Journal of Visualized Experiments

Preparation of 6-amino-2,4-dien-1-one Derivatives via Tricarbonyl(tropone)iron

--Manuscript Draft--

Article Type:	Invited Methods Article - JoVE Produced Video
Manuscript Number:	JoVE60050R1
Full Title:	Preparation of 6-amino-2,4-dien-1-one Derivatives via Tricarbonyl(tropone)iron
Keywords:	iron diene complex tropone aza-Michael reaction solvent free cationic iron complex demetallation
Corresponding Author:	Daniel Griffith, Ph.D. Lafayette College Easton, PA UNITED STATES
Corresponding Author's Institution:	Lafayette College
Corresponding Author E-Mail:	griffitd@lafayette.edu
Order of Authors:	Daniel Griffith, Ph.D.
	Zhiyuan Huang
	Zaki K. Phelan
	Rachel L. Tritt
	Shelby D. Valent
Additional Information:	
Question	**Response**
Please indicate whether this article will be Standard Access or Open Access.	Standard Access (US$2,400)
Please indicate the **city, state/province, and country** where this article will be **filmed**. Please do not use abbreviations.	Easton, PA, USA

TITLE:

Preparation of 6-Aminocyclohepta-2,4-dien-1-one Derivatives via Tricarbonyl(tropone)iron

AUTHORS AND AFFILIATIONS:

Zhiyuan Huang,[1] Zaki K. Phelan,[1] Rachel L. Tritt,[1] Shelby D. Valent,[1] Daniel R. Griffith[1]

[1]Department of Chemistry, Lafayette College, Easton, PA, USA

Corresponding Author:
Daniel R. Griffith (griffitd@lafayette.edu)

E-mail Adresses of Co-authors:
Zhiyuan Huang (huangz@lafayette.edu)
Zaki K. Phelan (phelanz@lafayette.edu)
Rachel L. Tritt (rtritt@wisc.edu)
Shelby D. Valent (sdv006@bucknell.edu)

KEYWORDS:

iron diene complex, tropone, *aza*-Michael reaction, solvent free, cationic iron complex, demetallation

SUMMARY:

Representative experimental procedures for the addition of amine nucleophiles to tricarbonyl(tropone)iron and subsequent demetallation of the resulting complexes are presented in detail.

ABSTRACT:

aza-Michael adducts of tricarbonyl(tropone)iron are synthesized by two different methods. Primary aliphatic amines and cyclic secondary amines participate in a direct *aza*-Michael reaction with tricarbonyl(tropone)iron under solvent-free conditions. Less nucleophilic aniline derivatives and more hindered secondary amines add efficiently to the cationic tropone complex formed by protonation of tricarbonyl(tropone)iron. While the protocol utilizing the cationic complex is less efficient overall for accessing the *aza*-Michael adducts than the direct, solvent-free addition to the neutral complex, it allows the use of a broader range of amine nucleophiles. Following protection of the amine of the *aza*-Michael adduct as a *tert*-butyl carbamate, the diene is decomplexed from the iron tricarbonyl fragment upon treatment with cerium(IV) ammonium nitrate to provide derivatives of 6-aminocyclohepta-2,4-dien-1-one. These products can serve as precursors to diverse compounds containing a seven-membered carbocyclic ring. Because the demetallation requires protection of the amine as a carbamate, the *aza*-Michael adducts of secondary amines cannot be decomplexed using the protocol described here.

INTRODUCTION:

Structurally complex amines containing a seven-membered carbocyclic ring are common to a

number of biologically active molecules. Notable examples include the tropane alkaloids[1] and several members of the *Lycopodium*[2], *Daphniphyllum*[3], and monoterpenoid indole alkaloid[4] families. However, such compounds are often more difficult to synthesize compared to compounds of similar complexity containing only five- or six-membered rings. Thus, we sought to develop a new avenue towards such compounds by attaching diverse amine nucleophiles to tropone[5]. The resulting adduct contains several functional handles for subsequent synthetic elaboration to diverse complex seven-membered ring-containing scaffolds that would be otherwise difficult to access.

While previous work with tropone[6,7] suggests that it would not be suitable for such a transformation, the related organometallic complex tricarbonyl(tropone)iron[8] (**1**, **Figure 1)** has proven to be a versatile synthetic building block that has been utilized in the synthesis of a number of natural products and complex molecules[9–13]. Furthermore, the uncomplexed double bond of tricarbonyl(tropone)iron has been shown to behave similar to an α,β-unsaturated ketone in reactions with, for example, dienes[14,15], tetrazines[16], nitrile oxides[17], diazoalkanes[8,10], and organocopper reagents[11]. Thus, we envisioned that an *aza*-Michael reaction of tricarbonyl(tropone)iron would provide an efficient entry to synthetically valuable aminated tropone derivatives.

Eisenstadt had previously reported that, following protonation of tricarbonyl(tropone)iron, the resulting cationic complex **2** (**Figure 1**) could undergo nucleophilic attack by aniline or *tert*-butylamine to produce aminated derivatives of the tropone iron complex[18]. However, the synthetic potential of this method remains unrealized. Indeed, no additions of other amines had been reported, and the demetallation of those products was not explored in Eisenstadt's report. We have adapted this protocol to demonstrate the addition of a wide variety of amine nucleophiles.

We also describe a method for direct *aza*-Michael additions to tricarbonyl(tropone)iron (**Figure 2**), which does not require synthesis of the cationic complex and generally proceeds in higher yields compared to the previously reported method. We also report herein a protocol for the demetallation of the resulting adducts. Overall, this protocol provides formal *aza*-Michael adducts of tropone in four steps from tropone (and three steps from the known iron complex).

PROTOCOL:

1. Synthesis of tricarbonyl(tropone)iron (1)[19]

1.1. In an argon-atmosphere glovebox, weigh out 4.1 g of diiron nonacarbonyl into an oven-dried 20 mL vial. Cap the vial and remove it from the glovebox.

CAUTION: Prolonged storage of diiron nonacarbonyl leads to some deterioration to give triiron dodecacarbonyl and finely divided metallic iron[20]. This deterioration is evidenced by the presence of a black solid within the shiny orange diiron nonacarbonyl. The iron impurity is pyrophoric and can ignite upon exposure to air. Storing the diiron nonacarbonyl under argon at 2-8 °C in a bottle

sealed with electrical tape appears to minimize this deterioration. The pyrophoric iron impurities can be destroyed *via* addition of dilute hydrochloric acid.

1.2. Add an oven-dried PTFE stir bar, 0.5 mL of tropone, and 10 mL of dry benzene to an oven-dried 50 mL round bottom flask.

NOTE: A round bottom flask with a 24/40 ground glass joint is preferred so that the solid diiron nonacarbonyl may be added rapidly with minimal spilling (see Step 1.5).

1.3. Degas the contents of the round bottom flask via three freeze-pump-thaw cycles as follows.

1.3.1. Submerge the flask in a dry ice-acetone bath until the contents solidify completely. Then, with the flask still submerged in the cold bath, evacuate the flask under vacuum for 2-3 min.

1.3.2. Allow the contents to thaw under static vacuum.

1.3.3. Repeat steps 1.3.1 and 1.3.2 twice.

1.3.4. After the final thaw, backfill the flask with argon and cover the flask with a rubber septum. Keep the flask under a positive pressure of argon.

1.4. Cover the flask with aluminum foil and commence vigorous magnetic stirring.

1.5. Briefly remove the rubber septum and add the previously weighed diiron nonacarbonyl in a single portion and replace the septum.

1.6. Immerse the flask in an oil bath at 55-60 °C and stir for 30 min.

1.7. After 30 min, remove the flask from the oil bath and allow to cool to room temperature.

1.8. Isolate the tropone complex via alumina column chromatography as follows.

1.8.1. Pack a chromatography column (~30 mm diameter) with 12 cm of alumina (Activity II/III) and hexanes.

1.8.2. Pipette the crude reaction mixture directly onto the alumina. Rinse the flask with a small amount (1-3 mL) of hexanes and add to the top of the column.

1.8.3. Drain the column until the solvent is level with the top of the alumina and add ~2 cm of sand.

1.8.4. Elute with hexanes until the blue-green band (triiron dodecacarbonyl) comes off the column.

1.8.5. Elute with 1:1 hexanes:methylene chloride until the red-orange tropone iron complex elutes completely.

1.8.6. Remove the solvent from the red-orange solution via rotary evaporation to obtain the tropone complex as a dark red oil that solidifies on standing.

NOTE: The tropone complex isolated in this fashion is occasionally contaminated with paramagnetic, iron-based impurities, as evidenced by severely broadened peaks in the ^{1}H NMR spectrum. These impurities can be removed by redissolving the complex in methylene chloride, and passing through a short plug of alumina, eluting with 1:1 hexanes:methylene chloride.

2. **Synthesis of tricarbonyl(5-ketocycloheptadienyl)iron tetrafluoroborate (2)**[21]

2.1. Add a PTFE magnetic stir bar, 432 mg of tricarbonyl(tropone)iron, and 10 mL of methylene chloride to a 50 mL round bottom flask.

2.2. Cool the flask in an ice bath and commence vigorous magnetic stirring.

2.3. Add 3.2 mL of concentrated sulfuric acid dropwise.

2.4. Vigorously stir the mixture at 0 °C for 30 min.

2.5. To a separate 100 mL round bottom flask, add a PTFE stir bar, 2.0 g of anhydrous sodium carbonate, and 10 mL of methanol.

2.6. Cool the flask containing the sodium carbonate mixture in an ice bath and vigorously stir it magnetically.

2.7. Upon completion of the 30-min period (step 2.4), cease magnetic stirring. Two layers should form.

2.8. Using a Pasteur pipette, transfer the viscous, brown lower layer to the rapidly stirring sodium carbonate suspension.

2.9. Stir for ~5 min, and then carefully and slowly add 50 mL of deionized water.

CAUTION: Vigorous bubbling is involved in this step.

2.10. Pour the mixture into a 250 mL separatory funnel and extract with methylene chloride (2x 50 mL).

2.11. Sequentially wash the combined organic layers with water (50 mL) and brine (50 mL).

2.12. Dry the organic layers over anhydrous magnesium sulfate.

2.13. Remove the magnesium sulfate via gravity or vacuum filtration and concentrate the filtrate via rotary evaporation to obtain a red-brown oil.

NOTE: The protocol may be paused at this point.

2.14. Add 3 mL of acetic anhydride to a 25 mL Erlenmeyer flask and cool it in an ice bath.

2.15. Add 1 mL of 48% aqueous tetrafluoroboric acid to the cold acetic anhydride dropwise.

CAUTION: The addition is highly exothermic. However, the exotherm is readily contained by controlling the temperature and rate of addition.

2.16. In a 100 mL round bottom flask submerged in an ice bath, add the mixture obtained from step 2.15 to the oil obtained in step 2.13.

2.17. Agitate the mixture with a stainless steel spatula for 5 min.

NOTE: The mixture generally takes on a gummy consistency upon agitation and the color becomes lighter.

2.18. Add 50 mL of diethyl ether to the mixture. Collect the resulting pale yellow solid via vacuum filtration using a Buchner funnel to obtain the cationic complex as its tetrafluoroborate salt.

3. Synthesis of *aza*-Michael adduct 4: Tricarbonyl[(2-5-η)-6-((2-phenylethyl)amino)cyclohepta-2,4-dien-1-one]iron

3.1. Add a PTFE magnetic stir bar, 150 mg of tricarbonyl(tropone)iron (**1**), and 0.154 mL of phenethylamine to a 1-dram vial. Cap the vial under an air atmosphere and commence magnetic stirring.

NOTE: Phenethylamine will be oxidized by air upon prolonged storage resulting in a yellow-brown color. Phenethylamine should be distilled prior to use if it is not colorless.

3.2. Monitor the reaction periodically by removing a small (~1 drop) aliquot from the reaction mixture, dissolving in $CDCl_3$, and acquiring a ^1H NMR spectrum.

NOTE: While this particular reaction is usually complete within 1 h, the reaction may be left to stir overnight.

3.3. Upon disappearance of the signals for tricarbonyl(tropone)iron in the ^1H NMR spectrum (see Representative Results and **Figure 3** and **Figure 4**), purify the crude reaction mixture *via*

chromatography on basic alumina (Activity II/III) as follows.

3.3.1. Pack a 30 mm diameter chromatography column with alumina (10-15 cm) and hexanes and apply the crude reaction mixture to the top of the column.

3.3.2. Elute the column with 1:1 hexanes:diethyl ether to remove the excess phenethylamine from the column. Monitor the elution via thin layer chromatography (TLC).

NOTE: The column was monitored using alumina TLC plates and a 1:1 diethyl ether:methylene chloride mixture as the mobile phase. If alumina TLC plates are not available, silica gel plates may be used (use 5% methanol in methylene chloride as the mobile phase).

3.3.3. After the excess amine has finished eluting, change the eluting solvent to 1:1 diethyl ether:methylene chloride to elute the product.

NOTE: The title compound elutes as a yellow band.

3.3.4. Combine the product-containing fractions (as judged by thin layer chromatography) and remove the solvent on a rotary evaporator to obtain the purified product as a dark yellow oil.

4. Synthesis of tricarbonyl[(2-5-η)-6-(2-methylanilino)cyclohepta-2,4-dien-1-one]iron (3)

4.1. Add a PTFE stir bar, 0.021 mL of *o*-toluidine, and 1.0 mL of diethyl ether to a 1-dram vial. Commence vigorous magnetic stirring.

4.2. Carefully add 33 mg of the cationic complex to the mixture. Allow the suspension to stir for 12 h.

4.3. Pour the reaction mixture into 5 mL of deionized water in a separatory funnel and extract the aqueous layer with 5 mL of ethyl acetate three times.

4.4. Wash the combined organic layers with 10 mL of brine before drying over anhydrous sodium sulfate.

4.5. Remove the sodium sulfate by gravity filtration and concentrate the filtrate *via* rotary evaporation to obtain the crude product.

4.6. Purify the crude product *via* column chromatography on basic alumina using a gradient of 30-50% diethyl ether in hexanes to obtain the pure product as a yellow solid.

5. Protection of amine 4 as a *tert*-butyl carbamate

5.1. Dissolve 76 mg of amine **4** in 2 mL of absolute ethanol in a 25 mL round bottom flask under air atmosphere.

5.2. Add 104 mg of di-*tert*-butyl dicarbonate followed by 40 mg of solid sodium bicarbonate to the reaction mixture.

5.3. Cap the flask with a rubber septum and sonicate the mixture for 1 h.

NOTE: This reaction may be allowed to run overnight.

5.4. Filter the crude reaction mixture through a bed of diatomaceous earth using a Buchner funnel. Wash the diatomaceous earth with ethanol until no more brown-colored solution comes out the bottom of the funnel.

5.5. Transfer the filtrate to a round bottom flask and concentrate on a rotary evaporator. Dissolve the resulting oil in ~2.5 mL of methylene chloride.

5.6. Add ~1.3 g of silica gel to the solution and remove the methylene chloride on the rotary evaporator until a fine, free-flowing solid is obtained.

5.7. Pack the silica gel into a 10 g silica cartridge for automated flash chromatography.

NOTE: An automated purification system was used in this protocol. However, conventional flash chromatography with silica gel may also be employed.

5.8. Run the column using a gradient starting from 90:10 hexanes:ethylacetate and ending at 20:80 hexanes:ethyl acetate over a period of 20 min. Collect the fractions containing the product (as indicated by the major peak detected at 254 nm absorbance) in a round bottom flask. Evaporate the hexanes and ethyl acetate on a rotary evaporator to obtain the purified product as a yellow oil.

6. Synthesis of *tert*-butyl (6-oxocyclohepta-2,4-dien-1-yl)(2-phenylethyl) carbamate (6)

6.1. In a 10 mL round bottom flask, dissolve 27 mg of iron complex **5** in 1 mL of methanol under air atmosphere and immerse the flask in an ice bath.

6.2. Commence magnetic stirring and add 33 mg of cerium(IV) ammonium nitrate.

6.3. After 30 min, add a second 33 mg portion of cerium(IV) ammonium nitrate, followed by a third 33 mg portion after an additional 30 min of stirring.

6.4. After adding the third portion of cerium(IV) ammonium nitrate, dilute the reaction mixture with ethyl acetate (5 mL).

6.5. Pour the mixture into a 30 mL separatory funnel containing 5 mL of saturated aqueous sodium bicarbonate. Separate the layers.

6.6. Re-extract the aqueous layer with ethyl acetate (2x 5 mL). Dry the combined organic layers over anhydrous sodium sulfate.

6.7. Remove the sodium sulfate via gravity or vacuum filtration and concentrate the filtrate on a rotary evaporator.

6.8. Dissolve the crude product in ~2.5 mL of methylene chloride, add ~1.3 g of silica gel, and remove the solvent on a rotary evaporator.

6.9. Pack the silica gel with the adsorbed crude product into a 10 g silica gel column for automated flash chromatography.

NOTE: An automated purification system was used in this protocol. However, conventional flash chromatography with silica gel may also be employed.

6.10. Run the column using a gradient starting from 90:10 hexanes:ethylacetate and ending at 20:80 hexanes:ethyl acetate over a period of 20 min. Collect the fractions containing the product (as indicated by the major peak detected at 254 nm absorbance) in a round bottom flask. Evaporate the hexanes and ethyl acetate on a rotary evaporator to obtain the purified product as a pale brown oil.

REPRESENTATIVE RESULTS:

All novel compounds in this study were characterized by ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectrometry. Previously reported compounds were characterized by ^{1}H NMR spectroscopy. NMR data for representative compounds are described in this section.

The ^{1}H NMR spectrum of tricarbonyl(tropone)iron is shown in **Figure 3.** The protons of the η^4-diene ligand give rise to the signals at 6.39 ppm (2 H), 3.19 ppm, and 2.75 ppm. The protons from the uncomplexed double bond appear at 6.58 and 5.05 ppm.

The progress of the *aza*-Michael addition is monitored via ^{1}H NMR by observing the disappearance of the signals from the uncomplexed double bond and a characteristic change in the chemical shift of the two furthest downfield η^4-diene protons from around 6.4 ppm to two well separated signals that typically appear between 5.3 and 6.0 ppm (see **Figure 3** and **Figure 4**). Furthermore, the *aza*-Michael adduct features signals corresponding to the two diastereotopic methylene protons (adjacent to the ketone within the seven-membered ring), which typically appear between 1.5 and 2.5 ppm.

Direct *aza*-Michael additions to tricarbonyl(tropone)iron generally proceeded in 60-95% yield, depending on the amine substrate (see Discussion). Secondary cyclic amines tend to give somewhat higher yields than primary aliphatic amines, possibly due to a greater resistance to decomposition during purification.

^{1}H NMR data for the cationic complex (in CD_3CN) is shown in **Figure 5** and features seven distinct multiplets. It should be noted that the complex decomposes over time in CD_3CN. However, the dried solid tetrafluoroborate complex can be stored indefinitely under ambient conditions. **Figure 6** shows ^{1}H and ^{13}C NMR data for the *o*-toluidine adduct **3**, prepared via the cationic complex **2** (**Figure 1**), which contains the same features described above for the phenethylamine adduct **4**.

Figure 7 shows ^{1}H and ^{13}C NMR spectra of *tert*-butyl carbamate **5**. The ^{1}H NMR spectrum is characterized by its broad peaks, caused by slow rotation of the carbamate C–N bond relative to the NMR time scale. In addition, the presence of the *tert*-butyl carbamate is evident from the large singlet at 1.5 ppm from the *tert*-butyl protons, as well as the signal at 154.3 ppm in the ^{13}C NMR spectrum corresponding to the carbonyl carbon of the carbamate group.

Upon decomplexation of the diene from the iron, the most notable aspect of the ^{1}H NMR spectrum (**Figure 8**) is the presence of four signals between 5.75 and 6.75 ppm, corresponding to the protons from the uncomplexed diene.

FIGURE AND TABLE LEGENDS:

Figure 1. Synthesis of 3 from tricarbonyl(tropone)iron via cationic complex 2. Tricarbonyl(tropone)iron is converted to cationic complex **2** in two steps, which was followed by nucleophilic addition of *ortho*-toluidine to the complex.

Figure 2. Synthesis of formal tropone *aza*-Michael adduct 6. Direct *aza*-Michael reaction of tricarbonyl(tropone)iron and phenethylamine was followed by amine protection and oxidative demetallation.

Figure 3. ^{1}H NMR spectrum (solvent: $CDCl_3$) of tricarbonyl(tropone)iron 1. The peaks at 6.59 ppm and 5.05 ppm correspond to the uncomplexed alkene hydrogens while those 6.39 ppm (2H), 3.19 ppm, and 2.75 ppm arise from the iron-complexed diene.

Figure 4. Spectral data for iron complex 4. (**a**) ^{1}H NMR spectrum; (**b**) ^{13}C NMR spectrum (solvent: $CDCl_3$). Notable peaks in the ^{1}H NMR spectrum include those from the iron-complexed diene (5.75, 5.48, 3.30, and 3.20 ppm) and the diastereotopic α–methylene protons (2.30 and 1.70 ppm).

Figure 5. ^{1}H NMR spectrum (solvent: CD_3CN) of cationic iron complex 2. The most notable difference from the ^{1}H NMR spectrum of **1** (the precursor to **2**) is the signals arising from the diastereotopic α-methylene protons (2.85 and 2.23 ppm).

Figure 6. **Spectral data for iron complex 3.** (**a**) ^{1}H NMR spectrum; (**b**) ^{13}C NMR spectrum (solvent: $CDCl_3$). Similar to the ^{1}H NMR spectrum of **4**, the ^{1}H NMR spectrum of **3** is characterized by signals arising from the iron-complexed diene (5.89, 5.51, 3.53, and 3.30 ppm) and the diastereotopic α–methylene protons (2.50 and 2.02 ppm).

Figure 7. Spectral data for *tert*-butyl carbamate 5. (**a**) ^{1}H NMR spectrum; (**b**) ^{13}C NMR spectrum (solvent: $CDCl_3$). The signal corresponding to the protons of the *tert*-butyl group of the carbamate appear at 1.52 ppm. Many signals also show characteristic broadening.

Figure 8. Spectral data for demetallated diene 6. (**a**) ^{1}H NMR spectrum; (**b**) ^{13}C NMR spectrum (solvent: $CDCl_3$). The most notable aspect of the ^{1}H NMR spectrum compared to those of the iron complexes in **Figure 4a**, **Figure 6a**, and **Figure 7a** is that all of the signals corresponding to the diene protons now appear above 5.75 ppm (6.57, 6.34, 6.10, and 5.99 ppm).

DISCUSSION:

Whether the solvent-free protocol involving direct addition to tricarbonyl(tropone)iron (**Figure 2**) or the indirect method utilizing the corresponding cationic complex as the electrophile (**Figure 1**) is to be employed depends on the amine substrate used. In general, the direct addition method is preferable since it requires fewer steps to generate the *aza*-Michael adducts from tropone and the overall yields are generally higher. However, this more direct method is generally limited to reasonably unhindered primary aliphatic amines and cyclic secondary amines (e.g., piperidine). Less nucleophilic substrates such as arylamines or more sterically hindered amines such as acyclic secondary amines or *tert*-butylamine do not directly add to tricarbonyl(tropone)iron. On the other hand, these substrates efficiently add to the corresponding cationic complex (**2**, **Figure 1**). Thus, the two protocols complement one another in that the direct addition reaction is generally more efficient and higher yielding, while the addition to the cationic complex enjoys a broader substrate scope.

For the direct addition to tricarbonyl(tropone)iron, reaction times tend to be substrate-dependent. Some additions are complete within minutes as judged by ^{1}H NMR analysis (e.g., unhindered primary amines) while some must be left overnight (e.g., morpholine). Upon completion, excess amine is removed via chromatography over Activity II/III alumina. However, for sufficiently volatile amine substrates, the excess amine may be removed *via* rotary evaporation and the crude material can then be subjected to protection as the corresponding carbamate (if applicable).

Adducts of primary aliphatic amines should be purified without delay and should be protected as carbamates as soon as is practicable, as we have generally experienced that such adducts will degrade over time. The degradation is generally accompanied by a color change from bright yellow to orange-brown. NMR analysis of such partially degraded samples showed the presence of tricarbonyl(tropone)iron, indicating that elimination of the amine had occurred.

We screened a variety of known protocols for removing the iron tricarbonyl group from the diene of the *aza*-Michael adducts[22–27]. The only successful protocol in our hands involved oxidative demetallation *via* treatment of the carbamate-protected adducts with cerium(IV) ammonium nitrate[28]. A representative result is described for demetallation of a *tert*-butyl carbamate-protected adduct. However, benzyl carbamates can also be demetallated using this protocol (no other carbamates were examined). Since tertiary amines cannot be protected as carbamates, we have thus far been unable to successfully demetallate those substrates despite extensive

experimentation, including attempts to temporarily protect the nitrogen from oxidation by quantitatively protonating it with trifluoroacetic acid.

This protocol represents an extension of a method reported by Eisenstadt[18] for addition of amines to cationic complex **2**. However, addition of only two amines to the complex was reported, and demetallation of the complex was not described. The work described herein more fully explores the scope of addition to the cationic complex. Furthermore, the protocol for the direct addition of certain amines to tricarbonyl(tropone)iron constitutes a more efficient method for synthesizing such amine adducts. In addition, successful demetallation of the complexes opens the way for diverse subsequent reactions to access more complex molecular architectures containing a seven-membered carbocyclic ring. Notably, the addition of diverse amine nucleophiles with different functionalized side chains can potentially enable an even more diverse set of downstream reactions. Exploration of such newly-opened synthetic routes to complex alkaloid-like architectures is currently under investigation in our laboratory.

ACKNOWLEDGMENTS:

Acknowledgement is made to the Donors of the American Chemical Society Petroleum Research Fund for support of this research. We acknowledge the Lafayette College Chemistry Department and the Lafayette College EXCEL Scholars program for financial support.

DISCLOSURES:

The authors have nothing to disclose.

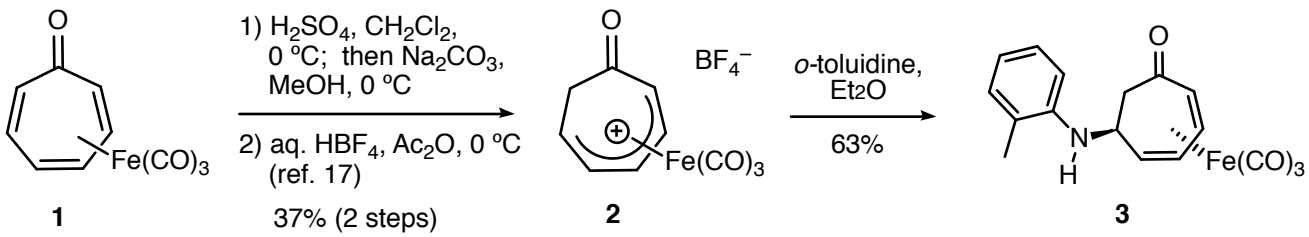
REFERENCES:

1. Pollini, G.P., Benetti, S., De Risi, C., Zanirato, V. Synthetic Approaches to Enantiomerically Pure 8-Azabicyclo[3.2.1]octane Derivatives. *Chemical Reviews*. **106**, 2434–2454 (2006).
2. Ma, X., Gang, D.R. The Lycopodium alkaloids. *Natural Product Reports*. **21** (6), 752 (2004).
3. Kobayashi, J., Kubota, T. The Daphniphyllum alkaloids. *Natural Product Reports*. **26** (7), 936–62 (2009).
4. Leonard, J. Recent progress in the chemistry of monoterpenoid indole alkaloids derived from secologanin. *Natural Product Reports*. **16**, 319–338 (1999).
5. Huang, Z., Phelan, Z.K., Tritt, R.L., Valent, S.D., Griffith, D.R. Formal aza-Michael additions to tropone: Addition of diverse aryl- and alkylamines to tricarbonyl(tropone)iron and $[(C_7H_7O)Fe(CO)_3]BF_4$. *Tetrahedron Letters*. **59** (37), 3432–3434 (2018).
6. Pauson, P.L. Tropones and Tropolones. *Chemical Reviews*. **55** (1), 9–136 (1955).
7. Pietra, F. Seven-Membered Conjugated Carbo-and Heterocyclic Compounds and Their Homoconjugated Analogs and Metal Complexes. Synthesis, Biosynthesis, Structure, and Reactivity. *Chemical Reviews*. **73** (4), 293–364 (1973).
8. Johnson, B.F.G., Lewis, J., Wege, D. Transition metal carbonyl complexes derived from cycloocta-2,4,6-trienone and cyclohepta-2,4,6-trienone. *Journal of the Chemical Society, Dalton Transactions*. **1976**, 1874–1880 (1976).
9. Franck-Neumann, M., Brion, F., Martina, D. Friedel-Crafts acylation of tropone-irontricarbonyl. Synthesis of β-thujaplicin and β-dolabrin. *Tetrahedron Letters*. **19** (50), 5033–5036 (1978).

10. Saha, M., Bagby, B., Nicholas, K.M. Cobalt-mediated propargylation/annelation: Total synthesis of (±)-cyclocolorenone. *Tetrahedron Letters*. **27** (8), 915–918 (1986).
11. Yeh, M.-C.P., Hwu, C.-C., Ueng, C.-H., Lue, H.-L. Michael Addition Reactions of the Highly Functionalized Zinc-Copper Reagents RCu(CN)ZnI to (Tropone)iron Tricarbonyl Promoted by Boron Trifluoride Etherate. *Organometallics*. **13** (5), 1788–1794 (1994).
12. Pearson, A.J., Srinivasan, K. Approaches to the synthesis of heptitol derivatives via iron-mediated stereocontrolled functionalization of cycloheptatrienone. *The Journal of Organic Chemistry*. **57** (14), 3965–3973 (1992).
13. Soulié, J., Betzer, J.-F., Muller, B., Lallemand, J.-Y. General access to polyhydroxylated nortropane derivatives through hetero diels -alder cycloaddition. *Tetrahedron Letters*. **36** (52), 9485–9488 (1995).
14. Rigby, J.H., Ogbu, C.O. Tricarbonyl(tropone)iron as a useful functionalized enone equivalent. *Tetrahedron Letters*. **31** (24), 3385–3388 (1990).
15. Franck-Neumann, M., Martina, D. Cycloadditions de la tropone avec le cyclopentadiene : synthese d'un intermediaire potentiel par utilisation de complexe metallique. *Tetrahedron Letters*. **18** (26), 2293–2296 (1977).
16. Ban, T., Nagai, K., Miyamoto, Y., Harano, K., Yasuda, M., Kanematsu, K. Periselective cycloaddition of tricarbonyliron complexes of seven-membered unsaturated compounds with 1,2,4,5-tetrazine. Masking and activating effects of tricarbonyliron complexes. *The Journal of Organic Chemistry*. **47** (1), 110–116 (1982).
17. Bonadeo, M., Gandolfi, R., De Micheli, C. Reactions of nitrile oxides and of 2,5-dimethyl-3,4-diphenylcyclopentadienone with tricarbonyltroponeiron and oxidation of the adducts with cerium(IV). *Gazzetta Chimica Italiana*. **107**, 577–578 (1977).
18. Eisenstadt, A. The reactivity of cycloheptadienyl-1-one iron tricarbonyl cation towards nucleophilic attack. *Journal of Organometallic Chemistry*. **113** (2), 147–156, (1976).
19. Rosenblum, M., Watkins, J.C. Cyclopentannulation reactions with organoiron reagents. Facile construction of functionalized hydroazulenes. *Journal of the American Chemical Society*. **112** (17), 6316–6322 (1990).
20. Pearson, A.J. *Iron Compounds in Organic Synthesis*. Academic Press. San Diego. (1994).
21. Eisenstadt, A. Fluxional behaviour of protonated substituted troponeiron tricarbonyls. *Journal of Organometallic Chemistry*. **97** (3), 443–451 (1975).
22. Shvo, Y., Hazum, E. A Simple Method for the Disengagement of Organic Ligands from Iron Complexes. *Journal of the Chemical Society, Chemical Communications*. 336–337 (1974).
23. Thompson, D.J. Reaction of tricarbonylcyclohexadieneiron complexes with cupric chloride. *Journal of Organometallic Chemistry*. **108** (3), 381–383 (1976).
24. Franck-Neumann, M., Heitz, M.P., Martina, D. Une methode simple de liberation des ligands organiques de leurs complexes de fer carbonyle. *Tetrahedron Letters*. **24** (15), 1615–1616 (1983).
25. Birch, A.J., Kelly, L.F., Liepa, A.J. Lateral control of skeletal rearrangement by complexation of thebaine with $Fe(CO)_3$. *Tetrahedron Letters*. **26** (4), 501–504 (1985).
26. Ripoche, I., Gelas, J., Grée, D., Grée, R., Troin, Y. A new stereoselective synthesis of chiral optically pure 4-piperidones. *Tetrahedron Letters*. **36** (37), 6675–6678 (1995).
27. Williams, I., Kariuki, B.M., Reeves, K., Cox, L.R. Stereoselective Synthesis of 2-Dienyl-Substituted Pyrrolidines Using an η^4-Dienetricarbonyliron Complex as the Stereodirecting

Element: Elaboration to the Pyrrolizidine Skeleton. *Organic Letters*. **8**, 4389–4392 (2006).
28. Coquerel, Y., Depres, J.-P., Greene, A.E., Cividino, P., Court, J. Synthesis of Substituted Cycloheptadienes by Catalytic Hydrogenation of Cycloheptatrieneiron Complexes. *Synthetic Communications*. **31**, 1291–1300 (2001).

Figure 1



1 **2** **3**

Figure 2

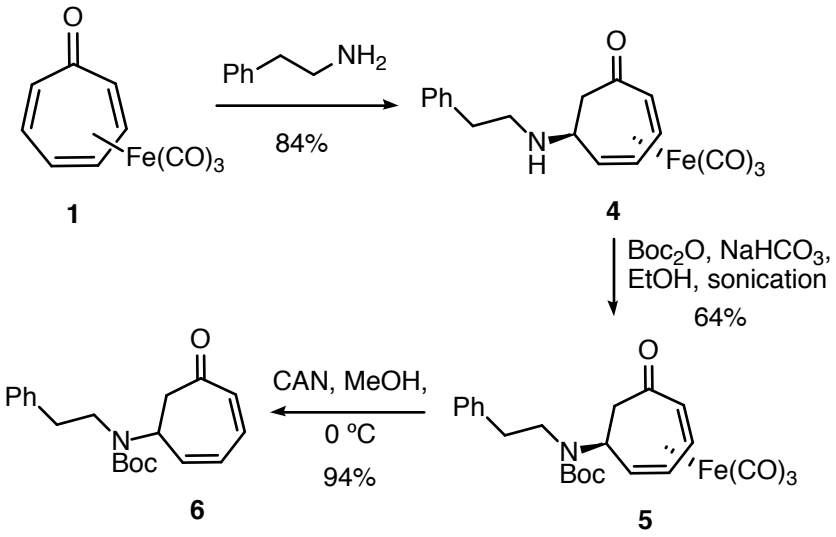


Figure 3

Click here to access/download;Figure;JoVE_Fig3.pdf

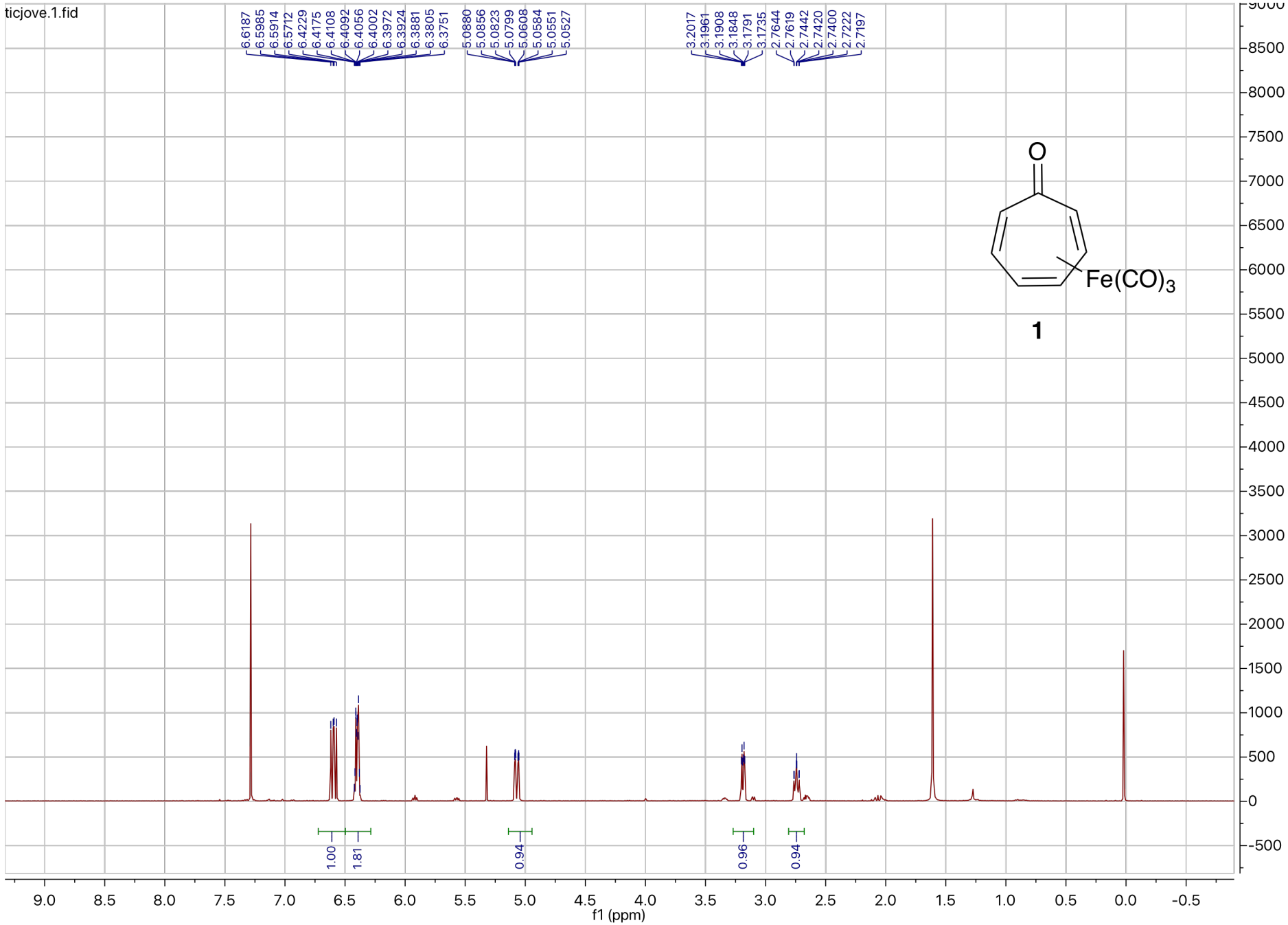
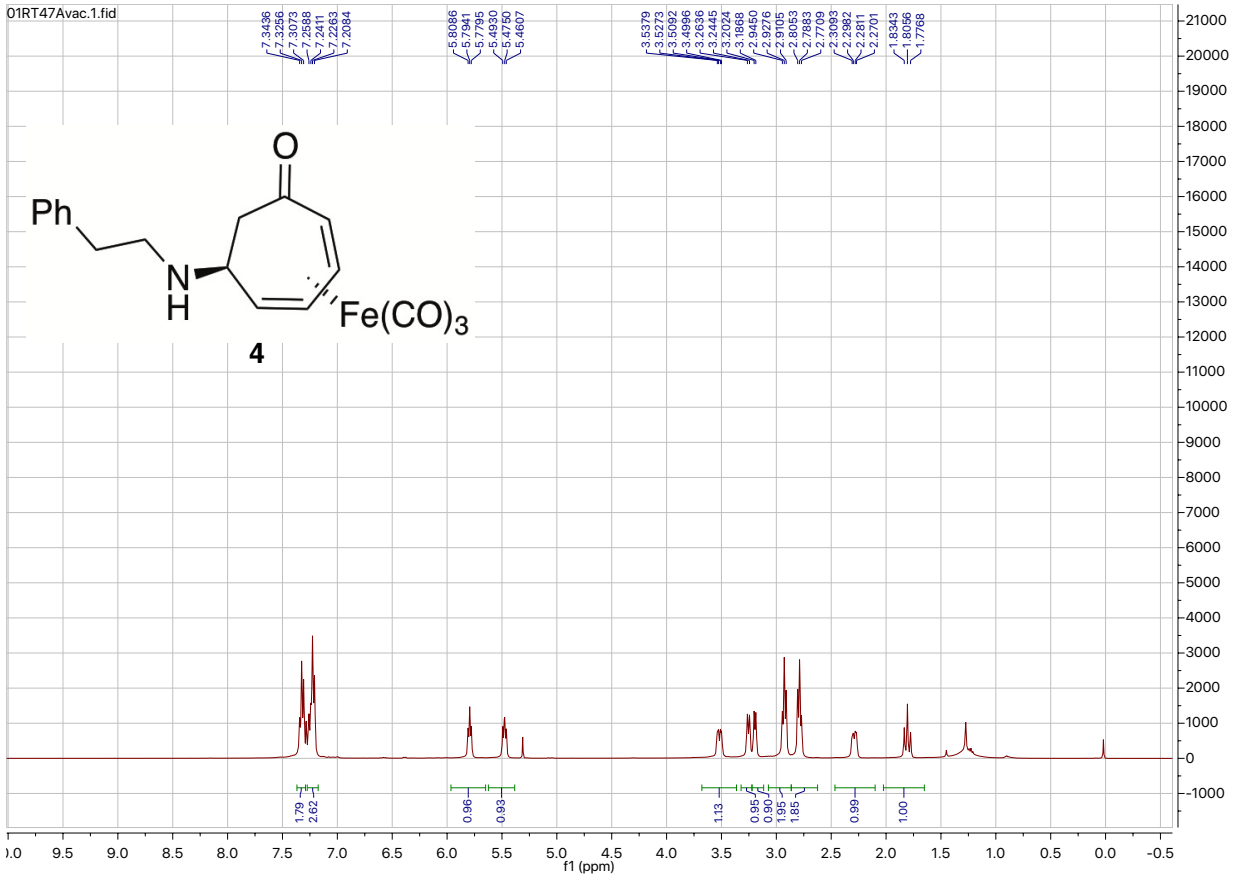


Figure 4

a)



b)

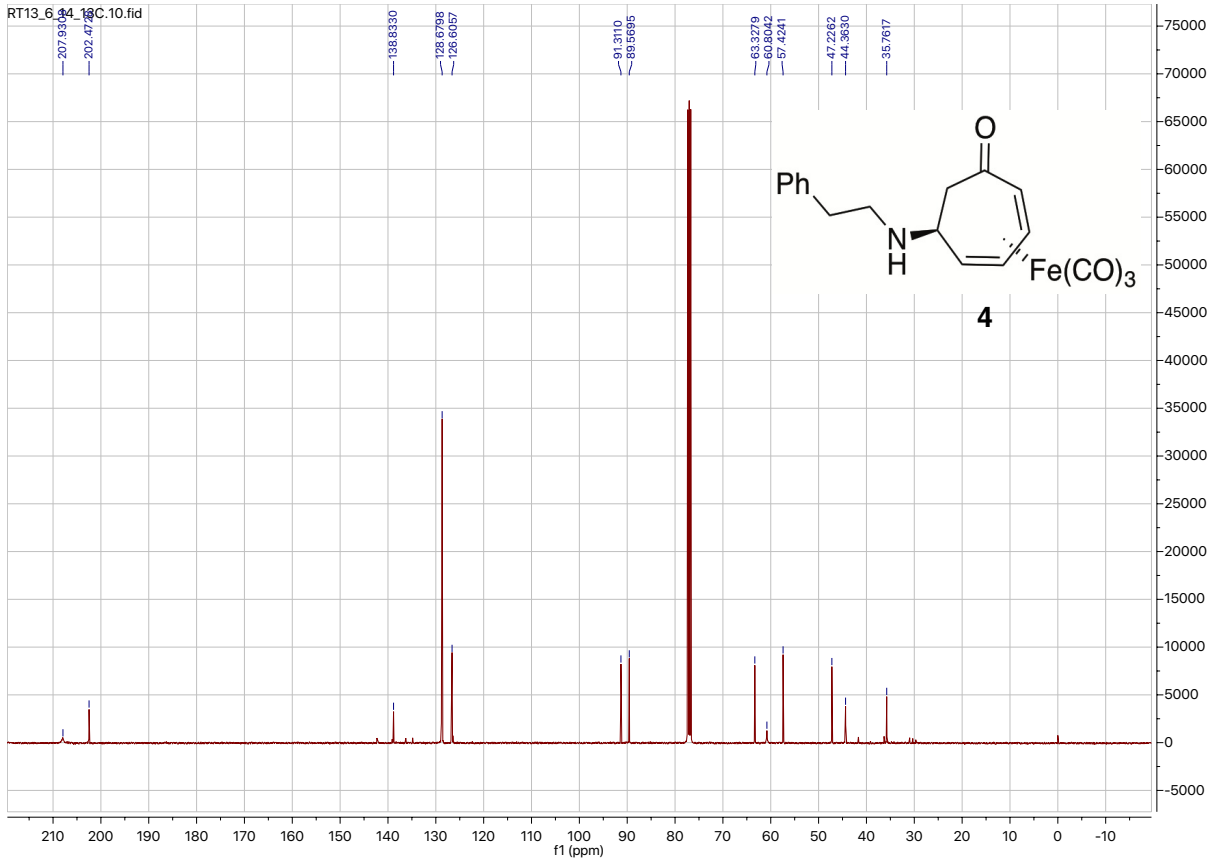


Figure 5

Click here to access/download;Figure;JoVE_Fig5.pdf

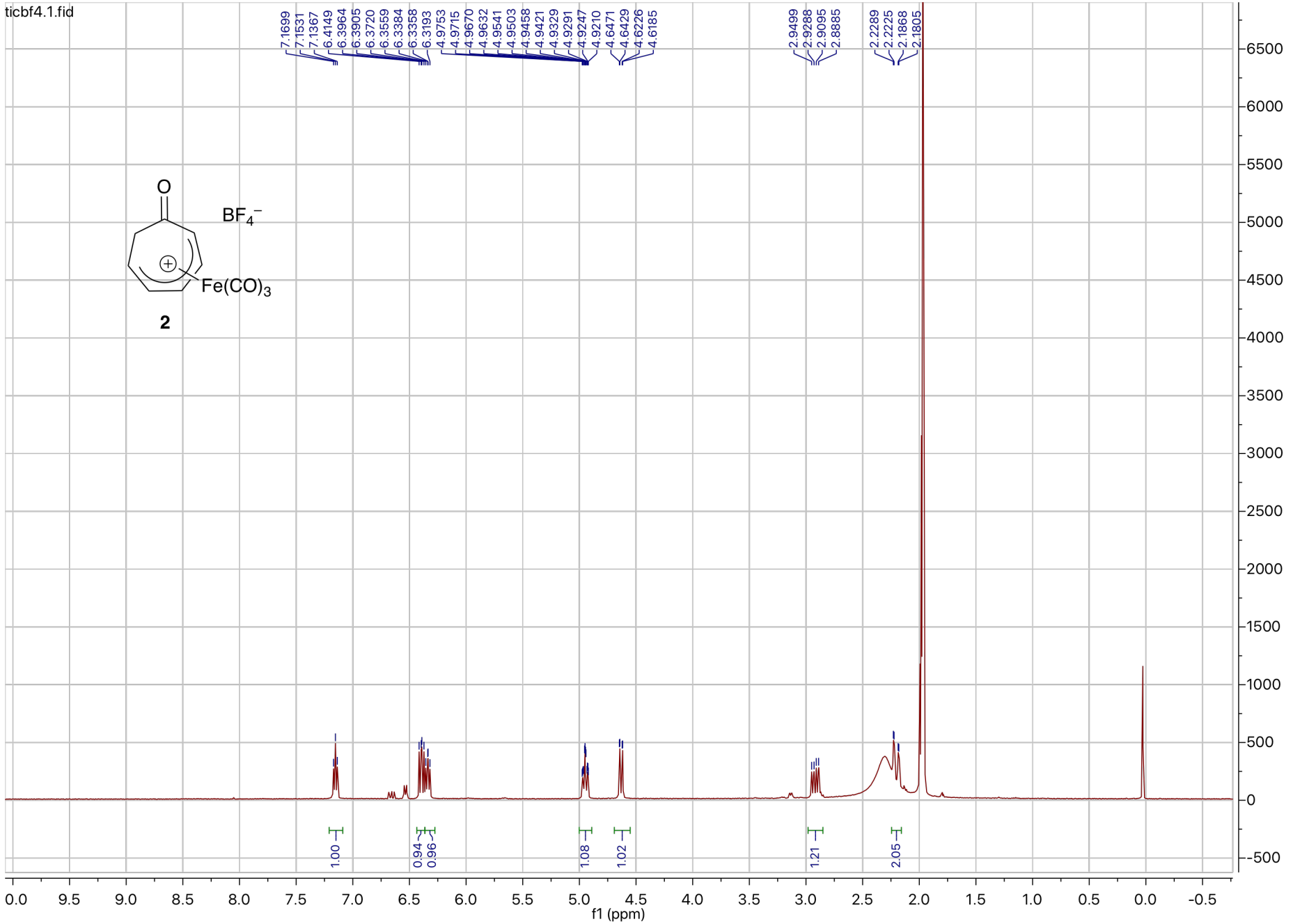
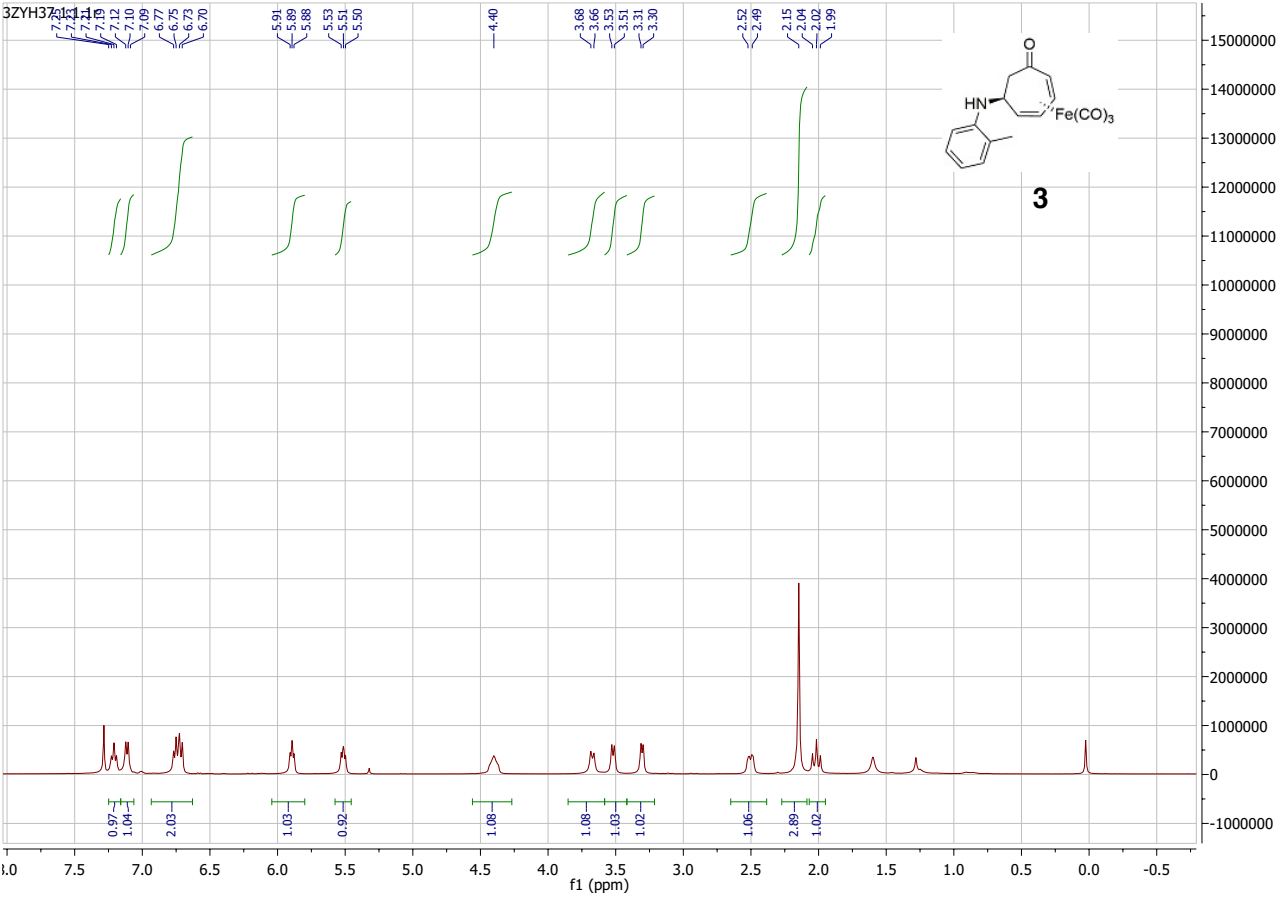


Figure 6

Click here to access/download;Figure;JoVE_Fig6.pdf

a)



b)

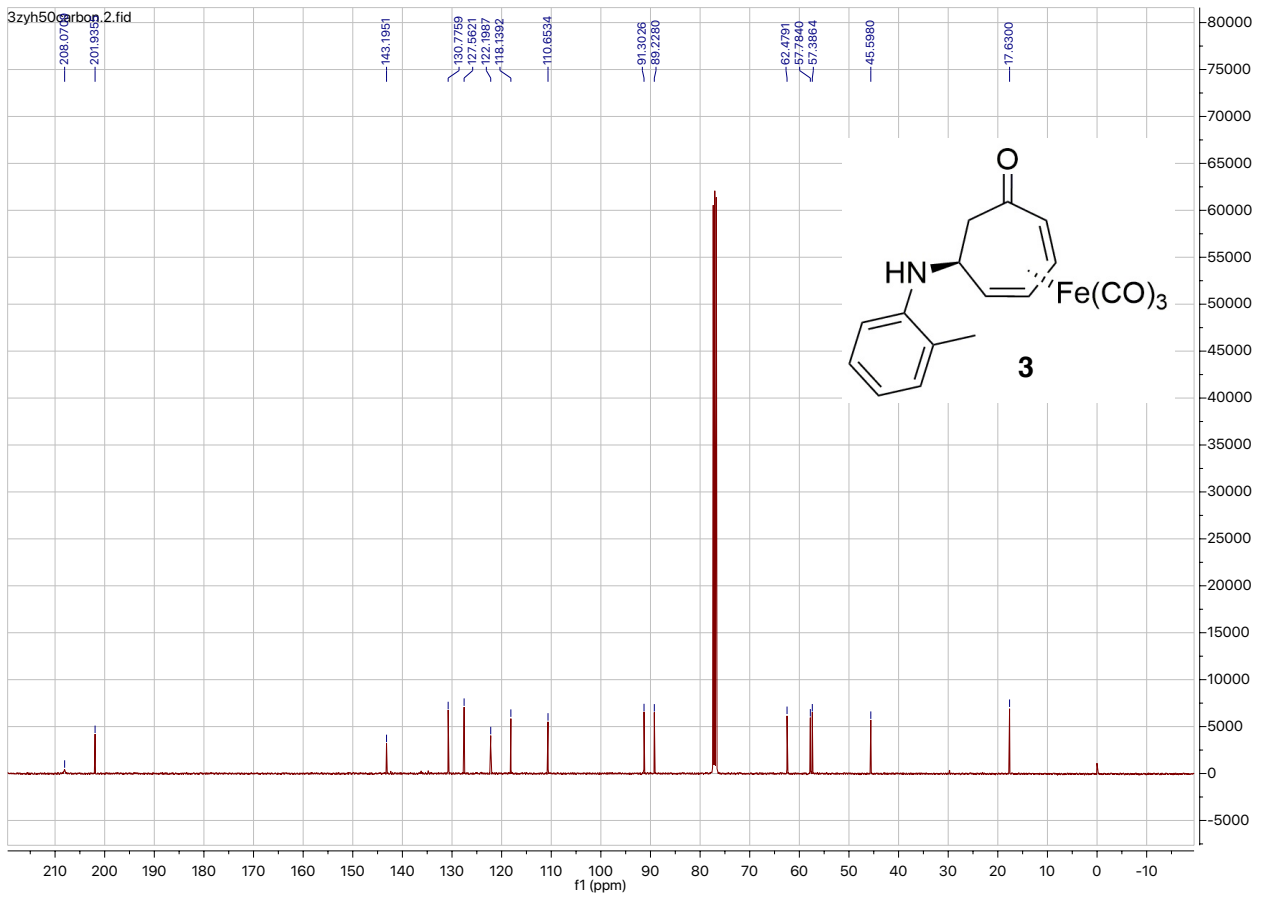
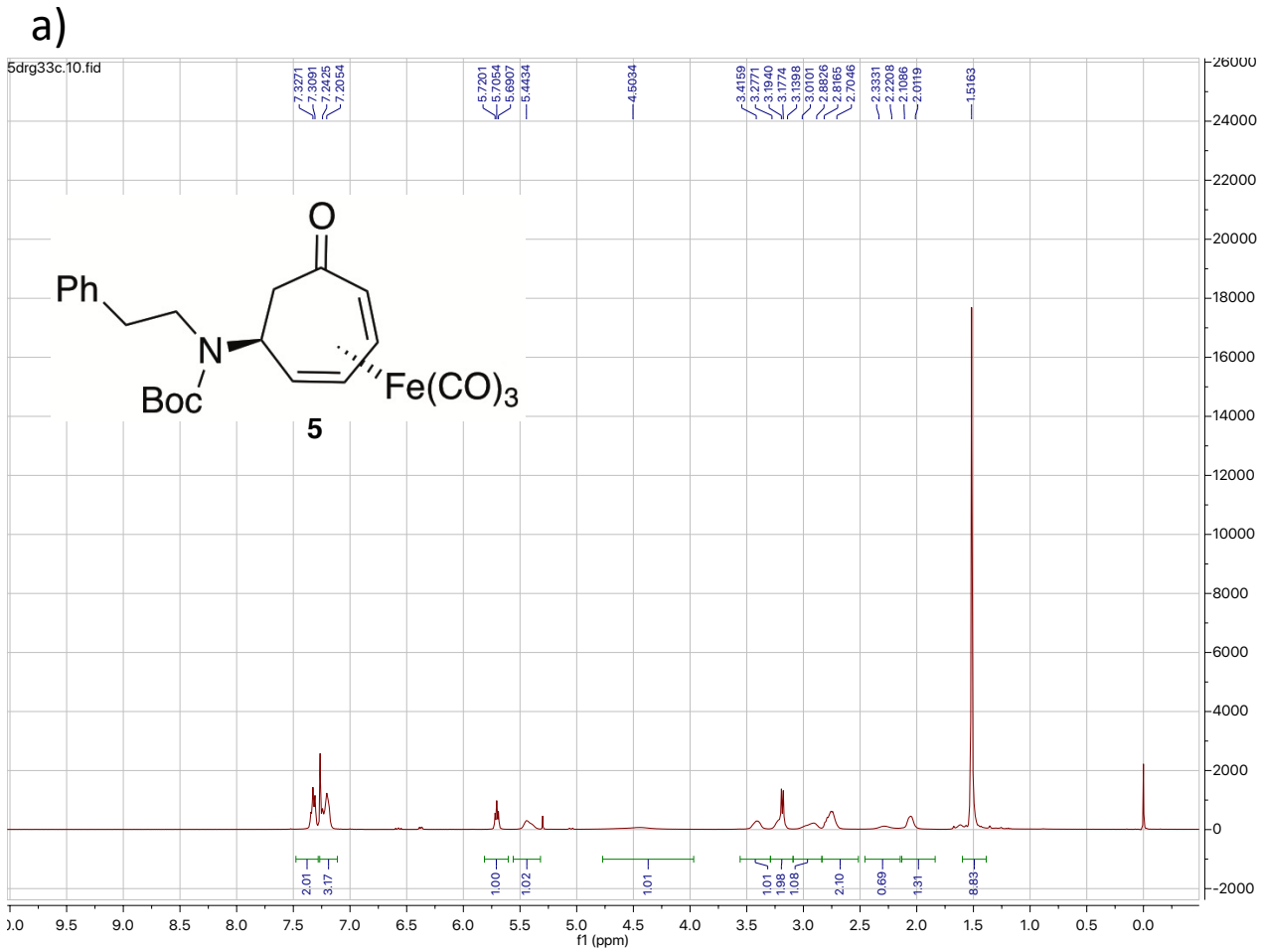


Figure 7

Click here to access/download;Figure;JoVE_Fig7.pdf



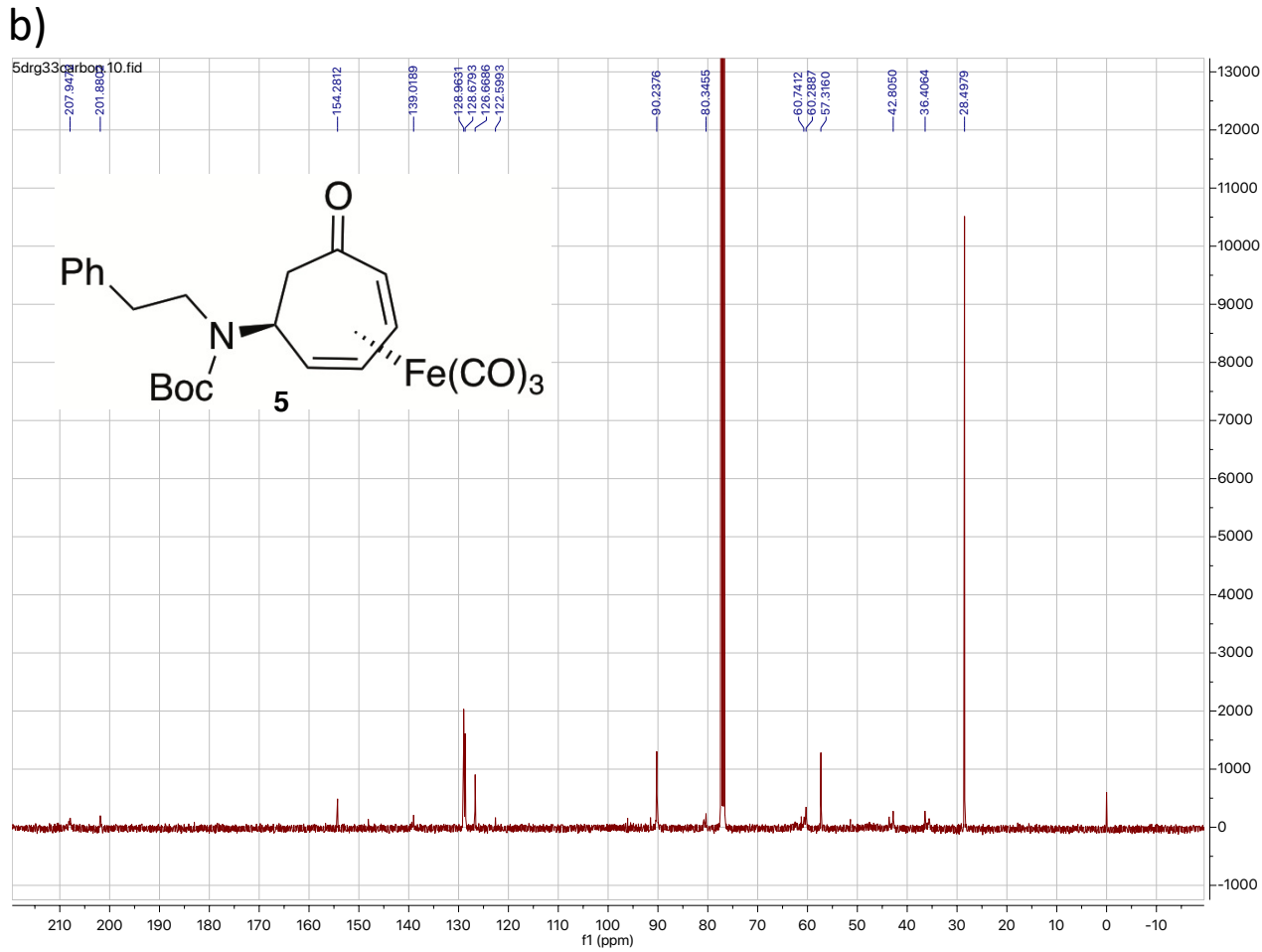
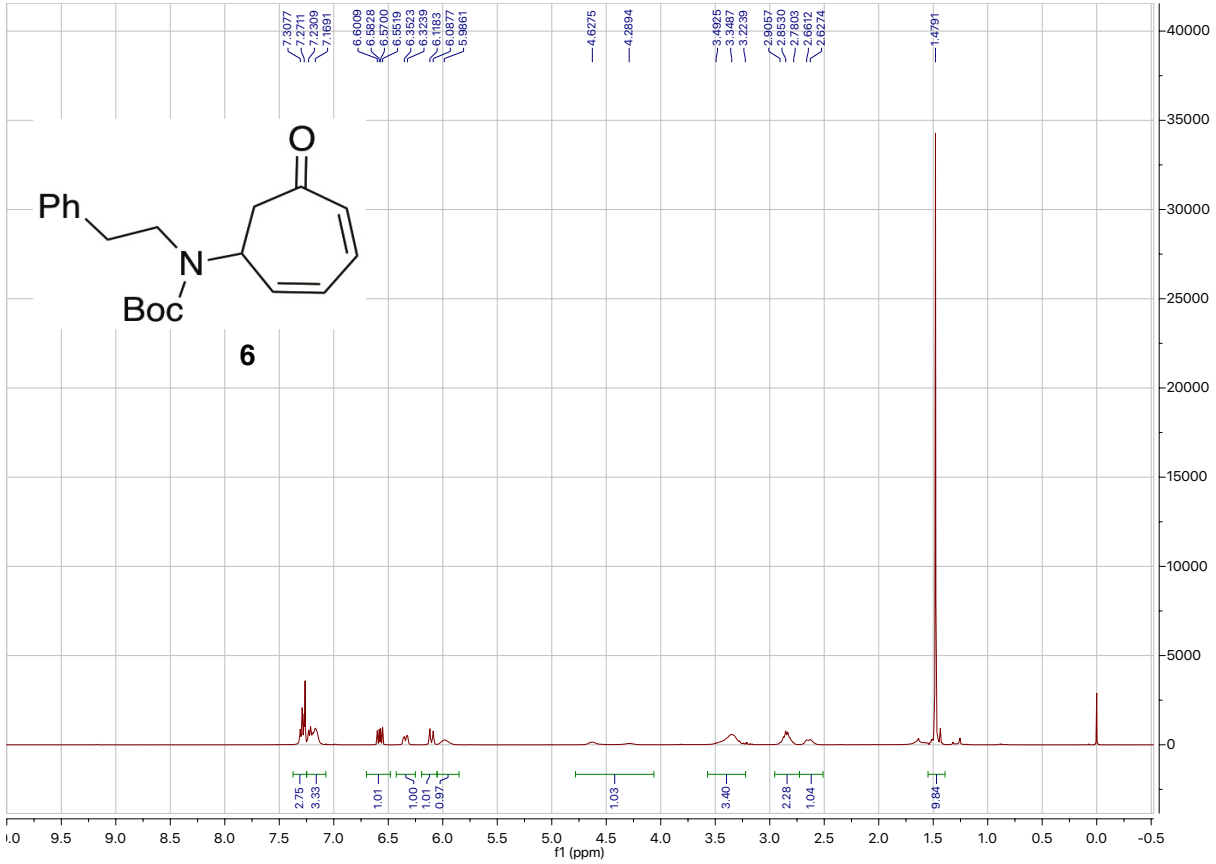


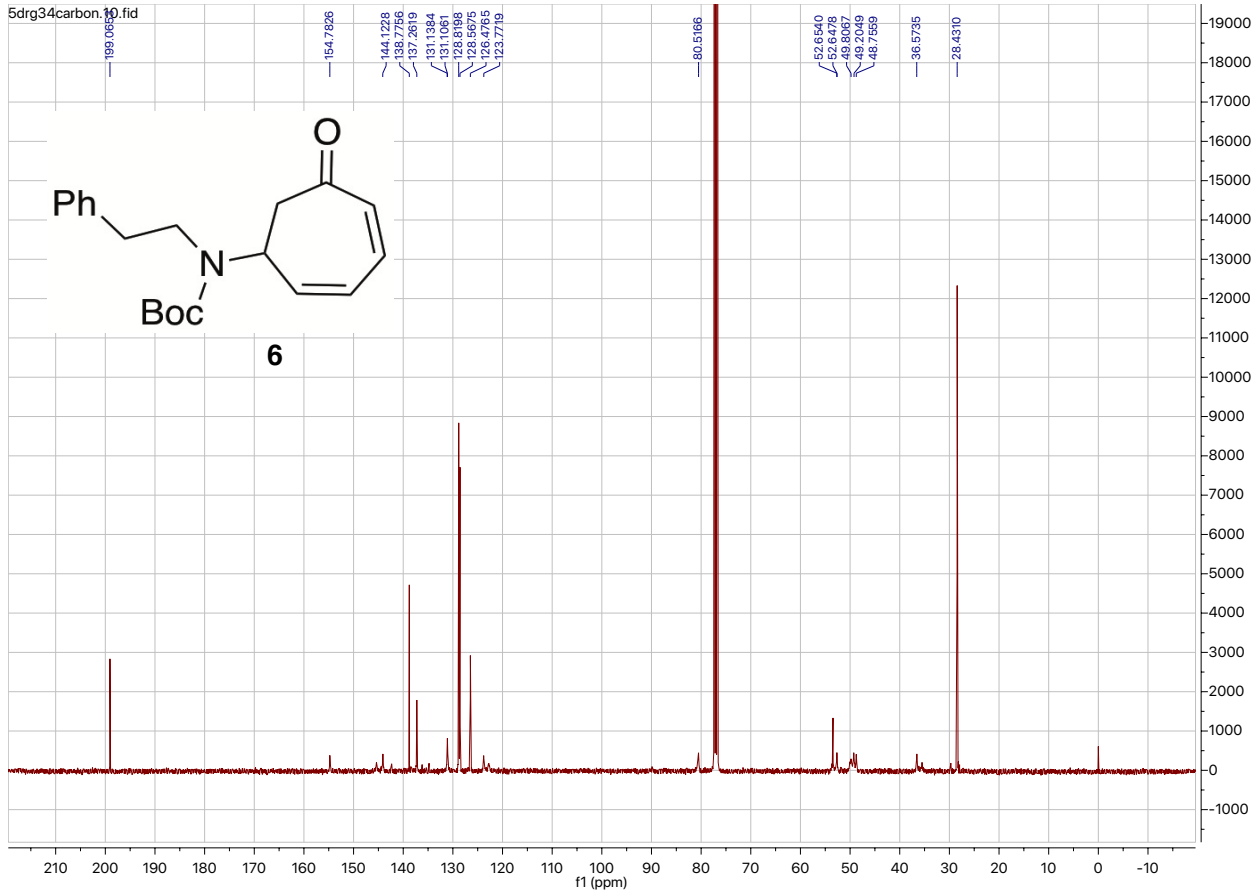
Figure 8

Click here to access/download;Figure;JoVE_Fig8.pdf

a)



b)



Name of Material/ Equipment	Company	Catalog Number	Comments/Description
10 g SNAP Ultra silica gel columns	Biotage		for automated column chromatography
Acetic anhydride	Fisher Scientific	A10-500	
Acetone	Fisher Scientific	A-16S-20	for cooling baths
Acetonitrile-D3	Sigma Aldrich	366544	
Benzene, anhydrous, 99.8%	Sigma Aldrich	401765	
Biotage Isolera Prime	Biotage	ISO-PSF	for automated chromatography
Celite; 545 Filter Aid	Fisher Scientific	C212-500	diatomaceous earth
Cerium(IV) ammonium nitrate, ACS, 99+%	Alfa Aesar	33254	
Chloroform-D	Acros	209561000	
Di-*tert* -butyl dicarbonate, 99%	Acros	194670250	
Ethyl acetate	Fisher Scientific	E145-4	
Ethyl alcohol, absolute - 200 proof	Greenfield Global	111000200PL05	
Ethyl ether anhydrous	Fisher Scientific	E138-1	
Hexanes	Fisher Scientific	H302-4	
iron nonacarbonyl 99%	Strem	26-2640	air sensitive, synonymous with diiron nonacarbonyl
Magnesium sulfate	Fisher Scientific	M65-500	
Methanol	EMD Millipore	MX0475-1	
Methylene chloride	Fisher Scientific	D37-4	
MP alumina, Act. II-III acc. To Brockmann	MP Biomedicals	4691	for column chromatography
o-toluidine 98%	Sigma Aldrich	466190	
Phenethylamine 99%	Sigma Aldrich	128945	distill prior to use if not colorless
Sodium bicarbonate	Fisher Scientific	S233-500	
Sodium carbonate anhydrous	Fisher Scientific	S263-500	
Sodium chloride	Fisher Scientific	S271-500	dissolved in deionized water to perpare a saturated
Sodium sulfate anhydrous	Fisher Scientific	S415-500	
Sonicator	Branson		model 2510
Sulfuric acid	Fisher Scientific	A300C-212	

Tetrafluoroboric acid solution, 48 wt.%	Sigma Aldrich	207934	aqueous solution
TLC Aluminium oxide 60 F254, neutral	EMD Millipore	1.05581.0001	for thin layer chromatography
Tropone 97%	Alfa Aesar	L004730-06	Light sensitive

aqueous solution

jove JOURNAL OF VISUALIZED EXPERIMENTS
1 Alewife Center #200
Cambridge, MA 02140
tel. 617.945.9051
www.jove.com

ARTICLE AND VIDEO LICENSE AGREEMENT

Title of Article:	**Preparation of Formal aza-Michael Adducts of Tropone via Tricarbonyl(tropone)iron**
Author(s):	**Zhiyuan Huang, Zaki K. Phelan, Rachel L. Tritt, Shelby D. Valent, Daniel R. Griffith**

Item 1: The Author elects to have the Materials be made available (as described at http://www.jove.com/publish) via:

☑ Standard Access ☐ Open Access

Item 2: Please select one of the following items:

☑ The Author is **NOT** a United States government employee.

☐ The Author is a United States government employee and the Materials were prepared in the course of his or her duties as a United States government employee.

☐ The Author is a United States government employee but the Materials were NOT prepared in the course of his or her duties as a United States government employee.

ARTICLE AND VIDEO LICENSE AGREEMENT

1. **Defined Terms.** As used in this Article and Video License Agreement, the following terms shall have the following meanings: "**Agreement**" means this Article and Video License Agreement; "**Article**" means the article specified on the last page of this Agreement, including any associated materials such as texts, figures, tables, artwork, abstracts, or summaries contained therein; "**Author**" means the author who is a signatory to this Agreement; "**Collective Work**" means a work, such as a periodical issue, anthology or encyclopedia, in which the Materials in their entirety in unmodified form, along with a number of other contributions, constituting separate and independent works in themselves, are assembled into a collective whole; "**CRC License**" means the Creative Commons Attribution-Non Commercial-No Derivs 3.0 Unported Agreement, the terms and conditions of which can be found at: http://creativecommons.org/licenses/by-nc-nd/3.0/legalcode; "**Derivative Work**" means a work based upon the Materials or upon the Materials and other pre-existing works, such as a translation, musical arrangement, dramatization, fictionalization, motion picture version, sound recording, art reproduction, abridgment, condensation, or any other form in which the Materials may be recast, transformed, or adapted; "**Institution**" means the institution, listed on the last page of this Agreement, by which the Author was employed at the time of the creation of the Materials; "**JoVE**" means MyJove Corporation, a Massachusetts corporation and the publisher of The Journal of Visualized Experiments; "**Materials**" means the Article and / or the Video; "**Parties**" means the Author and JoVE; "**Video**" means any video(s) made by the Author, alone or in conjunction with any other parties, or by JoVE or its affiliates or agents, individually or in collaboration with the Author or any other parties, incorporating all or any portion of the Article, and in which the Author may or may not appear.

2. **Background.** The Author, who is the author of the Article, in order to ensure the dissemination and protection of the Article, desires to have the JoVE publish the Article and create and transmit videos based on the Article. In furtherance of such goals, the Parties desire to memorialize in this Agreement the respective rights of each Party in and to the Article and the Video.

3. **Grant of Rights in Article.** In consideration of JoVE agreeing to publish the Article, the Author hereby grants to JoVE, subject to **Sections 4** and **7** below, the exclusive, royalty-free, perpetual (for the full term of copyright in the Article, including any extensions thereto) license (a) to publish, reproduce, distribute, display and store the Article in all forms, formats and media whether now known or hereafter developed (including without limitation in print, digital and electronic form) throughout the world, (b) to translate the Article into other languages, create adaptations, summaries or extracts of the Article or other Derivative Works (including, without limitation, the Video) or Collective Works based on all or any portion of the Article and exercise all of the rights set forth in (a) above in such translations, adaptations, summaries, extracts, Derivative Works or Collective Works and(c) to license others to do any or all of the above. The foregoing rights may be exercised in all media and formats, whether now known or hereafter devised, and include the right to make such modifications as are technically necessary to exercise the rights in other media and formats. If the "Open Access" box has been checked in **Item 1** above, JoVE and the Author hereby grant to the public all such rights in the Article as provided in, but subject to all limitations and requirements set forth in, the CRC License.

ARTICLE AND VIDEO LICENSE AGREEMENT

4. **Retention of Rights in Article.** Notwithstanding the exclusive license granted to JoVE in **Section 3** above, the Author shall, with respect to the Article, retain the non-exclusive right to use all or part of the Article for the non-commercial purpose of giving lectures, presentations or teaching classes, and to post a copy of the Article on the Institution's website or the Author's personal website, in each case provided that a link to the Article on the JoVE website is provided and notice of JoVE's copyright in the Article is included. All non-copyright intellectual property rights in and to the Article, such as patent rights, shall remain with the Author.

5. **Grant of Rights in Video – Standard Access.** This **Section 5** applies if the "Standard Access" box has been checked in **Item 1** above or if no box has been checked in **Item 1** above. In consideration of JoVE agreeing to produce, display or otherwise assist with the Video, the Author hereby acknowledges and agrees that, Subject to **Section 7** below, JoVE is and shall be the sole and exclusive owner of all rights of any nature, including, without limitation, all copyrights, in and to the Video. To the extent that, by law, the Author is deemed, now or at any time in the future, to have any rights of any nature in or to the Video, the Author hereby disclaims all such rights and transfers all such rights to JoVE.

6. **Grant of Rights in Video – Open Access.** This **Section 6** applies only if the "Open Access" box has been checked in **Item 1** above. In consideration of JoVE agreeing to produce, display or otherwise assist with the Video, the Author hereby grants to JoVE, subject to **Section 7** below, the exclusive, royalty-free, perpetual (for the full term of copyright in the Article, including any extensions thereto) license (a) to publish, reproduce, distribute, display and store the Video in all forms, formats and media whether now known or hereafter developed (including without limitation in print, digital and electronic form) throughout the world, (b) to translate the Video into other languages, create adaptations, summaries or extracts of the Video or other Derivative Works or Collective Works based on all or any portion of the Video and exercise all of the rights set forth in (a) above in such translations, adaptations, summaries, extracts, Derivative Works or Collective Works and (c) to license others to do any or all of the above. The foregoing rights may be exercised in all media and formats, whether now known or hereafter devised, and include the right to make such modifications as are technically necessary to exercise the rights in other media and formats. For any Video to which this **Section 6** is applicable, JoVE and the Author hereby grant to the public all such rights in the Video as provided in, but subject to all limitations and requirements set forth in, the CRC License.

7. **Government Employees.** If the Author is a United States government employee and the Article was prepared in the course of his or her duties as a United States government employee, as indicated in **Item 2** above, and any of the licenses or grants granted by the Author hereunder exceed the scope of the 17 U.S.C. 403, then the rights granted hereunder shall be limited to the maximum rights permitted under such statute. In such case, all provisions contained herein that are not in conflict with such statute shall remain in full force and effect, and all provisions contained herein that do so conflict shall be deemed to be amended so as to provide to JoVE the maximum rights permissible within such statute.

8. **Protection of the Work.** The Author(s) authorize JoVE to take steps in the Author(s) name and on their behalf if JoVE believes some third party could be infringing or might infringe the copyright of either the Author's Article and/or Video.

9. **Likeness, Privacy, Personality.** The Author hereby grants JoVE the right to use the Author's name, voice, likeness, picture, photograph, image, biography and performance in any way, commercial or otherwise, in connection with the Materials and the sale, promotion and distribution thereof. The Author hereby waives any and all rights he or she may have, relating to his or her appearance in the Video or otherwise relating to the Materials, under all applicable privacy, likeness, personality or similar laws.

10. **Author Warranties.** The Author represents and warrants that the Article is original, that it has not been published, that the copyright interest is owned by the Author (or, if more than one author is listed at the beginning of this Agreement, by such authors collectively) and has not been assigned, licensed, or otherwise transferred to any other party. The Author represents and warrants that the author(s) listed at the top of this Agreement are the only authors of the Materials. If more than one author is listed at the top of this Agreement and if any such author has not entered into a separate Article and Video License Agreement with JoVE relating to the Materials, the Author represents and warrants that the Author has been authorized by each of the other such authors to execute this Agreement on his or her behalf and to bind him or her with respect to the terms of this Agreement as if each of them had been a party hereto as an Author. The Author warrants that the use, reproduction, distribution, public or private performance or display, and/or modification of all or any portion of the Materials does not and will not violate, infringe and/or misappropriate the patent, trademark, intellectual property or other rights of any third party. The Author represents and warrants that it has and will continue to comply with all government, institutional and other regulations, including, without limitation all institutional, laboratory, hospital, ethical, human and animal treatment, privacy, and all other rules, regulations, laws, procedures or guidelines, applicable to the Materials, and that all research involving human and animal subjects has been approved by the Author's relevant institutional review board.

11. **JoVE Discretion.** If the Author requests the assistance of JoVE in producing the Video in the Author's facility, the Author shall ensure that the presence of JoVE employees, agents or independent contractors is in accordance with the relevant regulations of the Author's institution. If more than one author is listed at the beginning of this Agreement, JoVE may, in its sole

jove JOURNAL OF VISUALIZED EXPERIMENTS
1 Alewife Center #200
Cambridge, MA 02140
tel. 617.945.9051
www.jove.com

ARTICLE AND VIDEO LICENSE AGREEMENT

discretion, elect not take any action with respect to the Article until such time as it has received complete, executed Article and Video License Agreements from each such author. JoVE reserves the right, in its absolute and sole discretion and without giving any reason therefore, to accept or decline any work submitted to JoVE. JoVE and its employees, agents and independent contractors shall have full, unfettered access to the facilities of the Author or of the Author's institution as necessary to make the Video, whether actually published or not. JoVE has sole discretion as to the method of making and publishing the Materials, including, without limitation, to all decisions regarding editing, lighting, filming, timing of publication, if any, length, quality, content and the like.

12. **Indemnification.** The Author agrees to indemnify JoVE and/or its successors and assigns from and against any and all claims, costs, and expenses, including attorney's fees, arising out of any breach of any warranty or other representations contained herein. The Author further agrees to indemnify and hold harmless JoVE from and against any and all claims, costs, and expenses, including attorney's fees, resulting from the breach by the Author of any representation or warranty contained herein or from allegations or instances of violation of intellectual property rights, damage to the Author's or the Author's institution's facilities, fraud, libel, defamation, research, equipment, experiments, property damage, personal injury, violations of institutional, laboratory, hospital, ethical, human and animal treatment, privacy or other rules, regulations, laws, procedures or guidelines, liabilities and other losses or damages related in any way to the submission of work to JoVE, making of videos by JoVE, or publication in JoVE or elsewhere by JoVE. The Author shall be responsible for, and shall hold JoVE harmless from, damages caused by lack of sterilization, lack of cleanliness or by contamination due to the making of a video by JoVE its employees, agents or independent contractors. All sterilization, cleanliness or decontamination procedures shall be solely the responsibility of the Author and shall be undertaken at the Author's expense. All indemnifications provided herein shall include JoVE's attorney's fees and costs related to said losses or damages. Such indemnification and holding harmless shall include such losses or damages incurred by, or in connection with, acts or omissions of JoVE, its employees, agents or independent contractors.

13. **Fees.** To cover the cost incurred for publication, JoVE must receive payment before production and publication the Materials. Payment is due in 21 days of invoice. Should the Materials not be published due to an editorial or production decision, these funds will be returned to the Author. Withdrawal by the Author of any submitted Materials after final peer review approval will result in a US$1,200 fee to cover pre-production expenses incurred by JoVE. If payment is not received by the completion of filming, production and publication of the Materials will be suspended until payment is received.

14. **Transfer, Governing Law.** This Agreement may be assigned by JoVE and shall inure to the benefits of any of JoVE's successors and assignees. This Agreement shall be governed and construed by the internal laws of the Commonwealth of Massachusetts without giving effect to any conflict of law provision thereunder. This Agreement may be executed in counterparts, each of which shall be deemed an original, but all of which together shall be deemed to me one and the same agreement. A signed copy of this Agreement delivered by facsimile, e-mail or other means of electronic transmission shall be deemed to have the same legal effect as delivery of an original signed copy of this Agreement.

A signed copy of this document must be sent with all new submissions. Only one Agreement is required per submission.

CORRESPONDING AUTHOR

Name:	Daniel R. Griffith
Department:	Chemistry
Institution:	Lafayette College
Title:	Assistant Professor
Signature:	
Date:	3/27/2019

Please submit a **signed** and **dated** copy of this license by one of the following three methods:

1. Upload an electronic version on the JoVE submission site
2. Fax the document to +1.866.381.2236
3. Mail the document to JoVE / Attn: JoVE Editorial / 1 Alewife Center #200 / Cambridge, MA 02140

LAFAYETTE COLLEGE

Daniel R. Griffith
Assistant Professor of Chemistry

Easton PA 18042 ◆ TEL 610-330-5221 ◆ FAX 610-330-5714 ◆ http://chemistry.lafayette.edu ◆
griffitd@lafayette.edu

May 9, 2019

Dear Editors,

I have made the requested revisions to my manuscript titled, "Preparation of 6-aminocyclohepta-2,4-dien-1-one Derivatives via Tricarbonyl(tropone)iron." I have addressed the comments by the editorial team and reviewers as delineated below.

Editor's comments:

1. The manuscript has been thoroughly proofread.
2. No figures have been re-used from prior publications. Thus, after confirming with the review editor, no permissions are needed.
3. Highlighting in the protocol was adjusted such that only complete sentences are highlighted.
4. Short descriptions were added for each figure in the Figure Legend.
5. A revised Table of Equipment and Materials has been prepared that does not contain trademark symbols.
6. After consulting with the review editor, parts of the introduction and protocol that contained some overlap with previously published work has been revised. In addition, the title of the manuscript has been slightly modified to further differentiate it from previously published work.

Minor concern from Reviewer #2:

The experiment suggested by the reviewer was one we had previously attempted without success. A small addition pointing this out has been added to the Discussion section.

Thank you for your help in readying this submission for publication and I thank the reviewers for their thoughtful and helpful comments.

Sincerely,

Daniel Griffith