospheric conditions. All reagents were obtained from commercial sources. Dirhodium(II) caprolactamate $[\text{Rh}_2(\text{cap})_4 \cdot 2\text{CH}_3\text{CN}]$ was prepared as previously described.¹ Silica gel plates (0.25 mm, 60 F₂₅₄) were used for analytical thin layer chromatography and spots were visualized using 254 nm ultraviolet light before using potassium permanganate, vanillin, or anisaldehyde stains as visualizing agents. Chromatographic purifications were performed using silica gel (60 microns, 40-63 mesh) according to the method of Still.² Yields reported are for isolated compounds according to their mass unless otherwise noted. All products were characterized and in agreement with those that were previously described. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were obtained on a 400 MHz spectrometer as solutions in CDCl₃ unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ) relative to internal Me₄Si (δ 0.00) for ¹H and relative to internal chloroform (δ 77.0) for ¹³C; coupling constants are reported in Hertz (Hz).

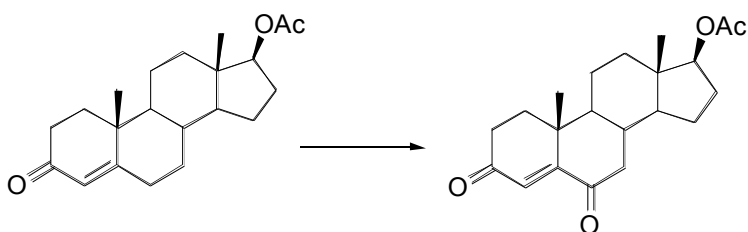
General Procedure for the Oxidation of α,β -Unsaturated Carbonyl Compounds. A 10 mL vial equipped with a stirbar was charged with substrate (1.36 mmol) and $\text{Rh}_2(\text{cap})_4$ (5 mg, 0.007 mmol). Solvent (2.5 mL) was added followed by the addition of TBHP (0.75 mL, 5.5 mmol, 4 equiv). The vial was loosely capped and stirred for 16 hrs, then the second portion of $\text{Rh}_2(\text{cap})_4$ (5 mg, 0.007 mmol) and TBHP (0.75 mL, 5.5 mmol, 4 equiv) was added. After an additional 24 hrs, the solution was concentrated and purified by column chromatography to obtain analytically pure compounds whose spectral characteristics were identical to those previously reported: *trans*-3-nonen-2,5-dione (**1**),³ ethyl-*(E)*-4-oxo-2-decenoate (**2**).⁴ *(E)*-4-oxo-2-pentenamide (**5**),⁵ 4-androsten-17 β -3,6-dione (**25**),⁶ 17 β -acetoxyandrost-4-en-3,6-dione (**26**),⁷ 4-androstene-3,6,17-trione (**27**),⁸ 4-cholesten-3,6-dione (**28**)⁹ and acids were purified by recrystallization in ethyl acetate and matched with those in the literature: *(E)*-4-oxo-2-nonenic acid (**3**),¹⁰ *(E)*-4-oxo-2-pentenoic acid (**4**),¹¹ 2-cyclohexenone-1-carboxylic acid (**7**).¹² and fumaric acid monomethyl ester (**8**).¹³



***(E)*-*N,N*-Diisopropyl-4-oxopent-2-enamide (**6**):** ¹H NMR (400 MHz, CDCl_3); 7.18 (d, $J = 16$ Hz, 1H), 6.88 (d, $J = 16$ Hz, 1H), 3.99 (m, 1H), 3.70 (m, 1H), 2.33 (s, 3H), 1.40 (d, $J = 16$ Hz, 6H), 1.25 (d, $J = 16$ Hz, 6H) ppm; ¹³C NMR (100 MHz, CDCl_3); 197.7, 164.6, 135.3, 134.7, 49.0, 46.1, 29.1, 21.3, 20.3 ppm. Exact mass calculated for $\text{C}_{11}\text{H}_{19}\text{NO}_2 + \text{H}$ (ESI) 198.1496; found 198.1490.

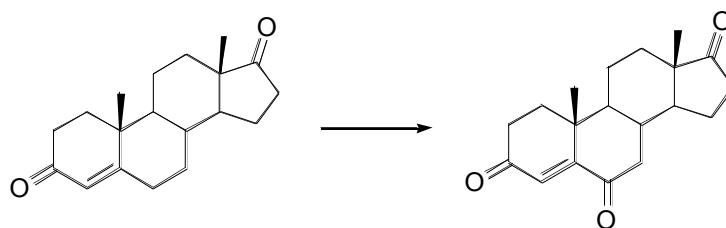


4-Androsten-17β-3,6-dione (25). Testosterone (577 mg, 2.0 mmol) was subjected to the standard oxidation procedure using $\text{Rh}_2(\text{cap})_4$ (14.8 mg, 0.020 mmol) and T-HYDRO (2.28 ml, 16.0 mmol) in two portions added at 0 h and 16 h. The crude product was purified via silica gel chromatography (25 % ethyl acetate in hexanes to 50 % ethyl acetate) to yield 136 mg (0.46 mmol, 23 %) of a white solid: m.p. 203-6 °C; 206-7 °C (lit.).⁶ ^1H NMR (CDCl_3 , 400 MHz): defining absorptions are at δ 6.15 (d, $J = 0.4$ Hz, 1H), 3.68 (t, $J = 8.4$ Hz, 1H), 2.66 (dd, $J = 15.6, 3.6$ Hz, 1H), 2.53 (ddd, $J = 17.2, 14.4, 4.8$ Hz, 1H), 2.44 (dddd, $J = 17.2, 4.8, 2.4, 0.4$ Hz, 1H), 2.15 (ddd, $J = 13.2, 4.8, 2.8$ Hz, 1H), 1.16 (s, 3H), 0.79 (s, 3H).

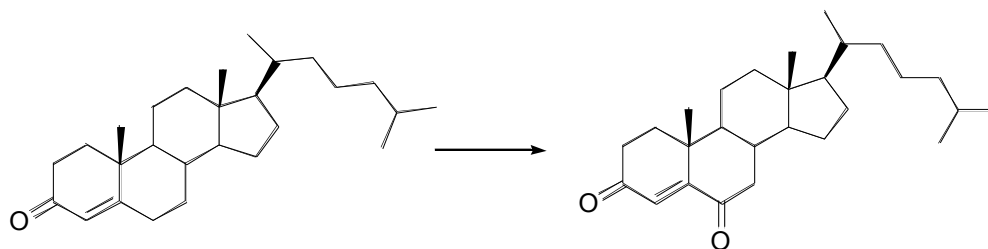


17β-Acetoxyandrost-4-en-3,6-dione (26). 17β-Acetoxyandrost-4-en-3-one (5, 1.32 g, 4.0 mmol) was stirred vigorously in 12 ml of water at room temperature in a 50 ml flask. Then $\text{Rh}_2(\text{cap})_4$ (29.5 mg, 0.040 mmol) was added, followed by addition of T-HYDRO[®] (4.6 ml; 32 mmol). The reaction became dark purple-red in color. The flask was closed with a rubber septum with a balloon and stirred for 24 h in a 40 °C oil bath. At that time additional portions of $\text{Rh}_2(\text{cap})_4$ (15 mg, 0.02 mmol) and T-HYDRO (2.3 ml; 16 mmol) were added, and the reaction solution was stirred for another 24 h. The reaction was extracted into diethyl ether (3 x 20 ml). The organic extracts were combined, dried over anhydrous MgSO_4 , filtered, then concentrated under reduced pressure to yield a crude yellow oil that was purified by silica gel chromatography (25 % ethyl acetate in hexanes) to yield 938 mg (2.72 mmol, 68 %) of a

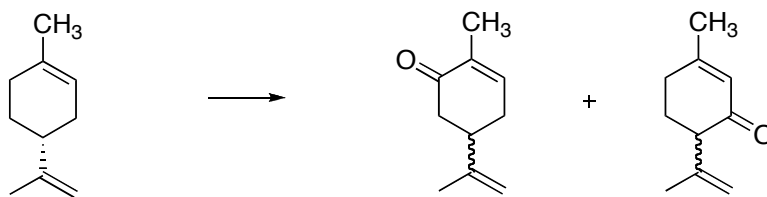
white solid. m.p.: 193-5 °C; 192-4 °C (lit.).⁷ ¹H NMR (CDCl₃, 400 MHz): defining absorptions are at δ 6.18 (s, 1H), 4.65 (t, *J* = 8.6 Hz, 1H), 2.68 (dd, *J* = 15.6, 3.6 Hz, 1H), 2.54-2.47 (comp, 2H), 2.06 (s, 3H), 1.18 (s, 3H), 0.85 (s, 3H).



4-Androstene-3,6,17-trione (27). 4-Androstene-3,17-dione⁴ (286 mg, 1.0 mmol) was subjected to catalytic oxidation by T-HYDRO[®] (1.7 ml; 12 mmol) using Rh₂(cap)₄ (11.1 mg, 0.015 mmol) as described for the oxidation of **26**. The crude product was purified via silica gel chromatography (25 % ethyl acetate in hexanes) to yield 186 mg (0.62 mmol, 62 %) of a light yellow solid. m. p.: 213-5 °C; 221-2 °C (lit.).⁸ ¹H NMR (CDCl₃, 400 MHz): defining absorptions are at δ 6.16 (d, *J* = 0.8 Hz, 1H), 2.76 (d, *J* = 12.0 Hz, 1H), 2.40-2.55 (comp, 2H), 1.17 (s, 3H), 0.90 (s, 3H).

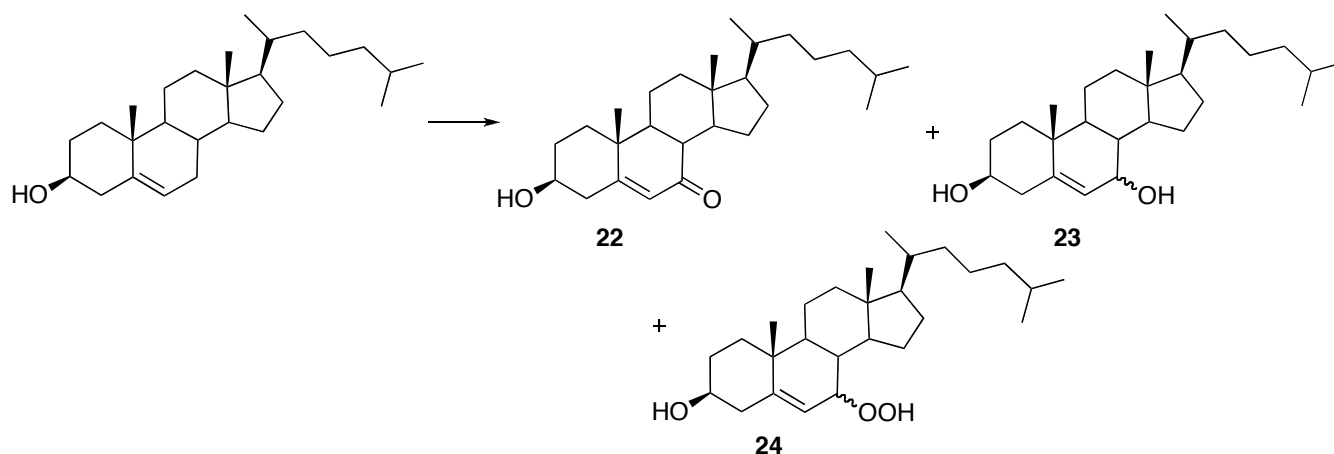


4-Cholesten-3,6-dione (28). 4-Cholesten-3-one (192 mg, 0.50 mmol) was subjected to the standard oxidation procedure using Rh₂(cap)₄ (3.7 mg, 5.0 μmol) and T-HYDRO (0.72 ml, 5.0 mmol) in two portions added at 0 h and 16 h). The crude product was purified by silica gel chromatography (16 % ethyl acetate in hexanes) to yield 102 mg (0.50 mmol, 50 %) of a white solid: m.p. = 121-3 °C; 123-5 °C (lit.).⁸ ¹H NMR (CDCl₃, 400 MHz): defining absorptions are at δ 6.16 (s, 1H), 2.67 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.53 (ddd, *J* = 17.2, 14.8, 5.2 Hz, 1H), 2.44 (ddd, *J* = 17.6, 4.4, 2.4 Hz, 1H), 2.02 (dd, *J* = 16.0, 12.4 Hz, 1H), 1.25 (s, 3H), 1.15 (s, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.71 (s, 3H) ppm.



Carvone (16). (+)-Limonene (0.229 g; 1.63 mmol) was stirred vigorously in 6 mL of water in a 6-dram vial. At that time $\text{Rh}_2(\text{cap})_4$ (12 mg; 0.016 mmol) was added, followed by one aliquot of T-HYDRO[®] (0.89 mL; 6.52 mmol). The reaction solution was then stirred for 20 hours in a 40 °C oil bath. The reaction was extracted using diethyl ether (3 X 20 mL) and the organic extracts were combined and dried using anhydrous MgSO_4 . The organic extracts were filtered and concentrated under reduced pressure to a crude oil, which was purified by silica gel chromatography (20 % ethyl acetate in hexanes) to yield racemic carvone (44%). The optical purity of carvone was identified by gas chromatography using a 30-m β -DM column (27.1 and 27.3 min for the two enantiomers). ¹H NMR data of the isolated carvone was in accordance with that from commercial sources.

Isopiperitenone (17). Oxidation of limonene was performed as previously described. The organic extracts were filtered and concentrated under reduced pressure to a crude oil, which was distilled. The distillate was purified by silica gel chromatography (25 % ethyl acetate in hexanes) to yield pure isopiperitenone (6.0 mg; 0.040 mmol) whose spectra matched those of standard samples. The reaction yield of isopiperitenone (7%) was determined on the reaction mixture by using gas chromatography with an SPB-5 column to compare the area percent of **17** with the isolated yield of carvone.

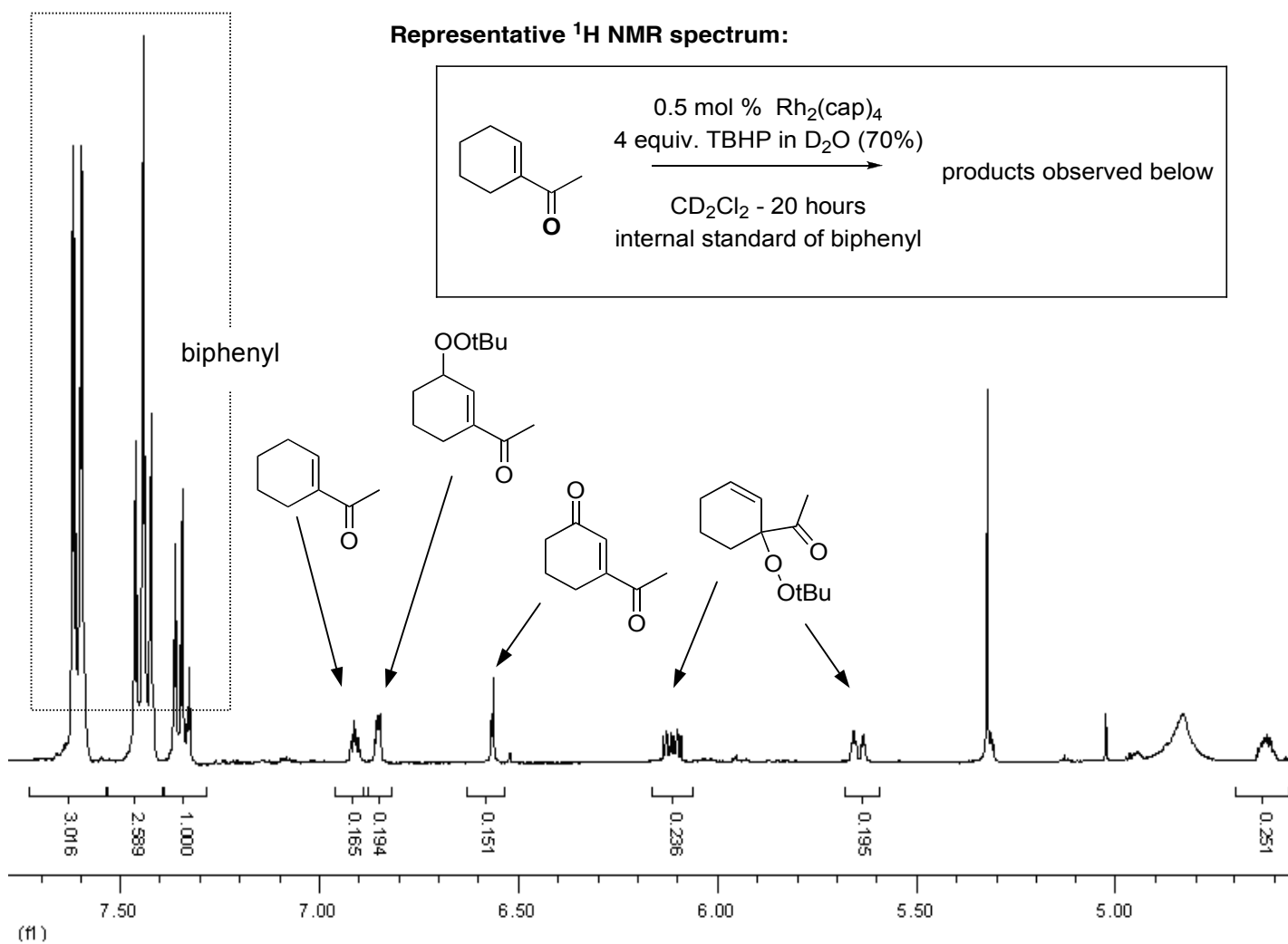
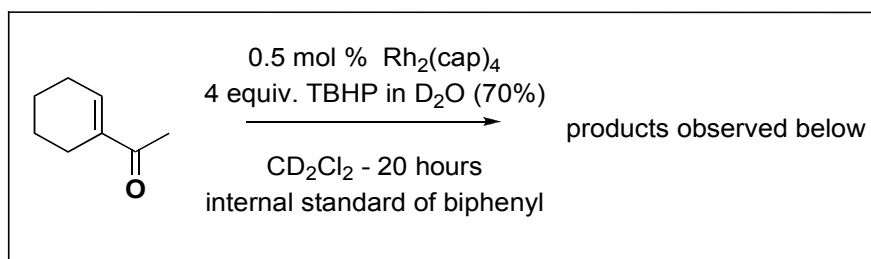


Oxidation of Cholesterol (19) - Isolation of 22, 23, and 24. Cholesterol (0.525 g; 1.36 mmol) and $\text{Rh}_2(\text{cap})_4$ (10 mg; 0.013 mmol) were dissolved in 5 mL of 1,2-dichloroethane in a 6 dram vial equipped with a stirbar. T-HYDRO[®] (0.74 mL; 5.43 mmol) was added, and the color of the reaction solution turned from purple to brown-red in color. The vial was loosely capped and stirred at room temperature. After 15 hours, the reaction was concentrated under reduced pressure to 1.01 g of a red-brown semi-solid. The crude material was purified by silica gel column chromatography (100 % hexanes to 1:1 hexanes: ethyl acetate, gradient) to afford 164 mg of **22**, 62 mg of α -**23**, 13 mg of β -**23**, 57 mg of α -**24**, 25 mg of β -**24**, and 106 mg of starting material (**21**). The full characterization of **22**, **23**, and **24** has been reported.⁷

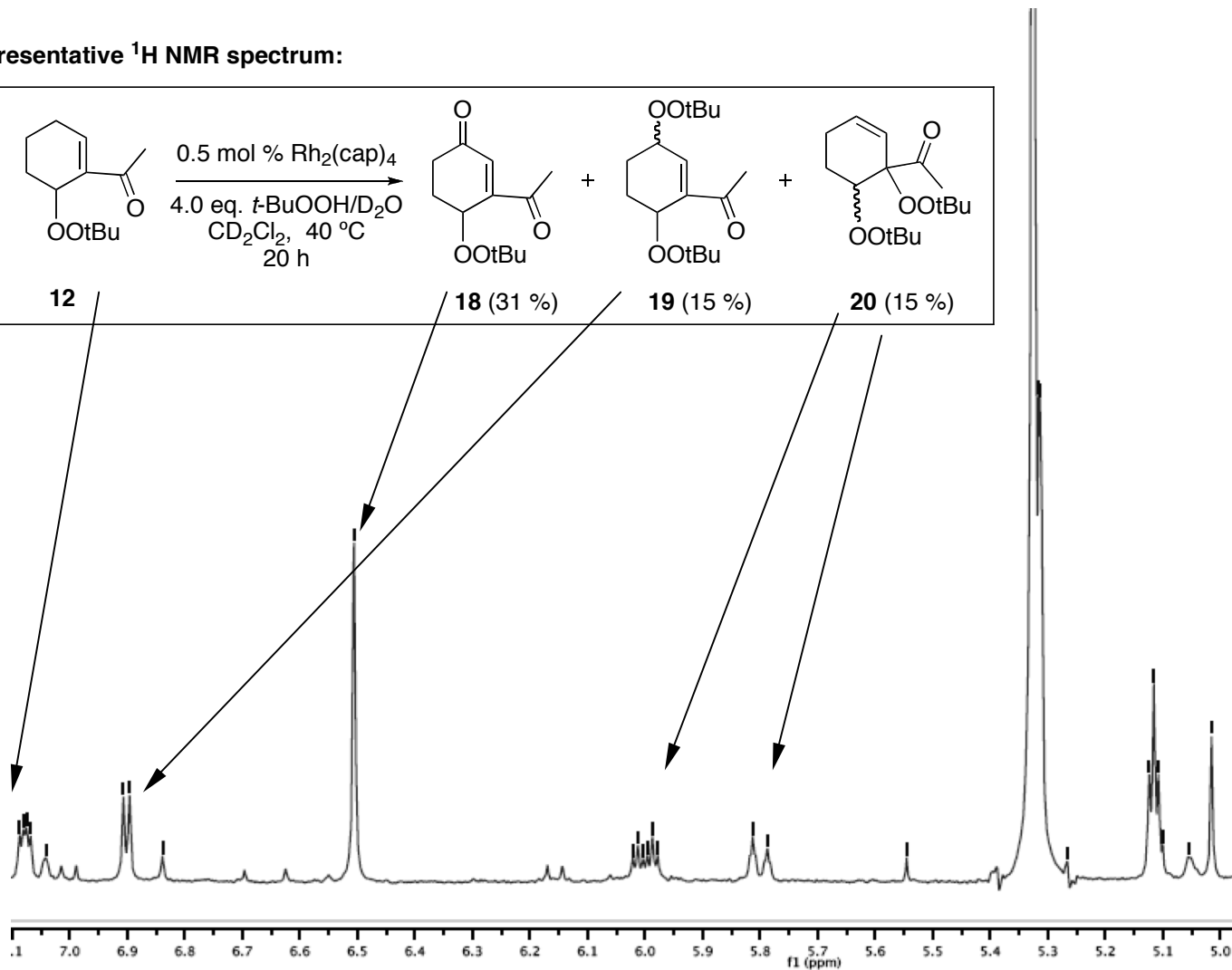
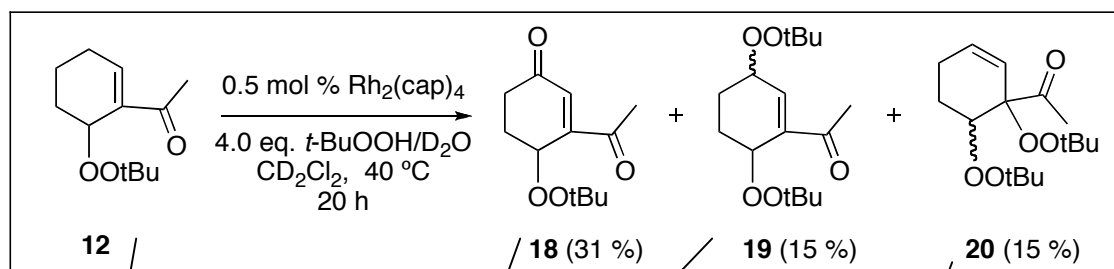
General Procedure for the ^1H NMR Studies of the Oxidation of **10, **12**, and **13** by TBHP with Dirhodium(II) Caprolactamate (eq **4**, **5**, and **6**):** A NMR tube was charged with analytically pure **10**, **12**, or **13** (10-20 mg) and biphenyl (1.0 equiv) followed by addition of 0.5 mol % of $\text{Rh}_2(\text{cap})_4$. Next, 0.75 mL of CD_2Cl_2 was added, and then the tube was capped and shaken to dissolve the organic material. At this time, a ^1H NMR spectrum was obtained ($t = 0$). The sample was retrieved from the instrument and treated with TBHP in D_2O (4.0 equiv) then heated in a $40\text{ }^\circ\text{C}$ oil bath for 20 hours. At 20 hours another ^1H NMR spectrum was obtained and the defining olefinic resonances (δ 6.91 for 1-acetylcyclohexane; δ 6.57 for **9**; δ 6.12 and 5.66 for **10**; δ 6.99 and 6.17 for **11**; δ 7.08 for **12**; δ 6.86 for **13**; δ 6.53 for **18**; δ 7.01 for **19**; δ 6.07 and 5.80 + 6.00 for **20**) were measured against the internal biphenyl standard.

General Procedure for the ^1H NMR Studies of the Oxidation of 1-Acetylcyclohexene by TBHP with Various Metal Catalysts (Table 2): A NMR tube was charged with 1-acetylcyclohexene (25 mg; 0.20 mmol) and biphenyl (31 mg; 0.20 mmol). Next, in separate experiments, 0.10 – 5.0 mol % of the selected metal catalyst was added to the tube, along with 0.25 – 0.50 equivalents of K_2CO_3 additive as indicated. Subsequently, 0.75 mL of CD_2Cl_2 was added, and then the tube was capped and shaken to dissolve the organic material. At this time, a ^1H NMR spectrum was obtained ($t = 0$). The sample was retrieved from the instrument and treated with TBHP in D_2O (0.077 mL; 0.80 mmol) then heated in a $40\text{ }^\circ\text{C}$ oil bath for 20 hours. At 20 hours another ^1H NMR spectrum was obtained, and the defining olefinic resonances (δ 6.91 for 1-acetylcyclohexane; δ 6.57 for **9**; δ 6.12 and 5.66 for **10**; δ 6.86 for **13**) were measured against the internal biphenyl standard.

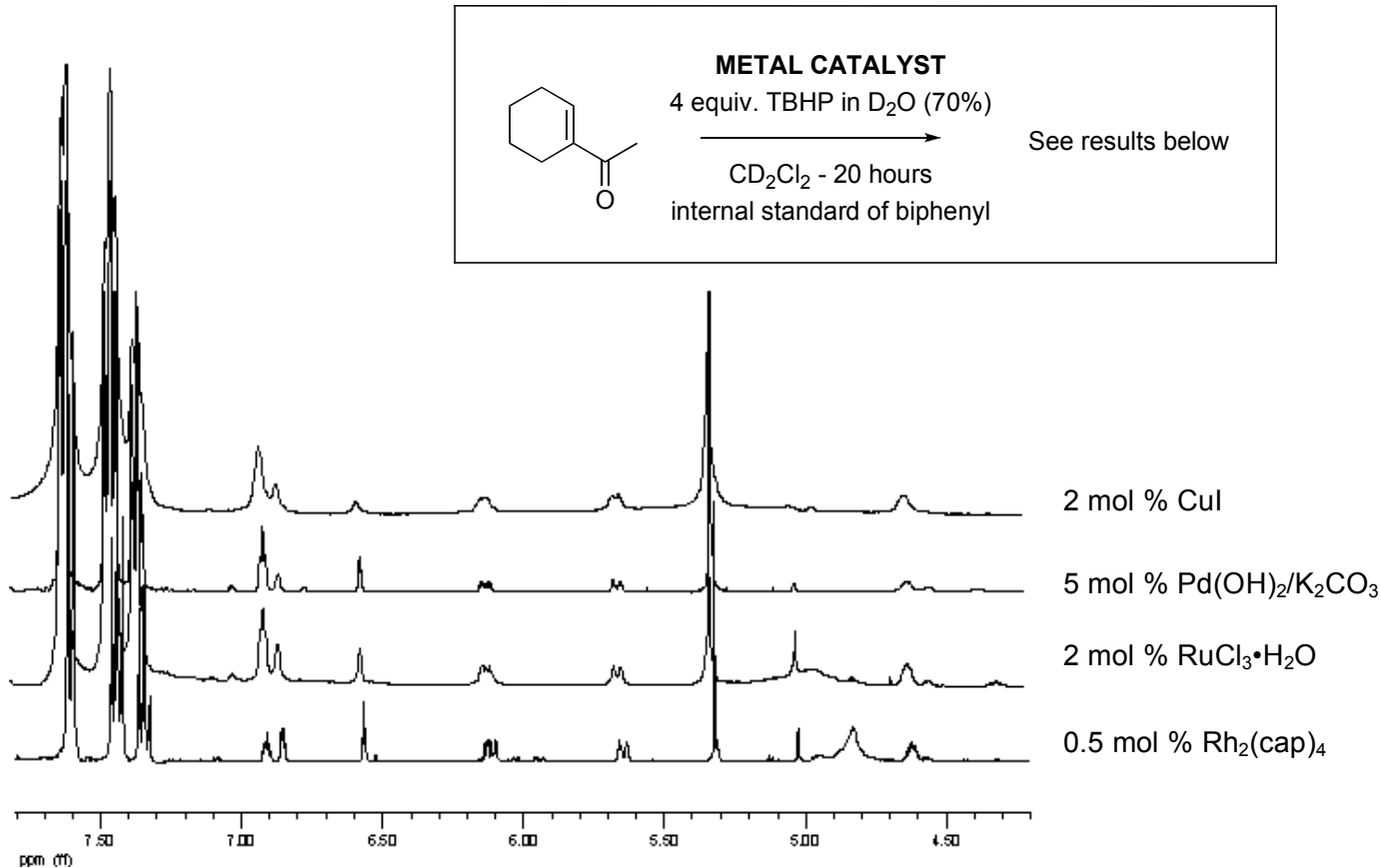
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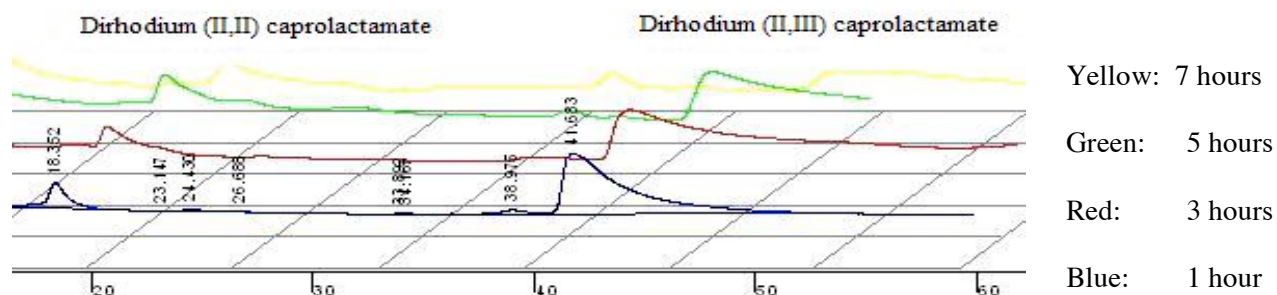
Representative ^1H NMR spectrum:

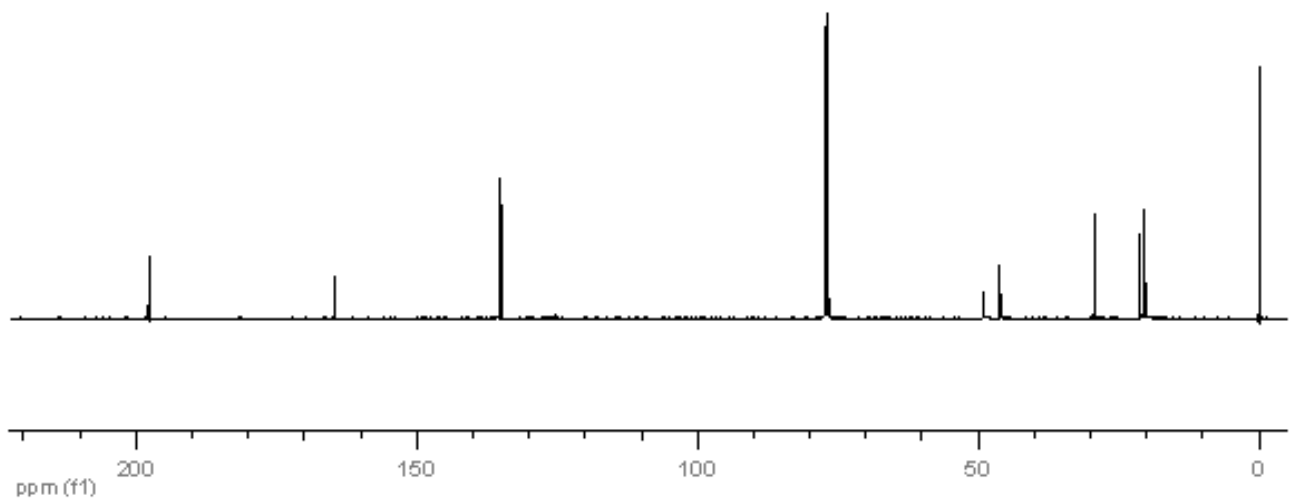
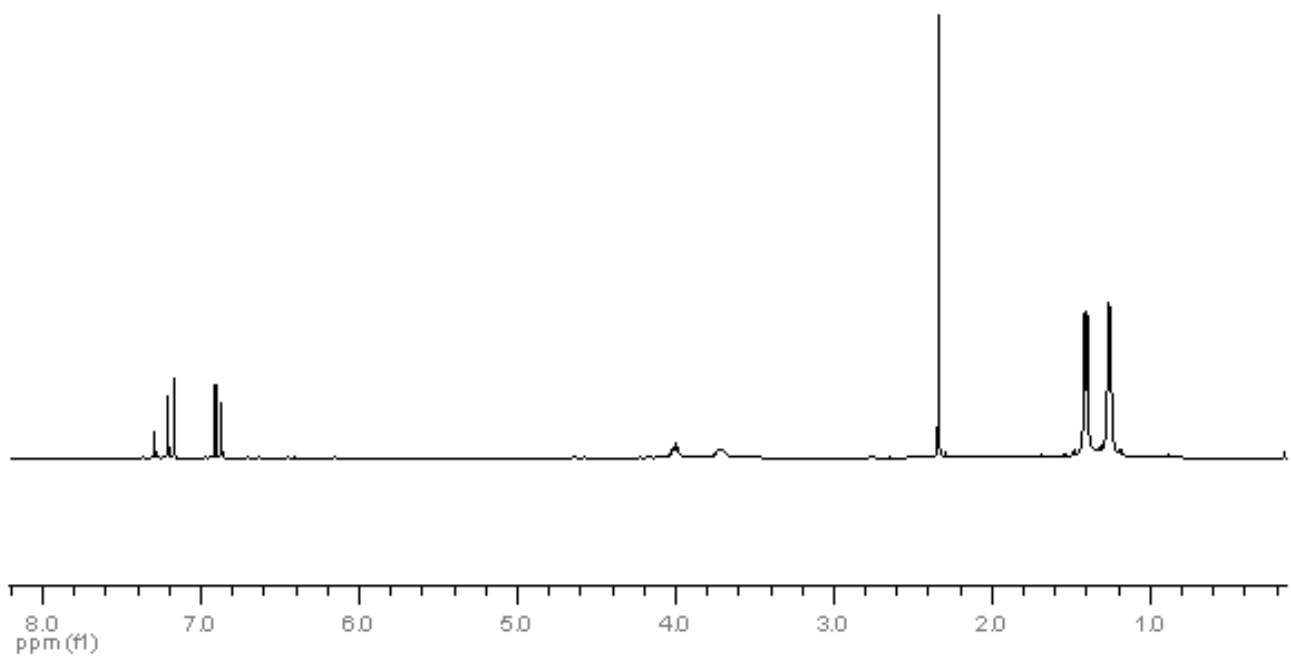
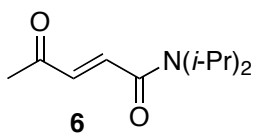


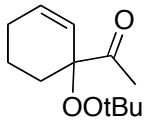
Representative ^1H NMR spectrum:



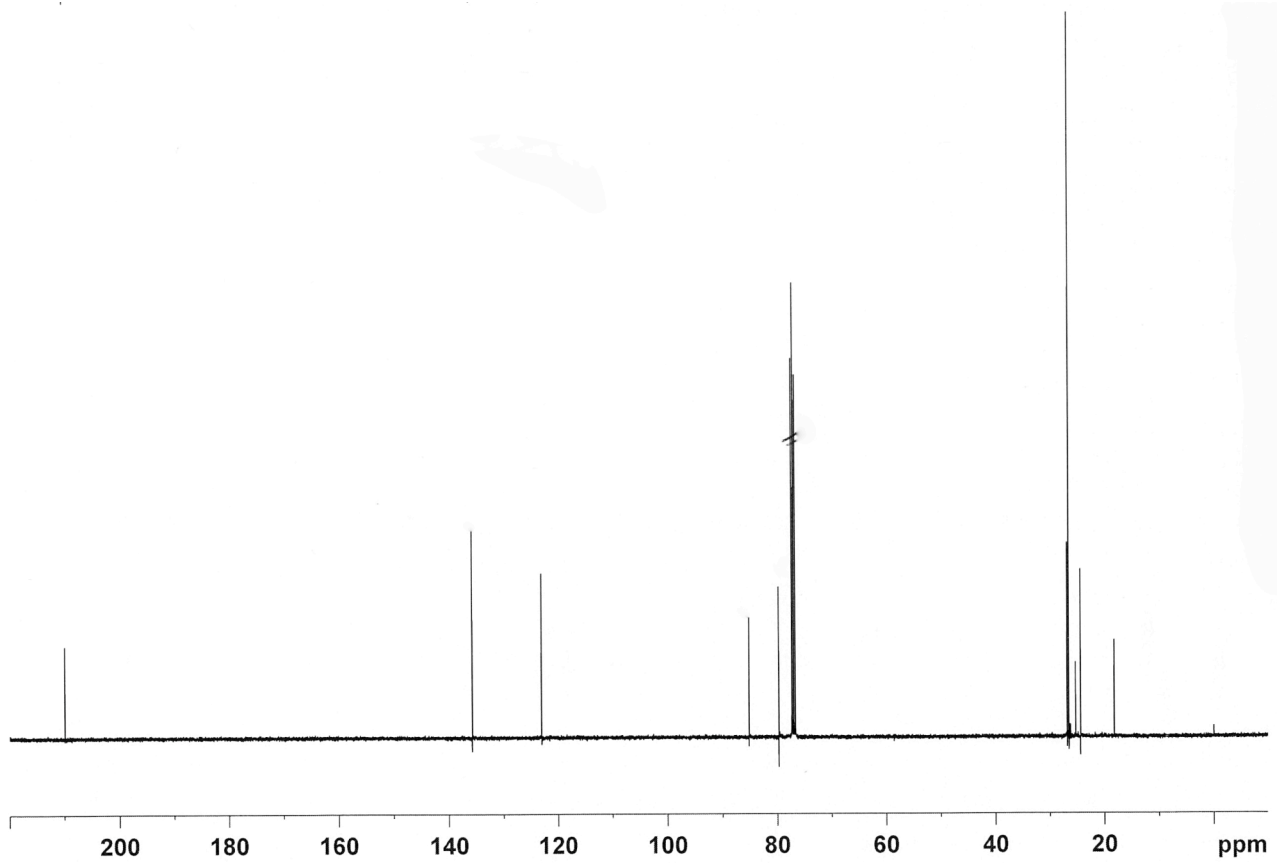
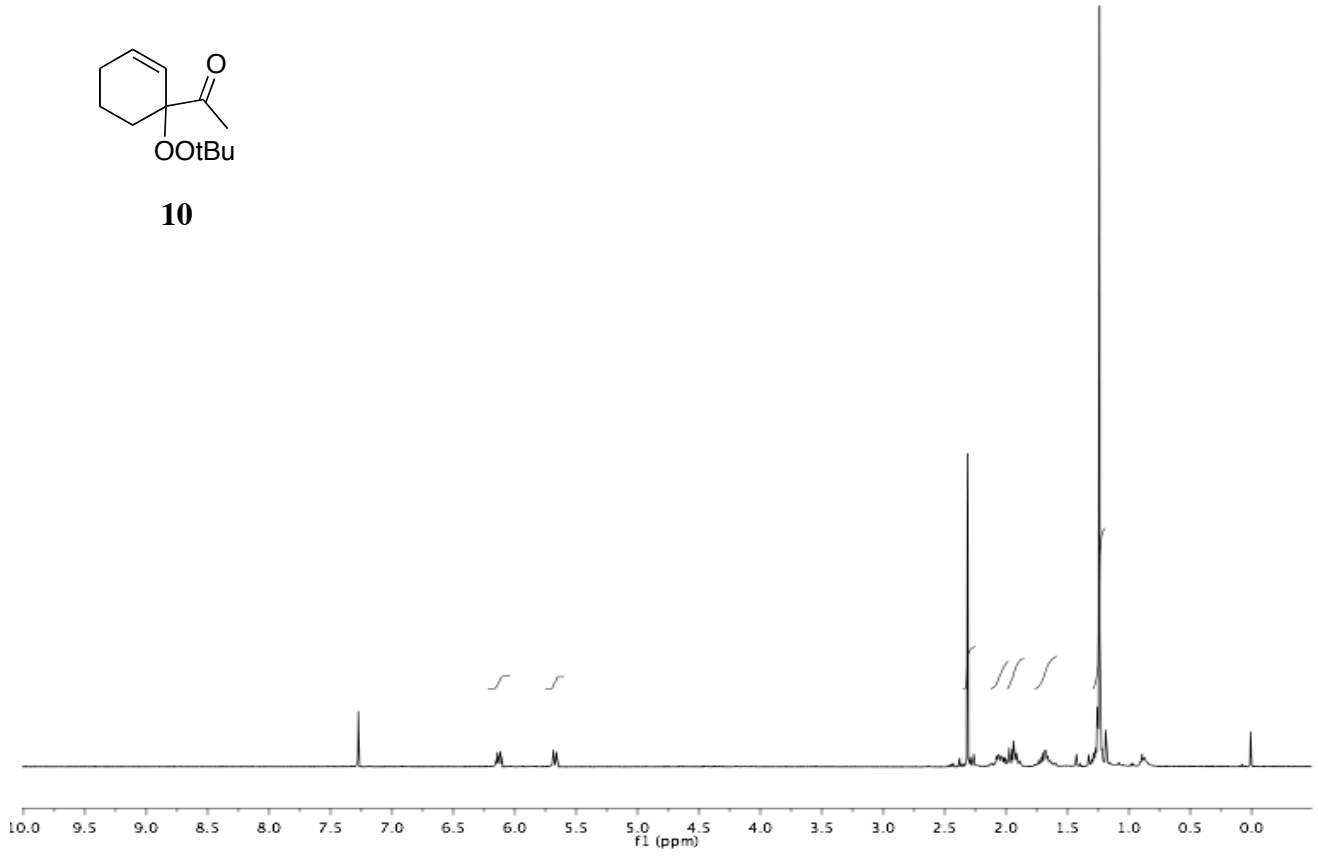
Dirhodium (II,III) caprolactamate HPLC detection (1, 3, 5, and 7 h). (10 x 0.5 cm Licosorb-CN, 1% acetonitrile in methanol, 1.0 mL/min; 254 nm wavelength detection). TBHP (0.27 M) in DCE with 1.0 mol % $\text{Rh}_2(\text{cap})_4$ without olefinic substrate. Note that dirhodium (II,III) caprolactamate is clearly visible even at 7 hours.

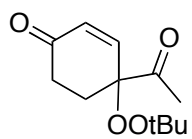




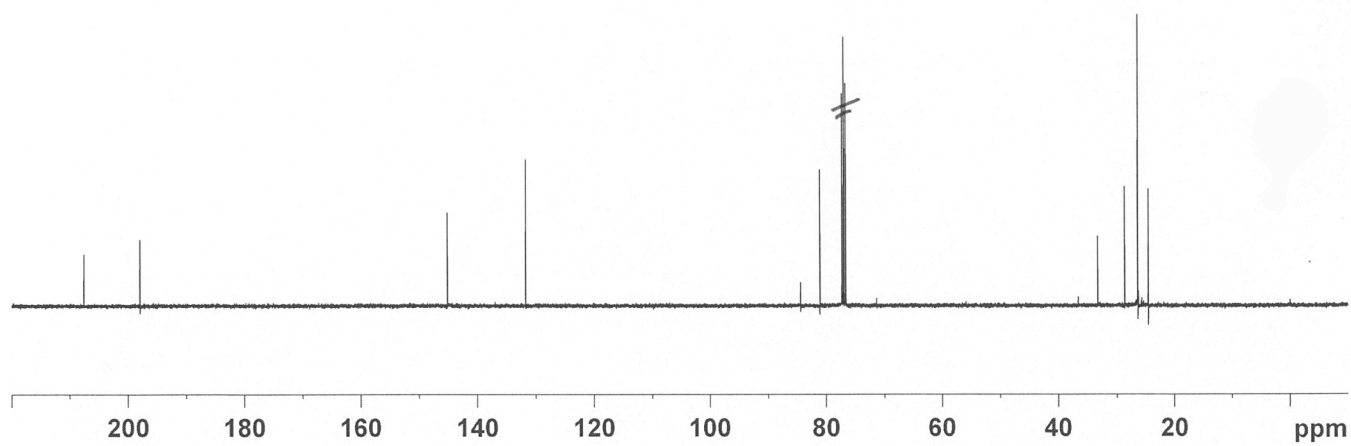
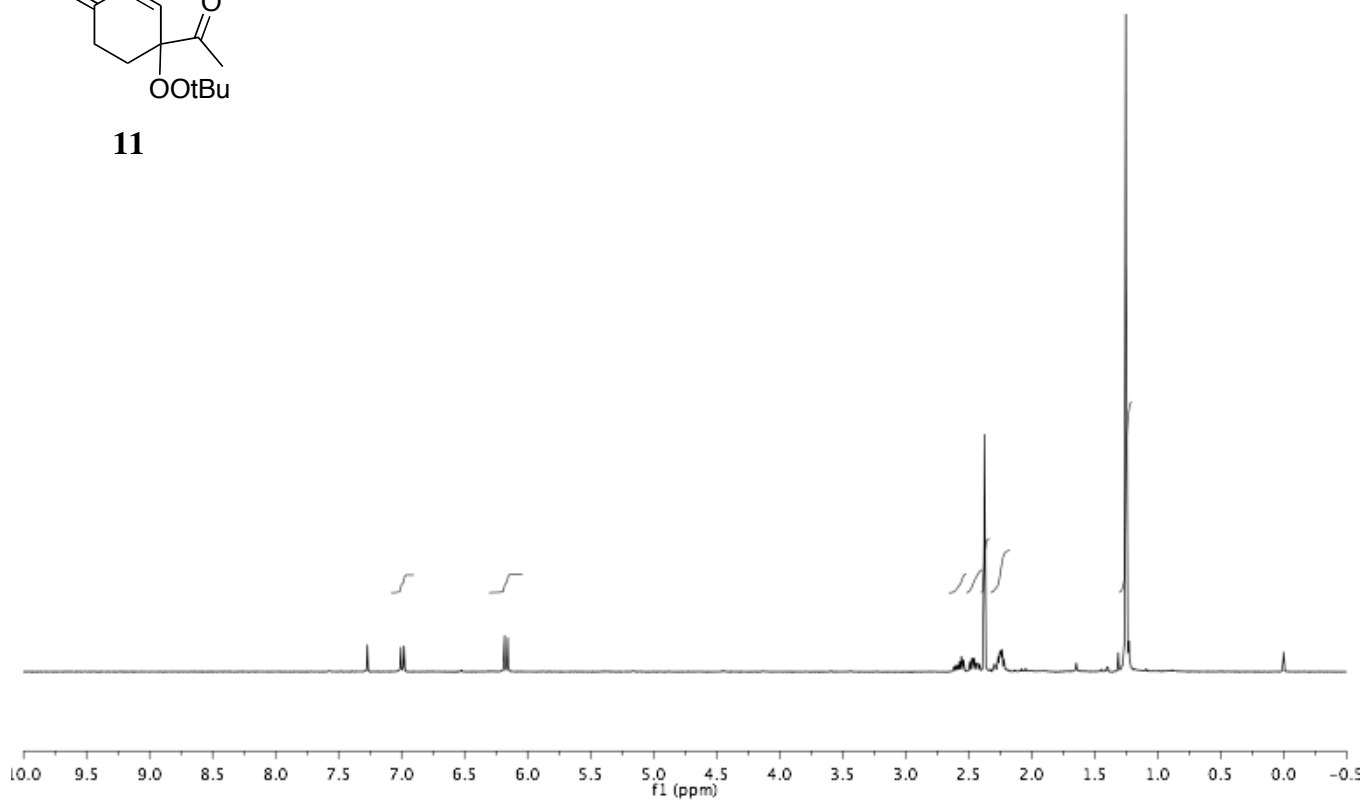


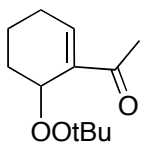
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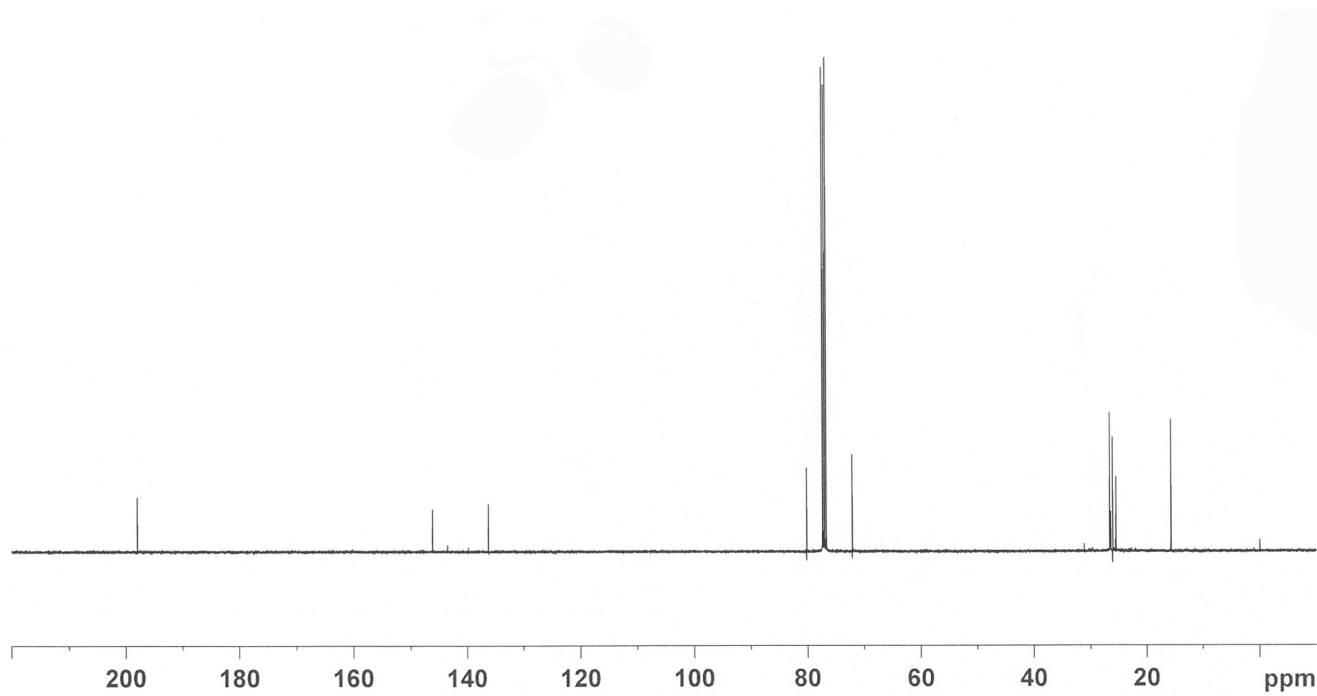
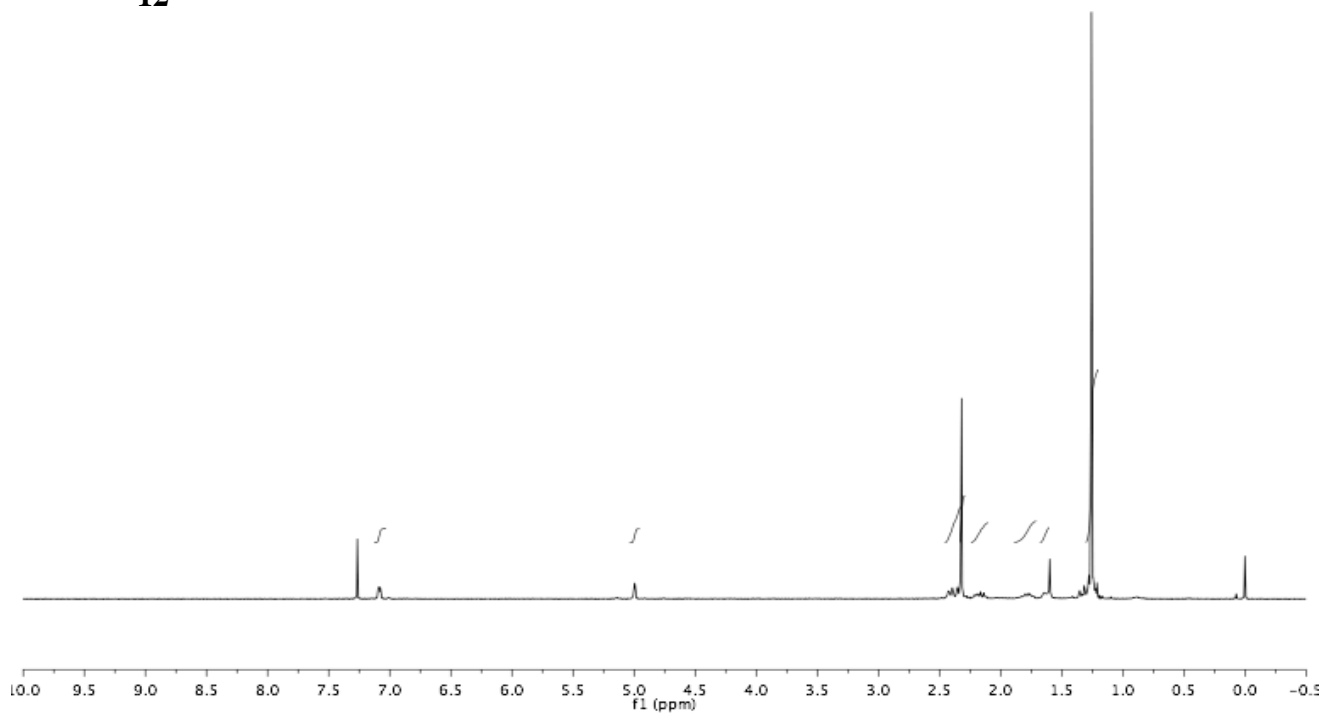


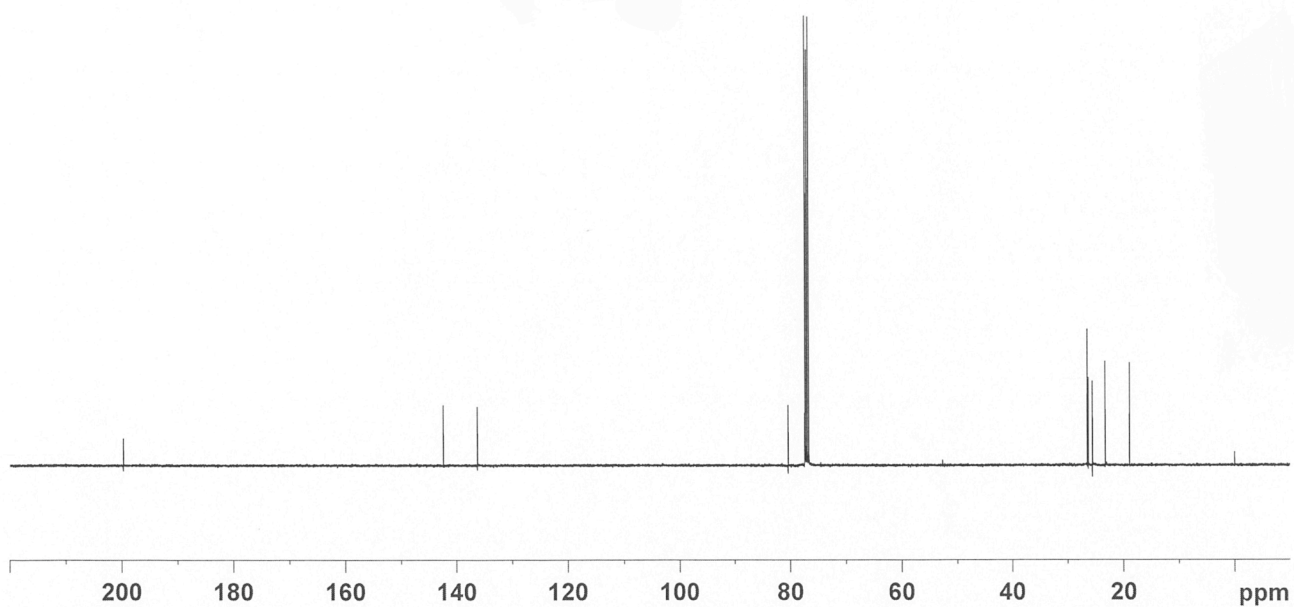
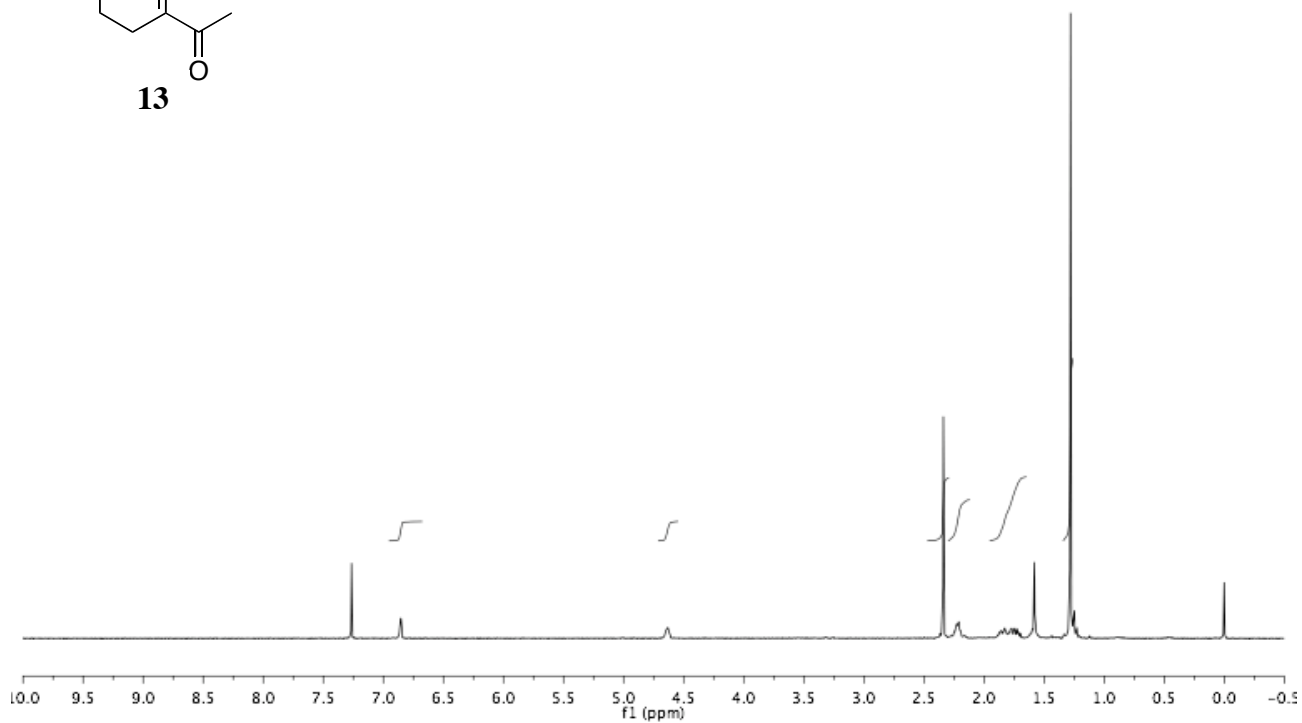
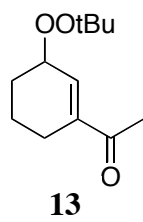
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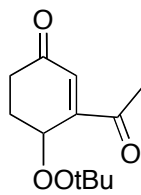




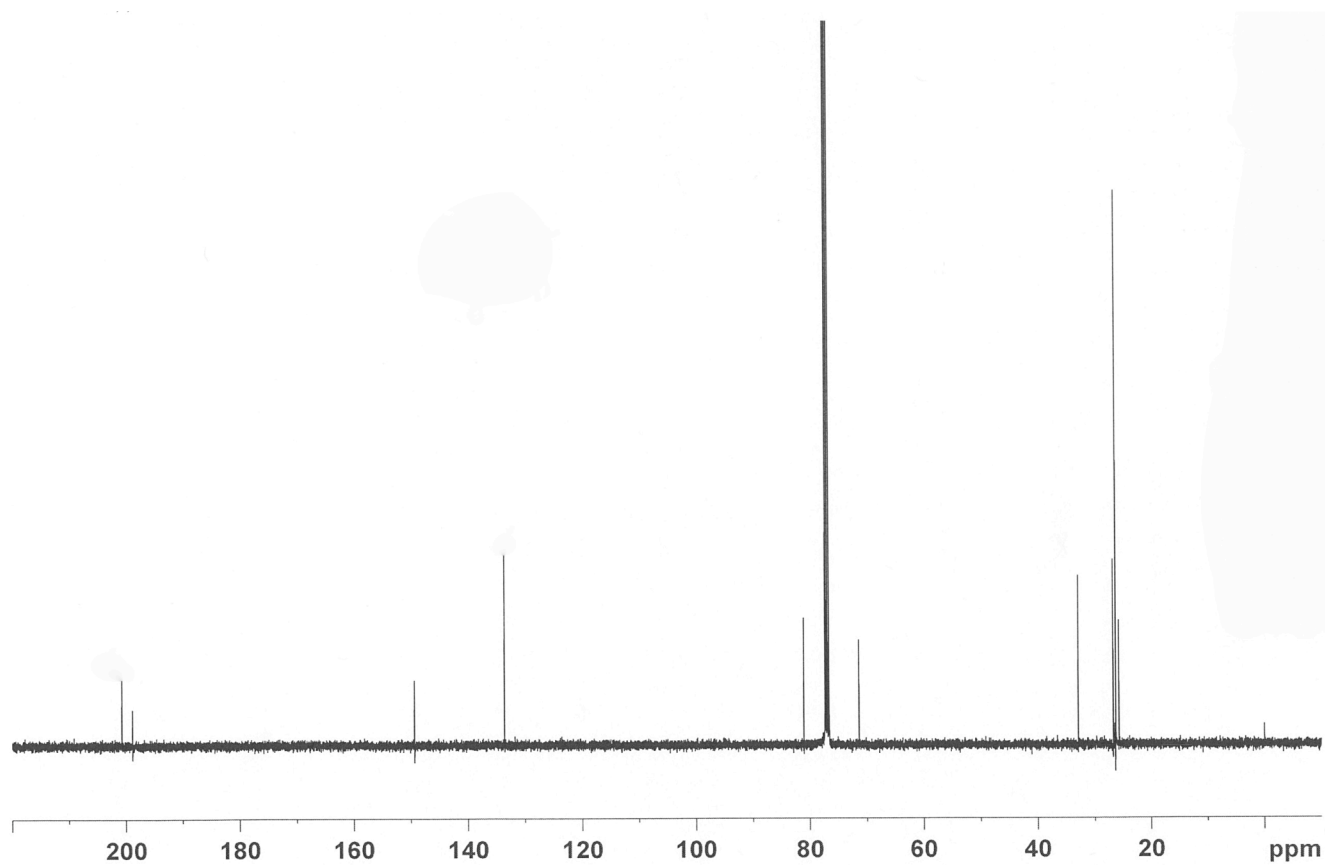
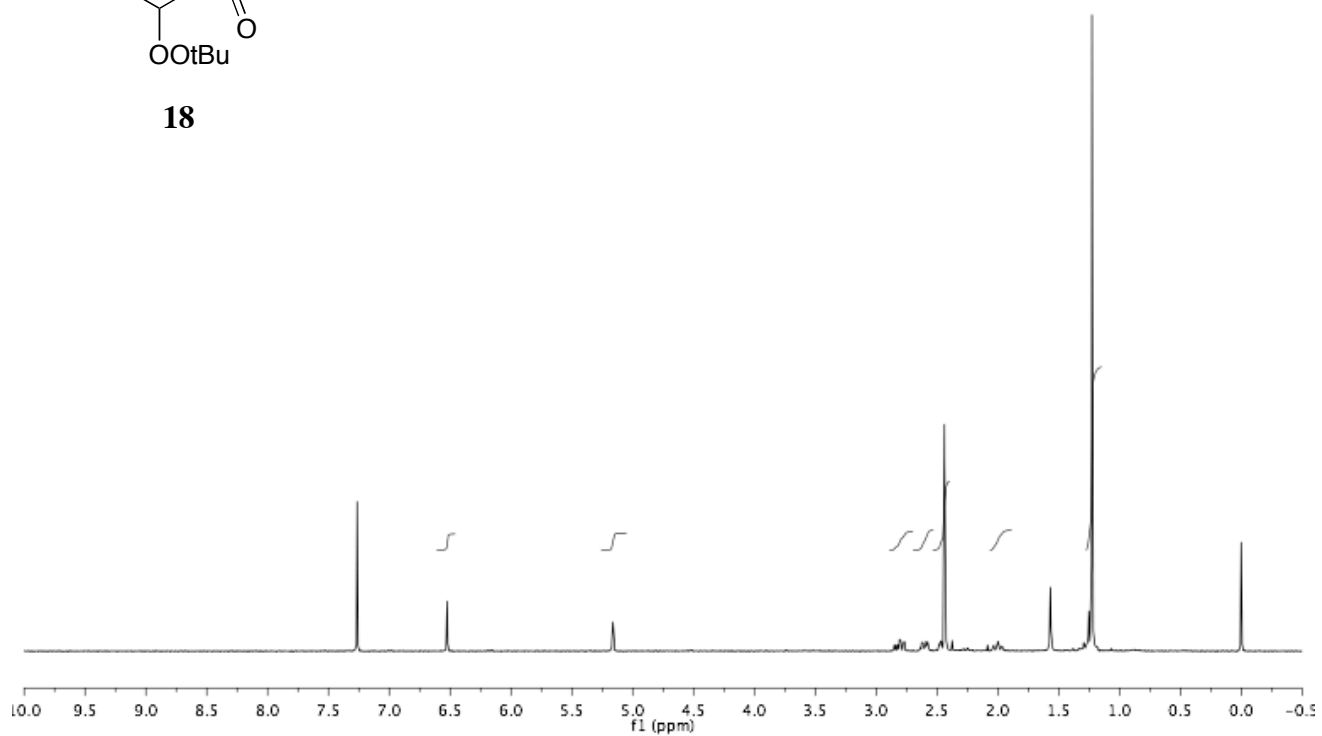
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