Development of Oxidation Reactions Based on Vanadium Pentoxide, Dimethylsulfoxide, and Synthetic Iron-Rich Clays

A Dissertation

Presented in Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy

with a

Major in Chemistry

in the

College of Graduate Studies

University of Idaho

by

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July 2015

Authorization to Submit Dissertation

This dissertation of Megha Karki, submitted for the degree of Doctor of Philosophy with a Major in Chemistry and titled “Development of Oxidation Reactions Based on Vanadium Pentoxide, Dimethylsulfoxide, and Synthetic Iron-Rich Clays," has been reviewed in final form. Permission, as indicated by the signatures and dates below, is now granted to submit final copies to the College of Graduate Studies for approval.

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Abstract

In this dissertation we offer a discussion on the development of three novel oxidation methods. Chapter 1 presents the dehydroaromatization of *N*-heterocycles using vanadium pentoxide. Tetrahydrocarbazole is readily aromatized to carbazole by vanadium pentoxide in refluxing acetic acid under both stoichiometric and catalytic conditions. Eight other substrates are similarly aromatized in good yields. An extended application of this methodology is the efficient one-pot Fischer indole synthesis and dehydrogenation to form carbazoles.

Chapter 2 describes a unique process for 1,2-dibromination of olefins using aqueous HBr and dimethyl sulfoxide. This novel methodology offers a simple, inexpensive, and mild alternative to the use of Br_2 or other bromine carrying reagents. The substrate scope includes 21 olefins brominated in good to excellent yields. Three of six styrene derivatives yielded bromohydrins in good yields under these reaction conditions.

Chapter 3 discloses the discovery of a synthetic iron-rich nontronite clay and its use as a dehydrogenating reagent. *N*-heterocycles such as 1,2,3,4-tetrahydrocarbazole, indoline, *N*-phenylbenzylamine are effectively aromatized by this new reagent in refluxing toluene. Extensive reaction optimization, investigation of substrate scope, characterization of the novel heterogeneous reagent is presented.

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• **Karki, M.;** Magolan J. Bromination of olefins with HBr and DMSO. *J. Org. Chem.* **2015**, *80* (7), 3701–3707.

PRESENTATIONS

• M. Karki and J. Magolan. Discovery of High Fe Non Clay as a Dehydrogenation Cataylst. 8th Singapore International Chemistry Conference (SICC-8), National University of Singapore, 2014 (*poster presentation*)

• M. Karki and J. Magolan. New DMSO based oxidative synthetic methods. The American Chemical Society Division of Organic Chemistry Graduate Research Symposium, University of California, Irvine, 2014 (*poster presentation*)

• M. Karki, J. Magolan. New applications of metal oxides for dehydrogenation chemistry. 244th ACS National Meeting, Philadelphia, 2012 *(oral presentation)*

• M. Karki, H. Araujo, J. Magolan. Solvent-free aerobic dehydrogenation on the surface of ferric oxide and silica. 95th Canadian Chemistry Conference and Exhibition, Calgary, 2012. (*poster presentation*)

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research and gave their best towards it. I have been fortunate to have made friends with all the graduate students in the chemistry department since 2010 to date. I would like to thank all of them for their enormous support during these five years.

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Thank you Shivji for everything!

Dedication

This is dedicated to all the restless minds who are passionate for organic chemistry.

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List of Schemes

List of Abbreviations

Bn	benzyl
d	doublet
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DIPEA	Diisopropylethylamine
DTBP	di-*tert*-butylperoxide
Equiv.	equivalents
Et	ethyl
Fe-non	high iron nontronite
FTIR	fourier transform infrared spectroscopy
h	hours
HRMS	high resolution mass spectrometry
Hz.	hertz
mL	milliliter
mmol	millimoles
M	molar
m	*meta* substitution
Me	methyl
m.p.	melting point
μW	microwave

NMR	nuclear magnetic resonance
o	*ortho* substitution
ODH	oxidative dehydrogenation
p	*para* substitution
ppm	parts per million
i-Pr	isopropyl
Ph	phenyl
q	quartet
R_F	relative to front
rt	room temperature
s	singlet
SEM	scanning electron microscopy
SM	starting material
S_NAr	nucleophilic aromatic substitution reaction.
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

Chapter 1: Dehydroaromatization with V_2O_5[1]

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Abstract

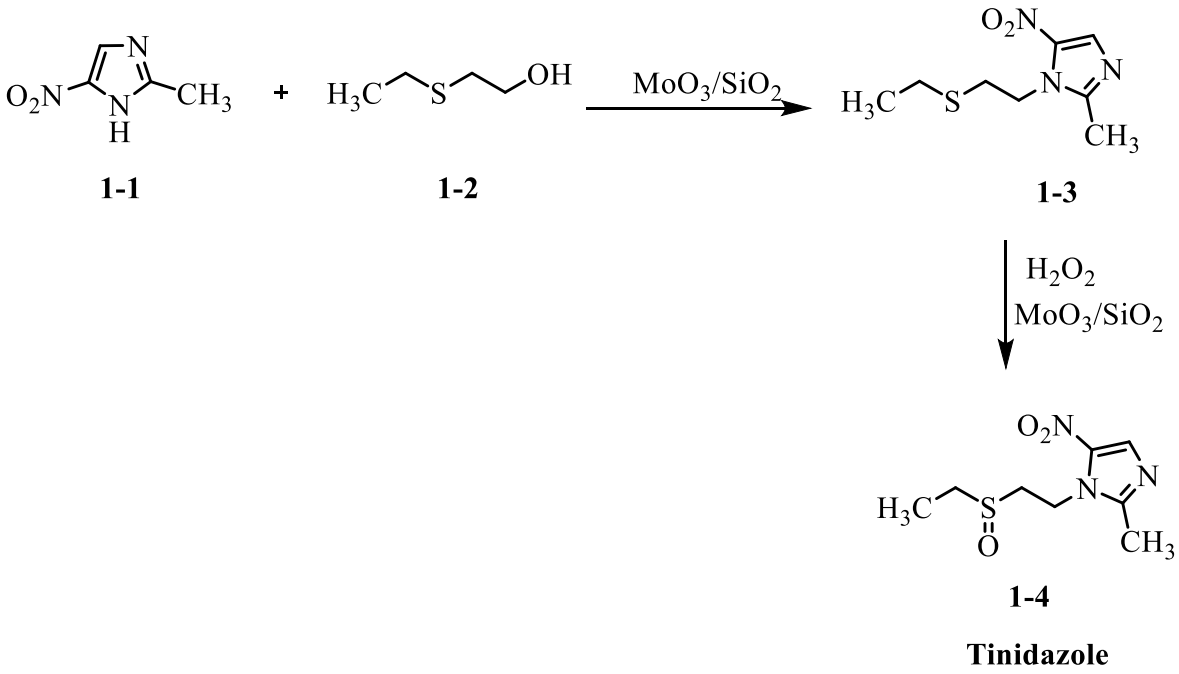
Vanadium pentoxide is evaluated as a dehydroaromatization reagent. Tetrahydrocarbazole is readily aromatized by V_2O_5 in refluxing acetic acid under both stoichiometric and catalytic conditions. Indoline, tetrahydroquinoline, and tetrahydroquinoxaline are effectively aromatized by V_2O_5/silica in refluxing toluene.

Key words: oxidation, arenes, heterocycles, vanadium pentoxide, carbazoles.

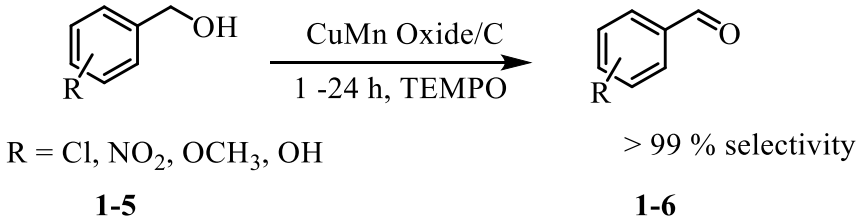
Section 1.1. Introduction

Section 1.1.1. Oxidative Dehydrogenation (ODH) Processes

Metal oxides occupy a prominent role in industrial catalysis[2-5] enabling many important transformations such as catalytic photodegradation of organics in waste water treatment[6-8] and manufacture of formaldehyde from methanol.[9-11] Due to their versatility as acid-base and redox catalysts, they play a major role in the synthesis of fine chemicals, pharmaceuticals (Scheme 1.1),[12] organic synthesis (Scheme 1.2)[13] and green chemistry.[14]

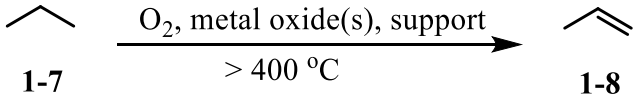


Scheme 1.1. Synthesis of pharmaceutical compound Tinidazole using silica supported molybdnum oxide.[12]



Scheme 1.2. Mixed metal oxide catalyzed oxidation of benzyl alcohols.[13]

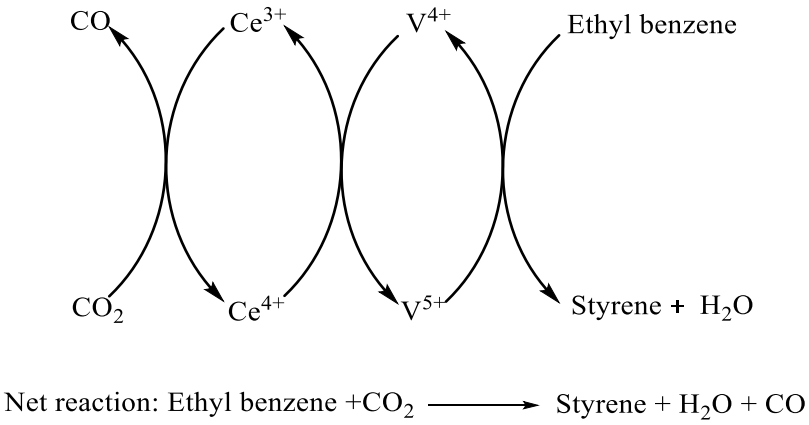
Catalytic oxidative dehydrogenation (ODH) is an industrial process for the synthesis of ethylene and other short chain alkenes **1-8** from the corresponding alkanes **1-7**.[15-18] ODH is performed at high temperature (>400 °C) over mixed metal oxide catalysts (Scheme 1.3).



Scheme 1.3. Oxidative dehydrogenation of propane over silica supported metal oxide.

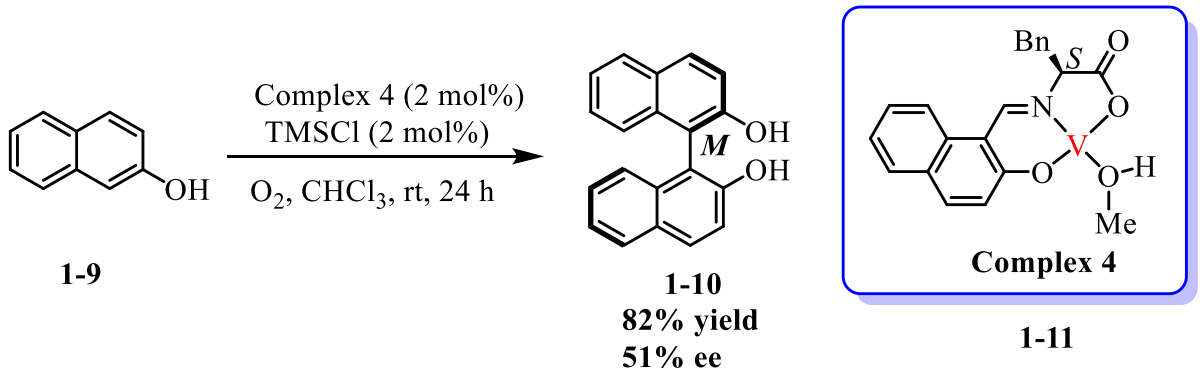
Section 1.1.2. Role of Vanadium Oxides in the Oxidative Processes

Vanadium pentoxide (V_2O_5), the most stable and common naturally occurring vanadium species, is the most frequently used component of the various mixed-oxide catalysts shown to be effective in ODH processes (Scheme 1.4).[19]



Scheme 1.4. $V_2O_5/Ce_{0.6}Zr_{0.4}O_2$-$Al_2O_3$ catalyzed oxidative dehydrogenation of ethylbenzene.[19]

Vanadium pentoxide[20-27] and several other oxovanadium complexes[28-38] have been previously used to mediate various oxidative transformations (Scheme 1.5).[39]



Scheme 1.5. Oxidative coupling of 2-naphthols catalyzed by chiral oxovanadium complex.[39]

Section 1.2. Results and Discussion

Section 1.2.1. Dehydrogenation of 1,2,3,4-tetrahydrocarbazole with V_2O_5/AcOH

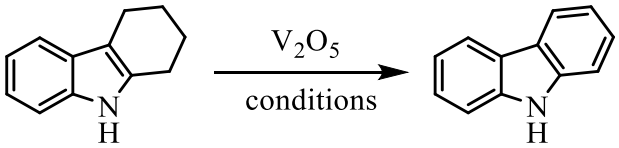
Given its prominence in this role of industrial oxidative dehydrogenation catalysis, we chose to investigate the suitability of V_2O_5 for dehydroaromatization of more complex substrates at less destructive temperatures. We began by investigating the conversion of 1,2,3,4-tetrahydrocarbazole **1-12** to carbazole **1-13** (Table 1). Similar reactions are commonly accomplished using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[40-42] (DDQ) or catalytic palladium-on-carbon[43-45] (Pd/C) in high boiling solvents, which have replaced reagents such as chloranil, SeO_2, MnO_2, elemental sulfur and selenium.[46] In terms of cost and toxicity, V_2O_5 compares favorably with DDQ. Employment of Pd/C for dehydrogenations is inherently limited to substrates without labile olefins.

As shown in Table 1.1, we found that 1,2,3,4-tetrahydrocarbazole **1-12** is inert to stoichiometric V_2O_5 in refluxing acetonitrile and dioxane, however, trace conversion into carbazole **1-13** is observed in toluene after four hours (entries 1–3). Product formation occurs smoothly in acetic acid with complete substrate conversion in two days and 79 % yield of carbazole **1-13** isolated (entries 4–6). With 2.0 equivalents of V_2O_5 the reaction time is reduced to 24 hours with slightly improved product yield (entry 7). Catalytic V_2O_5 with excess co-oxidants di-*tert*-butyl peroxide (DTBP) and H_2O_2 are modestly successful with conversions of 46% and 37%, respectively, after 24 hours reaction time (entries 8 and 9). Other co-oxidants including O_2 (1 atm) and benzoquinone are less effective (<10 % conversion).

Surprisingly, complete conversion of 1,2,3,4-tetrahydrocarbazole **1-12** into carbazole **1-13** is also observed when catalytic V_2O_5 (0.2 equiv) is employed in the absence of an added terminal oxidant (entry 10). Even with 5 mol % of V_2O_5, under an argon atmosphere in degassed

acetic acid, complete conversion is achieved in 3.5 days (entry 11). We observe trace ethyl acetate in the crude ^{1}H NMR spectra of these reactions presumably resulting from reduction of acetic acid to ethanol. We thus hypothesize that acetic acid is acting as the terminal oxidant. A number of efficient and green dehydrogenations of amines have appeared in the literature in recent years.[47-51] We find V_2O_5-mediated dehydroaromatization of cyclic amines to be generally ineffective in acetic acid. As shown in Table 1.2, for example, treatment of indoline **1-14** with stoichiometric V_2O_5 in acetic acid results in no reaction apart from trace formation of *N*-acetyl indoline (entry 1). We hypothesize that protonation of the amine by the solvent yields an ammonium acetate species that is inert to oxidation by V_2O_5.

Table 1.1. Reaction optimization of dehydrogenation of 1,2,3,4-tetrahydrocarbazole



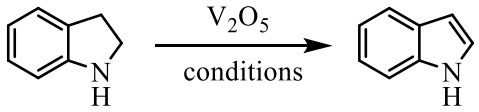
1-12 **1-13**

Entry	V_2O_5 equiv.	Solvent	Temp (° C)	Time (h)	Conversion[a] (Yield)[b]
1	1.0	CH_3CN	82	4	0
2	1.0	dioxane	101	4	0
3	1.0	toluene	111	4	2
4	1.0	AcOH	118	4	39
5	1.0	AcOH	118	24	59
6	1.0	AcOH	118	48	>99 (79)
7	2.0	AcOH	118	24	98 (83)
8	0.2[c]	AcOH	118	24	46
9	0.2[d]	AcOH	118	24	37
10	0.2	AcOH	118	72	>99 (80)
11	0.05	AcOH[e]	118	96	98 (68)

[a]Determined by ^{1}H NMR. [b]Isolated yield after chromatography. [c]Di-*tert*-butyl peroxide (DTBP, 3.0 equiv.) was added. [d]H_2O_2 (30 % aq., 3.0 equiv.) was added. [e]Solvent degassed by Argon bubbling for 10 min.; reaction run under Ar atmosphere.

Section 1.2.2. Optimization of Dehydroaromatization of Indoline with V_2O_5

Table 1.2. Reaction optimization of dehydrogenation of indoline



1-14 **1-15**

Entry	V_2O_5 equiv.	SiO_2 (mg)	Solvent	Temp (° C)	Time (h)	Conversion[a] (yield)[b]
1	1.2	-	AcOH	118	4	n/a[c]
2	1.2	-	toluene	111	4	60
3	1.2	-	toluene	111	22	76
4	1.2	200	toluene	111	22	86
5	1.2	800	toluene	111	22	96 (82)
6	0	800	toluene	111	22	33
7	0.2[d]	800	toluene	111	40	98 (75)

[a]Determined by ^{1}H NMR. [b]Isolated yield after chromatography. [c]Only starting material and trace *N*-acetyl indoline observable by ^{1}H NMR. [d]Di-*tert*-butyl peroxide (DTBP, 2.0 equiv.) was added.

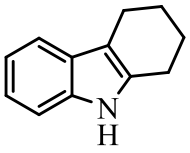
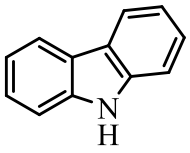
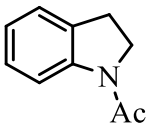
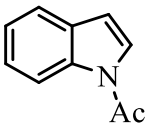
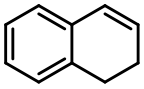
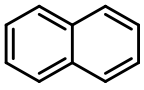
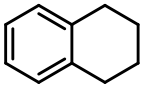
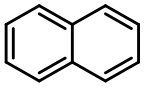
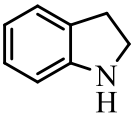
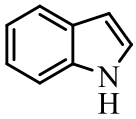
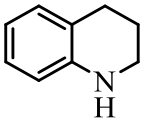
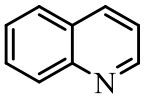
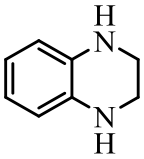
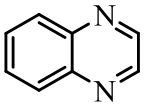
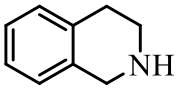
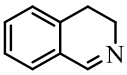
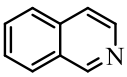
However, replacement of the acetic acid solvent with toluene results in successful dehydrogenation of indoline **1-14** to indole **1-15** (entries 2 and 3). The reaction is improved by addition of silica gel (entries 4 and 5), our goal being to crudely mimic 'industrial' oxidative dehydrogenation conditions. Addition of 800 mg of silica per mmol of substrate increases conversion to 96 % in 22 hours with 82 % isolated yield of indole **1-15**.

A control reaction performed in the absence of vanadium reveals that silica alone also mediates partial dehydrogenation of indoline **1-14** (entry 6, 33 % conversion). Catalytic V_2O_5 with excess DTBP (2.0 equiv) and silica (800 mg/mmol of substrate) are also effective conditions resulting in 75 % yield of indole **1-15** after 40 hours reaction time (entry 7).

Section 1.2.3. Substrate Scope

The results of dehydroaromatization experiments with eight substrates are summarized in Table 1.3. The first four substrates (Table 1.3, entries 1–4), without basic N–H moieties, are most effectively dehydrogenated in acetic acid. *N*-Acetyl indoline **1-16** is unreactive in toluene and slow to dehydrogenate in acetic acid (Table 3, entries 2a and 2b). With 2 equivalents of V_2O_5 complete substrate consumption requires 6 days, and *N*-acetyl indole **1-17** is obtained in 61% yield (Table 1.3, entry 2a). When V_2O_5 loading is reduced to 5 mol% just 28% conversion is observed after 8 days (entry 2b). 1,2-Dihydro- and 1,2,3,4-tetrahydronaphthalenes **1-18** and **1-20** react poorly under these conditions. Treatment of dihydronapthalene **1-18** with 2 equivalents of V_2O_5 in refluxing AcOH for 4 days results in incomplete conversion of the substrate and only 36 % isolated yield of naphthalene **1-19 (**entry 3). 1,2,3,4-Tetrahydronapthalene **1-20** is essentially unreactive with just 4 % conversion into naphthalene **1-19** observable by ^{1}H NMR spectroscopy after four days (entry 4). The next three substrates, all nitrogen-containing heterocycles, are inert to V_2O_5 in refluxing acetic acid but are readily aromatized by V_2O_5/silica in refluxing toluene both with excess V_2O_5 and catalytic V_2O_5 with excess DTBP as a terminal oxidant offering indole **1-15**, quinoline **1-22**, and quinoxaline **1-24** in good yields (entries 5–7). In all three cases, employment of catalytic V_2O_5 requires longer reaction times than the corresponding stoichiometric reaction.

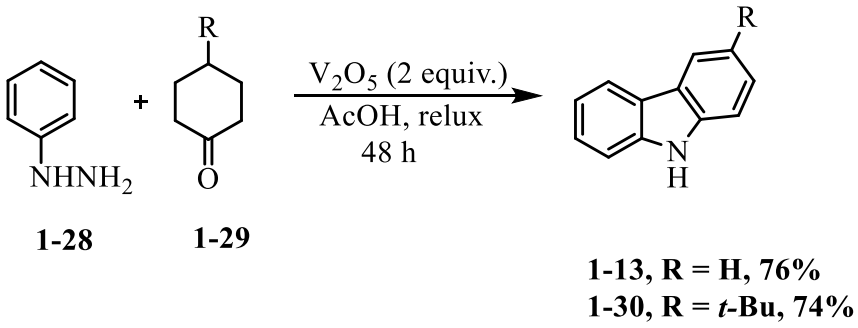
Table 1.3. Substrate scope of dehydroaromatization with V_2O_5

Entry	Conditions[1]	Substrate	Product(s)	Time(h)	Yield[2]
1a	V_2O_5 (2.0 equiv.), AcOH	 **1-12**	 **1-13**	24	83
1b	V_2O_5 (1.0 equiv.), AcOH			48	79
1c	V_2O_5 (0.05 equiv.), AcOH			96	68
2a	V_2O_5 (2.0 equiv.), AcOH	 **1-16**	 **1-17**	144	61
2b	V_2O_5 (0.05 equiv.), AcOH			192	(28)[3]
3	V_2O_5 (2.0 equiv.), AcOH	 **1-18**	 **1-19**	96	36
4	V_2O_5 (2.0 equiv.), AcOH	 **1-20**	 **1-19**	96	(4)[3]
5a	V_2O_5 (1.2 equiv.), SiO_2, toluene	 **1-14**	 **1-15**	22	82
5b	V_2O_5 (0.2 equiv.), DTBP, SiO_2, toluene			40	75
6a	V_2O_5 (2.0 equiv.), SiO_2, toluene	 **1-21**	 **1-22**	41	75
6b	V_2O_5 (0.2 equiv.), DTBP, SiO_2, toluene			108	61
7a	V_2O_5 (2.0 equiv.), SiO_2, toluene	 **1-23**	 **1-24**	24	88
7b	V_2O_5 (0.2 equiv.), DTBP, SiO_2, toluene			84	79
8	V_2O_5 (2.0 equiv.), SiO_2, toluene	 **1-25**	 **1-26**  **1-27**	48	25(18), 31(19)

[1.] Reactions were performed in refluxing AcOH, 118 °C, or refluxing toluene, 111 °C; where SiO_2 is indicated, 800 mg SiO_2 per mmol of substrate was used; where di-*tert*-butylperoxide (DTBP) is indicated, 3.0 equiv. were used. [2.] Isolated yield after chromatography. [3.] Product was not isolated and yield was estimated based on crude mass recovery and ^{1}H NMR analysis of reaction mixture.

Treatment of tetrahydroisoquinoline **1-25** with two equivalents of V_2O_5 for 48 hours consumes all of the substrate and yields a mixture of 3,4-dihydroisoquinoline **1-26** and isoquinoline **1-27** that can be isolated in modest yields (25 % and 31 %, respectively; entry 8). In the case of tetrahydroisoquinoline **1-25** use of catalytic V_2O_5 and excess DTBP is not viable yielding a complex mixture of products.

Finally, we demonstrate a one-pot Fischer indole synthesis–dehydrogenation sequence that enables the preparation of two carbazoles[52,53] directly from phenylhydrazine **1-28** and cyclohexanones **1-29** using V_2O_5 (2 equiv.) in refluxing acetic acid (Scheme 1.6). Carbazole **1-13** and 3-*tert*-butylcarbazole **1-30** are obtained in 76 % and 74 % yield, respectively, after a 48 hour reaction time.



1-28 **1-29**

1-13, R = H, 76%
1-30, R = *t*-Bu, 74%

Scheme 1.6. One pot Fischer-indole synthesis - dehydrogenation using V_2O_5

Section 1.3. Summary

In conclusion, our evaluation of the capacity of V_2O_5 to mediate dehydroaromatization reactions has resulted in a number of synthetically useful examples of this approach. Such dehydrogenations are commonly accomplished using more expensive and/or more toxic catalysts or reagents such as Pd/C and DDQ. Vanadium pentoxide is a common industrial catalyst and represents an inexpensive alternative that is suitable for select substrates. Vanadium pentoxide is also an effective oxidant for a two-step, one-pot carbazole formation via Fischer indole synthesis and dehydrogenation. Notably, catalytic V_2O_5 effectively dehydrogenates 1,2,3,4-tetrahydrocarbazole **1-12** to carbazole **1-13** in refluxing acetic acid. In this case, we hypothesize that the solvent plays the role of terminal oxidant.

Section 1.4. Experimental

General Considerations: Unless otherwise noted, commercially available reagents and solvents were used without further purification. ^{1}H and ^{13}C NMR experiments were performed on a Bruker AVANCE 300 MHz instrument and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Reaction progress was monitored by thin-layer chromatography

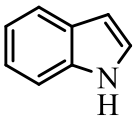
(TLC, EMD Chemicals Inc, Silica Gel 60 F254), visualized under UV light, and plates were developed using *p*-anisaldehyde or potassium permanganate stains. Flash chromatography was performed using silica gel (Sorbent Technologies, particle size 40-63 µm).

Section 1.4.1. General Procedure for Vanadium Pentoxide Catalyzed Dehydroaromatization Reaction.

Procedure 1: Catalytic V_2O_5, DTBP, silica, toluene

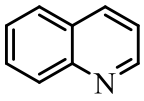
Substrate (1.0 mmol), V_2O_5 (0.2 mmol), di-*tert*-butylperoxide (3.0 mmol), silica gel (800 mg, *Sorbent Technologies, particle size 40-63 µm*), and toluene (6 mL) were added to a round bottomed flask equipped with a stir bar and reflux condenser. The reaction mixture was stirred at reflux temperature under an argon atmosphere at the specified temperature (Table 1.) until complete disappearance of starting material was observed by TLC. After the reaction was over, it was cooled and filtered through a celite plug. The solids were washed repeatedly with chloroform. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (gradient elution with EtOAc and hexanes).

Substrates used: Indoline, 1,2,3,4-tetrahydroquinoline, tetrahydroquinoxaline



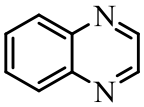
1-15

Indole (1-15). The standard procedure was used with indoline **1-14**, (112.1µL, 1.0 mmol), V_2O_5 (36.4 mg, 0.2 mmol), di-*tert*-butylperoxide (551.0 µL, 3.0 mmol), silica gel (800 mg), and toluene (6 mL). After 40 h of refluxing, the reaction was worked up and purified as described above to yield compound **1-14** as white crystals. (0.088 g, 75 % yield). ^{1}H and ^{13}C NMR spectra matched an authentic sample.



1-22

Quinoline (1-22). The standard procedure was used with 1,2,3,4-tetrahydroquinoline **1-21**, (125.5 µL, 1.0 mmol), V_2O_5 (36.4 mg, 0.2 mmol), di-*tert*-butylperoxide (551.0 µL, 3.0 mmol), silica gel (800 mg), and toluene (6 mL). After 108 h of refluxing, the reaction was worked up and purified as described above to yield compound **1-22** as yellow oil. (0.079 g, 61 % yield). ^1H and ^{13}C NMR spectra matched an authentic sample.



1-24

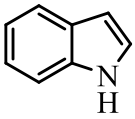
Quinoxaline (1-24). The standard procedure was used with 1,2,3,4-tetrahydroquinoxaline **1-23**, (134.2 mg, 1.0 mmol), V_2O_5 (36.4 mg, 0.2 mmol), di-*tert*-butylperoxide (551.0 µL, 3.0 mmol), silica gel (800 mg), and toluene (6 mL). After 84 h of refluxing, the reaction was worked up and purified as described above to yield compound **1-24** as colorless oil. (0.103 g, 79 % yield). ^1H and ^{13}C NMR spectra matched an authentic sample.

Procedure 2: V_2O_5, silica, toluene

Substrate (1.0 mmol), V_2O_5 (2 mmol), silica gel (800 mg, *Sorbent Technologies, particle size 40-63 µm*), and toluene (6 mL) were added to a round bottomed flask equipped with a stir bar and reflux condenser. The reaction mixture was stirred at reflux temperature under an argon atmosphere at the specified temperature (Table 1.) until complete disappearance of starting

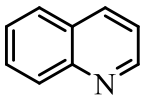
material was observed by TLC. After the reaction was over, it was cooled and filtered through a celite plug. The solids were washed repeatedly with chloroform. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (gradient elution with EtOAc and hexanes).

Substrates used: Indoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, tetrahydroquinoxaline



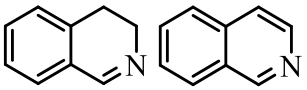
1-15

Indole (1-15). The standard procedure was used with indoline **1-14**, (112.1µL, 1.0 mmol), V_2O_5 (364 mg, 2 mmol), silica gel (800 mg), and toluene (6 mL). After 40 h of refluxing, the reaction was worked up and purified as described above to yield compound **1- 15** as white crystals. (0.096 g, 82 % yield). ^{1}H and ^{13}C NMR spectra matched an authentic sample.



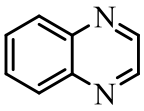
1-22

Quinoline (1-22). The standard procedure was used with 1,2,3,4-tetrahydroquinoline **1-21**, (125.5 µL, 1.0 mmol), V_2O_5 (364 mg, 2 mmol), silica gel (800 mg), and toluene (6 mL). After 41 h of refluxing, the reaction was worked up and purified as described above to yield compound **1-22** as yellow oil. (0.097 g, 75 % yield). ^{1}H and ^{13}C NMR spectra matched an authentic sample.



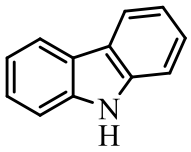
1-26 **1-27**

Isoquinoline (1-27) and 3,4-dihydroisoquinoline (1-26). The standard procedure was used with 1,2,3,4-tetrahydroisoquinoline **1-25**, (125.1 µL, 1.0 mmol), V_2O_5 (364 mg, 2 mmol), silica gel (800 mg), and toluene (6 mL). After 48 h of refluxing, the reaction was worked up and purified as described above to yield compound **1-27** as colorless liquid (0.040 g, 31 % yield) and compound **1-26** as light brown oil (0.033 g, 25 % yield). ^{1}H and ^{13}C NMR spectra matched an authentic sample.



1-24

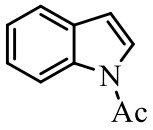
Quinoxaline (1-24). The standard procedure was used with 1,2,3,4-tetrahydroquinoxaline **1-23**, (134.2 mg, 1.0 mmol), V_2O_5 (364 mg, 2 mmol), silica gel (800 mg), and toluene (6 mL). After 84 h of refluxing, the reaction was worked up and purified as described above to yield compound **1-24** as colorless oil. (0.102 g, 79 % yield). ^{1}H and ^{13}C NMR spectra matched an authentic sample.



1-13

Tetrahydrocarbazole to carbazole (cat. V_2O_5, AcOH): 1,2,3,4-Tetrahydrocarbazole **1-12** (1.0 mmol), V_2O_5 (0.05 mmol), and acetic acid (6 mL) were added to a round bottomed flask equipped with a stir bar and reflux condenser. The reaction mixture was stirred at reflux temperature under an Argon atmosphere for 5 days. The reaction was cooled to RT, water was added and the aqueous layer was extracted three times with chloroform. The combined extracts were washed with brine and dried over sodium sulfate, concentrated *in vacuo*, and the residue was purified by column chromatography (EtOAc/Hexanes) to offer carbazole **1-13** in 68 % yield. ^{1}H and ^{13}C NMR spectra matched an authentic sample.

*Similar procedure was followed for the dehydrogenation of 1,2,3,4-tetrahydrocarbazole **1-12** with 2.0 equiv. and 1.0 equiv. of V_2O_5 in refluxing acetic acid for 24 and 48 hours to give 83% and 79% yield respectively.*

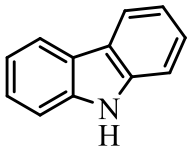


1-17

***N*-acetylindoline to *N*-acetylindole (V_2O_5, AcOH):** *N*-acetylindoline **1-16** (1.0 mmol), V_2O_5 (2 mmol), and acetic acid (6 mL) were added to a round bottomed flask equipped with a stir bar and reflux condenser. The reaction mixture was stirred at reflux temperature under an Argon atmosphere for 6 days. The reaction was cooled to RT, water was added and the aqueous layer was extracted three times with chloroform. The combined extracts were washed with brine and dried over sodium sulfate, concentrated *in vacuo*, and the residue was purified by column

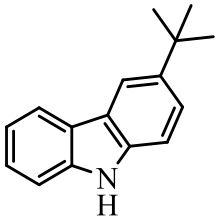
chromatography (EtOAc/Hexanes) to offer *N*-acetylindole **1-17** as yellow solid (0.097 g, 61 % yield). ^{1}H and ^{13}C NMR spectra matched an authentic sample.

One pot Fischer Indole Synthesis and Dehydrogenation



1-13

Carbazole (1-13). Phenylhydrazine **1-28** (1.0 mmol), cyclohexanone **1-29** (1.0 mmol), V_2O_5 (2.0 mmol), and acetic acid (6 mL) were added to a round bottomed flask equipped with a stir bar and reflux condenser. The reaction mixture was stirred at reflux temperature under an Argon atmosphere for 48 hours. The reaction was cooled to RT, water was added and the aqueous layer was extracted three times with chloroform. The combined extracts were washed with brine and dried over sodium sulfate, concentrated *in vacuo*, the residue was purified by column chromatography (EtOAc/Hexanes) to offer carbazole **1-13** in 76 % yield. ^{1}H and ^{13}C NMR spectra matched an authentic sample.



1-30

3-*tert*-butylcarbazole (1-30). Phenylhydrazine **1-28** (1.0 mmol), 4-*tert*-butylcyclohexanone **1-29** (1.0 mmol), V_2O_5 (2.0 mmol), and acetic acid (6 mL) were added to a round bottomed flask equipped with a stir bar and reflux condenser. The reaction mixture was stirred at reflux temperature under an Argon atmosphere for 48 hours. The reaction was cooled to RT, water was added and the aqueous layer was extracted three times with chloroform. The combined

extracts were washed with brine and dried over sodium sulfate, concentrated *in vacuo*, the residue was purified by column chromatography (EtOAc/Hexanes) to offer 3-*tert*-butylcarbazole **1-30** in 74 % yield. ^{1}H and ^{13}C NMR spectra matched an authentic sample.

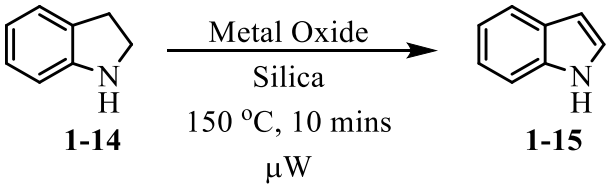
Section 1.5. Additional unpublished work

Section 1.5.1. Evaluation of Other Metal Oxides towards Dehydroaromatization under Microwave Irradiation

Microwave accelerated synthesis is emerging as a powerful technique in organic synthesis.[54,55] Solvent free reactions are best done under microwave conditions as it allows for a uniform heating of solid reaction mixture. Based on the results obtained with V_2O_5 for the dehydroaromatization in solvent, we decided to evaluate different metal oxides towards dehydroaromatization of *N*-heterocyclic compounds under solvent-free conditions under microwave heating. We screened different metal oxides for the oxidative dehydrogenation of indoline **1-14** to indole **1-15**. Silica was used as a solid support. The reactions were carried out using microwave irradiation at 150 °C for 10 minutes (Table 1.4).

V_2O_5/silica was further optimized by varying reaction time, temperature, and amount of V_2O_5. Notably, silica alone yielded some oxidation. A minimum of two molar equivalents of V_2O_5 at a temperature of 120 ºC were required to complete the reaction. With 4 equiv. of V_2O_5, at 150ºC, the reaction was complete in 10 minutes.

Table 1.4. Screening of metal oxides for the dehydroaromatization of indoline [a]

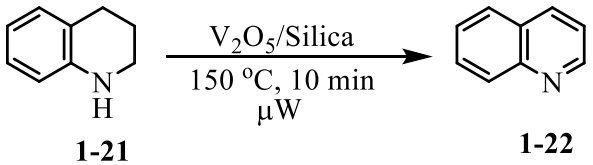


1-14 **1-15**

Entry	Metal Oxide	**1-14:1-15** ^{1}H NMR ratio
1	Zinc (II) oxide	89:11
2	Lead oxide	88:12
3	Alumina	86:14
4	Nickel (II) oxide	84:16
5	Lead (IV) oxide	83:17
6	Copper (II) oxide	83:17
7	Manganese (III) oxide	82:18
8	Magnesium (II) oxide	81:19
9	Iron (III) oxide	72:28
10	Chromium (VI) oxide	61:39
11	Copper (I) oxide	57:43
12	Molybdenum (IV) oxide	43:57
13	Vanadium (V) oxide	0:100

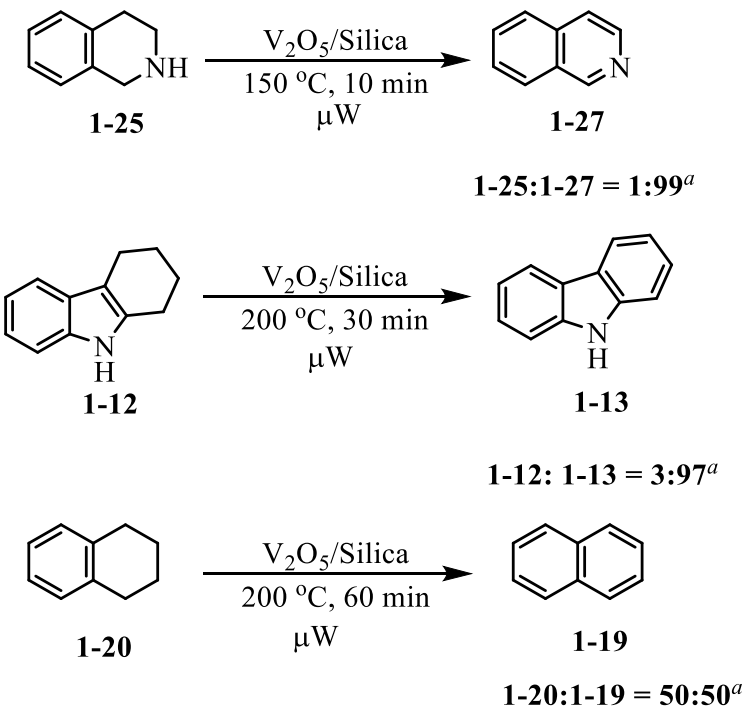
[a] Reaction conditions; 1 mmol substrate, metal oxide (4 equiv.), Silica (800 mg). Reaction work up: Filtration with chloroform.

Substrate scope of microwave assisted V_2O_5 catalyzed dehydroaromatization was evaluated and the results are summarized in Scheme 1.7.



1-21 **1-22**

1-21:1-22 = 5:95[a]



[a]Determined as ^{1}H NMR starting material to product ratio.

Scheme 1.7. Dehydroaromatization of *N*-heterocycles with V_2O_5 under μW irradiation.

Although the dehydroaromatization reaction of *N*-heterocycles gave excellent conversion to products based on ^{1}H NMR starting material to product ratio under microwave conditions, the isolated yields of products, and mass recovery in general, were found to be poor (< 50% in all cases). Due to these low yields the microwave approach of this methodology was abandoned.

Section 1.5.2. General Experimental Procedure for Microwave Reactions

Substrate (1 mmol), metal oxide (4 equiv.) and silica (800 mg) were ground together using a mortar and pestle and the reaction mixture was transferred to a 5 ml microwave vial. The reaction was heated in the microwave reactor (Biotage Initiator) at 150 ºC or 200 ºC for the specified time (Scheme 1.7). Completion of the reaction was monitored by TLC. Products were

recovered by filtration and repeated washing with chloroform. The residue was concentrated *in vacuo* and starting material to product ratios were determined based on crude ^{1}H NMR.

Section 1.6. References

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Chapter 2. Bromination of Olefins with HBr and DMSO[1]

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Abstract

A simple and inexpensive methodology is reported for the conversion of alkenes to 1,2-dibromo alkanes via oxidative bromination using HBr paired with dimethylsulfoxide which serves as the oxidant as well as co-solvent. The substrate scope includes 21 olefins brominated in good to excellent yields. Three of six styrene derivatives yielded bromohydrins under the reaction conditions.

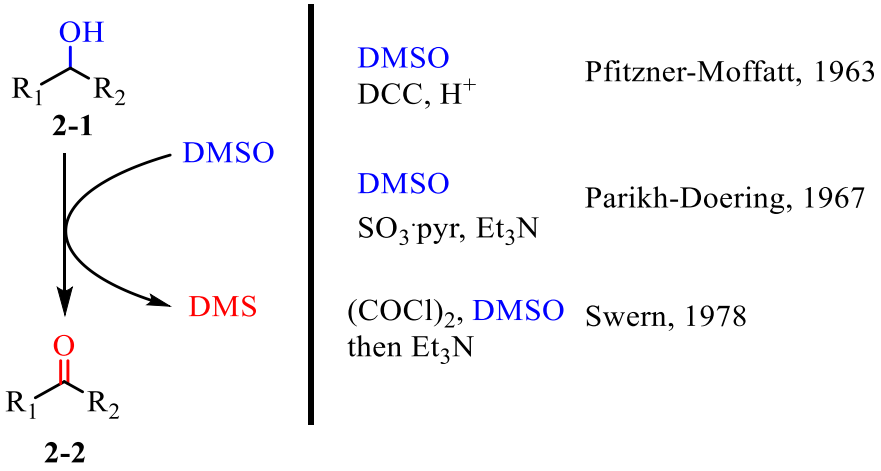
Keywords: Bromination, dimethylsulfoxide, HBr, alkene, 1,2-dibromoalkane, bromohydrin

Section 2.1 Introduction

Section 2.1.1. Introduction to DMSO-Based Oxidations

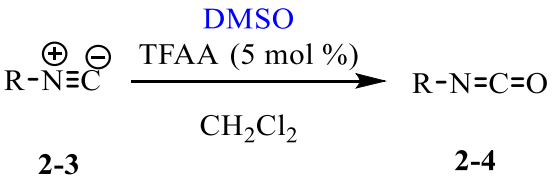
Dimethylsulfoxide (DMSO) is a widely used polar aprotic solvent for small scale and industrial synthetic applications.[2] In the presence of various activating reagents DMSO is also a mild terminal oxidant employed primarily for the oxidation of alcohols (Scheme 2.1).[3-5] One of the earliest uses of DMSO as an oxidant was shown by Pfitzner and Moffatt in 1963.[6] An alcohol was oxidized in dry DMSO with dicyclohexylcarbodiimide (DCC) to an aldehyde or ketone with no trace over oxidation to acid in the case of primary alcohols. It was soon realized that other electrophiles such as acetic anhydride,[7] phosphorous pentoxide,[8] sulfur trioxide and pyridine,[9] could also 'activate' DMSO toward oxidation. In 1978, Swern *et al*. presented a reliable oxidation of alcohols to aldehydes or ketones using oxalyl chloride as the activator of DMSO.[10] Since DMSO-based oxidations are metal-free, mild, and inexpensive, we are

interested in expanding the use of this oxidant beyond its traditional application to alcoholic substrates.



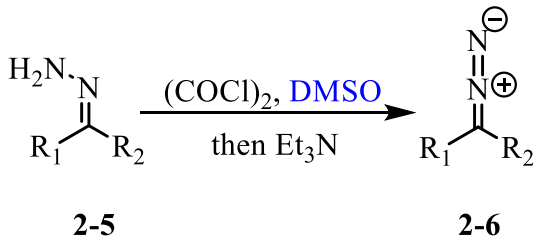
Scheme 2.1. Oxidation of alcohols to acids and ketones via 'activated' DMSO.[6,9,10]

Substrates other than alcohols have also been oxidized by DMSO. Ganem and co-workers reported a smooth and efficient oxidation isonitriles to isocyanates by DMSO, catalyzed by trifluoroacetic anhydride (Scheme 2.2).[11]



Scheme 2.2 Trifluoroacetic anhydride catalyzed oxidation of isonitriles by DMSO.[11]

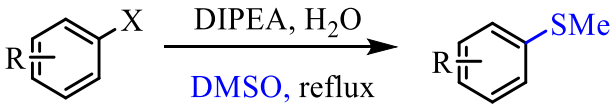
Another report of DMSO being activated by oxalyl chloride to dehydrogenate hydrozones to yield diazo compounds was published in 2007 by Brewer and co-workers (Scheme 2.3).[12]



2-5 **2-6**

Scheme 2.3. Dehydrogenation of hydrazones with activated DMSO.[12]

In 2014, our group reported synthesis of aryl methyl sulfides via an S_NAr process using DMSO as the formal source of thiomethyl moiety in the presence of diisopropylethylamine. To our knowledge, this work was the first example of a synthetically useful role for the dimethyl sulfide that is generated as a byproduct of DMSO-based oxidation. In this case, DMSO served as a formal equivalent of NaSMe in the context of a nucleophilic aromatic substitution reaction (Scheme 2.4).[13]



2-7 **2-8**

R = -NO_2, -CN, -CHO
X = -F, -Cl, -NO_2

12 examples
21-81 % yields

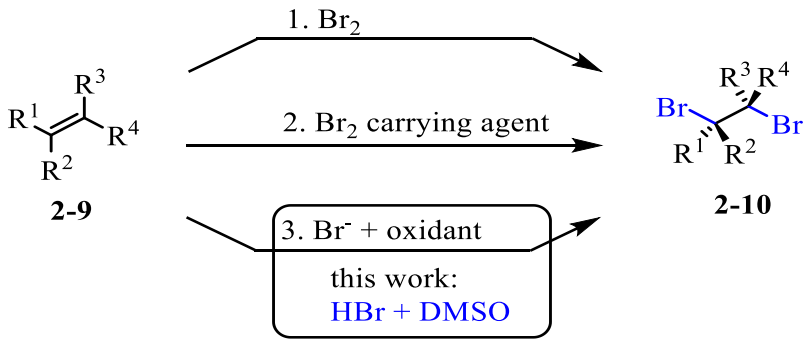
Scheme 2.4. DMSO as the source of '–SMe' for aryl methyl sulfides synthesis.[13]

Following our use of DMSO as formal source of thiomethyl moiety,[13] we began to consider the potential development of other novel DMSO-based synthetically useful oxidative transformations.

Section 2.1.2. Introduction to Alkene Bromination

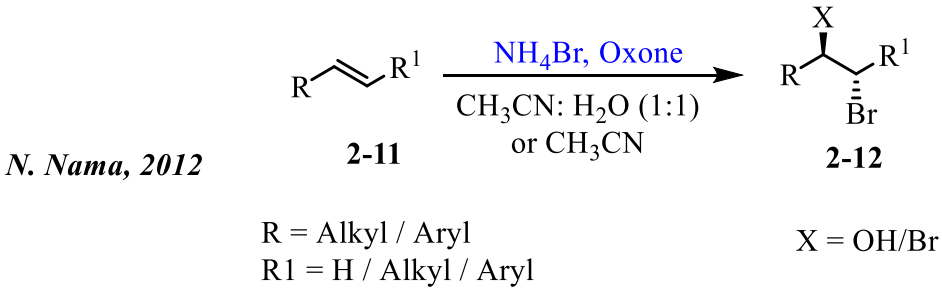
Vicinal dibromoalkanes (**2**) are useful synthetic precursors to cyclopropanes,[14,15] alkynes,[16] and vinylbromides of value in cross-coupling chemistry.[16,17] Their various

preparations from alkenes (**1**) can be classified into three general approaches as illustrated in Scheme 2.5. 1) treatment with molecular bromine in a halogenated solvent[18] or alternative media,[19-22] 2) treatment with a bromine carrying agent such as a tribromide salt[23-27] or analogous reagent,[28-34] and 3) treatment with bromide ion in the presence of a stoichiometric oxidant such as Oxone,[35-41] H_2O_2,[42-45] O_2,[46,47] Selectfluor,[48] and others.[49-57]

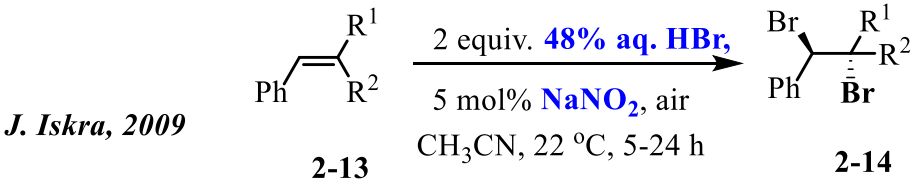


Scheme 2.5. General approaches to bromination of olefins.

The third of these strategies, oxidative bromination, is analogous to the biological solution to electrophilic halogenation which employs haloperoxidase (H_2O_2) or flavin dependent halogenase (O_2) enzymes to produce 'X^+' from X^-.[58] Selected examples from a large pool of recent dibromination methods present in the literature are shown in Scheme 2.6.[34,59,60]



Scheme 2.6a



Scheme 2.6b

Scheme 2.6. Examples of recent methods for bromination of olefins in the literature.[59,60]

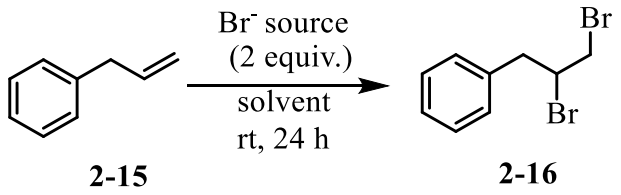
In their 2008 comparative review of 24 methods, Eissen and Lenoir concluded that many recently-developed bromination methods that circumvent the use of molecular bromine suffer from significantly higher resource demands and waste production compared to the traditional choice of Br_2 in CCl_4.[61] The authors emphasize the need for continued development in this field and highlight oxidative bromination in general, and the use of H_2O_2/HBr[44] specifically, as the most favorable of current methods based on a number of environmental, health, and safety factors. Herein we present our discovery of a procedurally facile and inexpensive oxidative bromination of olefins using HBr/DMSO.

Section 2.2. Results and Discussion

Section 2.2.1. Reaction Discovery

In the present case, to explore the potential applicability of DMSO to oxidative bromination we began by treating allylbenzene **2-15** with four bromide reagents in DMSO (Table 2.1).

Table 2.1. Reaction discovery.[a]



2-15 **2-16**

Entry	Br^- reagent	Solvent	Yield (%)[b]
1	Bu_4NBr	DMSO	0
2	KBr	DMSO	0
3	NaBr	DMSO	0
4	HBr (48 % aq.)	DMSO	13
5	HBr (48 % aq.)	$CHCl_3$	0

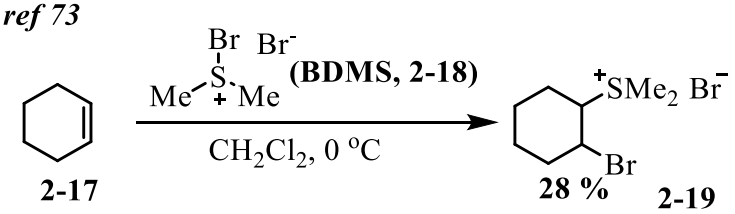
[a] Reaction conditions: Substrate (0.5 mmol), DMSO (0.5 mL), 'Br^- source' (2-10 equiv); reaction workup with Et_2O/H_2O. [b] NMR yield with CH_2Br_2 as an internal standard.

Although no reaction occurred with Bu_4NBr, KBr, or NaBr in DMSO, we were pleased to observe that HBr yielded some of the desired 2,3-dibromopropylbenzene **2-16** (entry 4). The reaction did not proceed when DMSO was replaced with chloroform (entry 5) in which case trace hydrobromination was observed but most of the substrate remained unreacted.

In previous literature the pairing of HBr and DMSO has been used for the alpha oxidation of ketones,[62-65] bromination of arenes,[66-68] and benzylic oxidation.[69] In most cases, it was believed that HBr reacts with DMSO to yield bromodimethylsulfonium bromide **2-18**

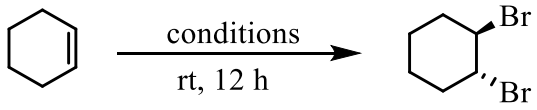
(BDMS), a well-established electrophilic bromination reagent that is more commonly prepared from dimethylsulfide and bromine.[70] BDMS **2-18** is an orange solid that precipitates from dichloromethane solution upon addition of DMS and Br_2.[71] Most commonly this reagent has been used to brominate various arenes and carbonyl derivatives.[70] In 2008, Das and co-workers reported bromination of olefins with BDMS **2-18** in acetonitrile.[72] Earlier, similar reaction conditions were employed by Chow and Bakker to form 1-bromo-2-sulfonium bromides, such as **2-19**, which precipitated in low yields upon treatment of olefins with BDMS 2-18in CH_2Cl_2 or CH_3CN at 0° C (Scheme 2.7.).[73]

a. ref 73



2-17 **28 %** **2-19**

b. our observations



2-20 **2-21**

a. HBr (aq, 2 equiv), DMSO 16 %
b. BDMS (1 equiv), DMSO 9 %
c. BDMS (1 equiv), DMSO, H_2O 18 %

Scheme 2.7. Relevant precedent[a] and comparison of HBr with BDMS.[b]

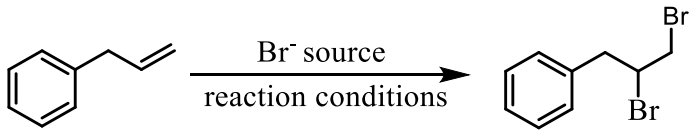
We compared directly the reactivity of HBr in DMSO to BDMS **2-18** in DMSO using cyclohexene **2-20** as the substrate (Scheme 2.7b). In neither case was precipitation of sulfonium salts observed but rather exclusive conversion to *trans*-1,2-dibromocyclohexane **2-21** in low yields after 12 hours at room temperature. Upon addition of water to the BDMS/DMSO reaction (intended to mimic the water present in our HBr/DMSO system) the rates of the two

processes were similar with 18 % and 16 % yields respectively after 12 hours at room temperature. These observations lend support to the notion that the active brominating species in the HBr/DMSO process is BDMS.

Section 2.2.2. Reaction Optimization

We conducted a brief optimization of this reaction (Table 2.2.). The yield of (2,3-dibromopropyl)benzene **2-16** from allylbenzene **2-15** was improved to 57 % and 96 % by increasing the amount of HBr to 5 and 10 equivalents respectively and extending reaction time to 24 hours (entries 2 and 3). When the reaction temperature was warmed to 65 °C, a yield of 86 % was observed in just 12 hours with 5 equiv. of HBr (entry 4). A screen of co-solvents identified the two solvent mixture of DMSO and $CHCl_3$ (1:1) as optimal giving nearly quantitative conversion, and 80 % isolated yield, of the desired product after 12 hours at 65 °C.

Table 2.2. Reaction Optimization[a]



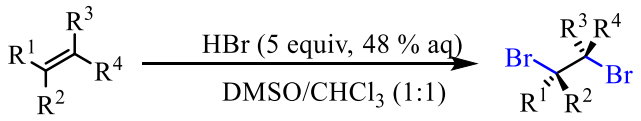
2-15 **2-16**

Entry	Solvent	HBr (equiv)	Temperature (°C)	Time (h)	Yield (%)[b]
1	DMSO	2	rt	24	13
2	DMSO	5	rt	24	57
3	DMSO	10	rt	24	96
4	DMSO	5	65	12	86
5[c]	DMSO/$CHCl_3$	5	65	12	98

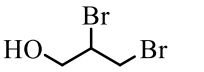
[a] Reaction conditions: Substrate (0.5 mmol), DMSO (0.5 mL), 'Br$^-$ source' (2-10 equiv); reaction workup with Et_2O/H_2O. [b] ^1H NMR yield with CH_2Br_2 as an internal standard. [c] DMSO (0.5 mL), $CHCl_3$ (0.5 mL).

Section 2.2.3. Substrate Scope

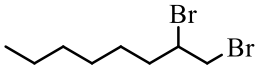
The substrate scope of this bromination was evaluated with 10 terminal olefins and 8 polysubstituted olefins (Scheme 2.8).



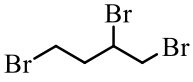
2-9 **2-10**



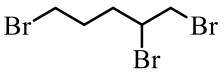
2-22: 90% yield[1]
(rt, 24 h)



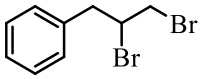
2-23: 86% yield[1]
(65 °C, 12 h)



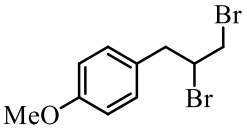
2-24: 61% yield[1]
(65 °C, 24 h)



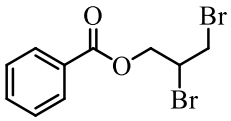
2-25: 74% yield[1]
(65 °C, 24 h)



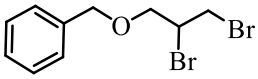
2-16: 80% yield[1]
(65 °C, 12 h)



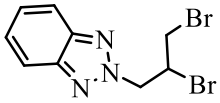
2-26: 90% yield[1]
(65 °C, 12 h)



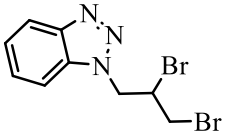
2-27: 62% yield[1]
(65 °C, 6 h)



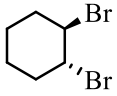
2-28: 65% yield[1]
(65 °C, 5 h)



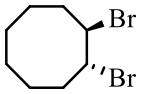
2-29: 70% yield[1]
(65 °C, 24 h)



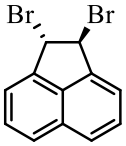
2-30: 81% yield[1]
(65 °C, 24 h)



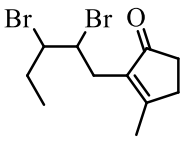
2-21: 72% yield[1]
(rt, 12 h)



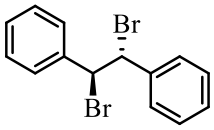
2-31: 99% yield[1]
(rt, 24 h)



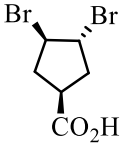
2-32: 67% yield[1]
(35 °C, 32 h)



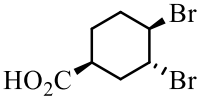
2-33: 50% yield[1]
(rt, 24 h)



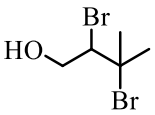
2-34: 87% yield[1]
(65 °C, 40 h)



2-35: 61% yield[1]
(65 °C, 12 h)



2-36: 74% yield[1]
(65 °C, 12 h)



2-37: 66% yield[1]
(65 °C, 2 h)

[1]Isolated yield after chromatography.

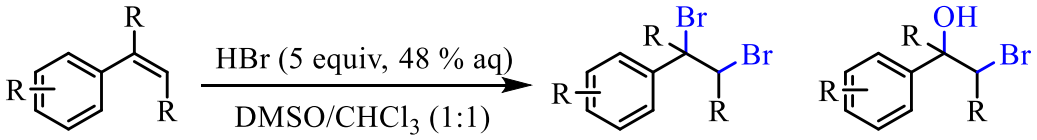
Scheme 2.8: Substrate Scope

Allyl alcohol was converted to 2,3-dibromopropan-1-ol **2-22** in 90 % yield in 24 h at room temperature. 1-Octene was brominated in 12 h at 65 °C to yield the corresponding dibromooctane **2-23** in 86 % isolated yield. Allylbenzene and *p*-(methoxyallyl)benzene were readily brominated to give bromoalkanes **2-16** and **2-26** in 80 % and 90 % yield, respectively.

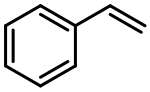
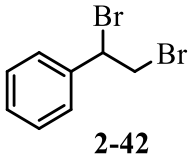
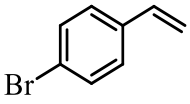
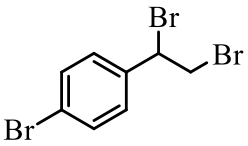
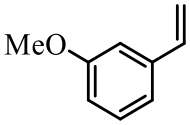
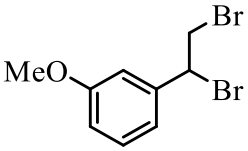
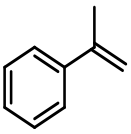
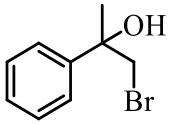
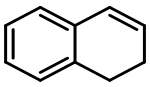
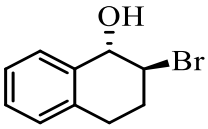
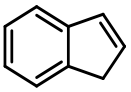
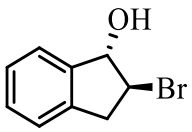
Reaction of allyl benzoate gave dibromide **2-27** in 6 h with 62 % isolated yield. Longer reaction times resulted in considerable hydrolysis of the ester. *N*-Allyl benzotriazoles gave compounds **2-29** and **2-30** in good yields. For cyclohexene, the reaction temperature was lowered to room temperature to avoid loss the volatile substrate. The reaction was completed in 12 h giving trans-1,2-dibromocyclohexane **2-21** in 72 % isolated yield. Conversion of cyclooctene was also completed at room temperature in 24 h to give **2-31** in 99 % yield. The temperature was also lowered for two other substrates, acenaphthylene and *cis*-jasmone, to minimize the formation of unidentified side products. In these cases, the desired dibromoalkanes **2-32**and **2-33** were obtained in 67 % and 50 % yield after 32 and 24 h, respectively. A reaction time of 40 h at 65 °C was required for complete conversion of *trans*-stilbene to the corresponding product **2-34**, which was obtained in 87 % yield. Carboxylic acids are well tolerated under these reaction conditions with compounds **2-35** and **2-36** obtained in good yields. Compound **2-36** was isolated as a single diastereomer in 74 % yield. Finally, 3-methylbut-2-en-1-ol reacted rapidly to give the dibromo alcohol **2-37** in 66 % yield. We next applied this reaction to a series of styrene derivatives (Table 2.3). Styrene **2-41**, *p*-bromostyrene **2-43**, and *m*-methoxystyrene **2-45** behaved as expected giving the corresponding dibromides in good yields. However, in the case of α-methylstyrene **2-47**, we observed nearly exclusive formation of the *trans*-bromohydrin **2-48** which was isolated in 93 % yield. Similarly 1,2-dihydronaphthalene **2-49** and indene **2-51** afforded *trans*-bromohydrins **2-50** and **2-52**

respectively in good isolated yields. In these two cases a small amount of dibromination was also observed via crude ^{1}H NMR. A control experiment was conducted to determine the potential that bromohydrins **2-39**, **2-41**, and **2-43** are formed via initial bromination and subsequent substitution of –Br with –OH. We subjected 1,2-dibromoindane (prepared via standard Br_2-based bromination of indene) to our HBr/DMSO reaction conditions. We observed complete conversion of 1,2-dibromoindane to bromohydrin **2-43** in 12 hours. Thus it is possible that substrates **2-48**, **2-50**, and **2-52** undergo initial dibromination before conversion to bromohydrins. The isolated bromohydrins have a *trans* relationship between hydroxyl and bromide groups. Therefore, if a substitution of –Br to –OH occurs, the observed stereochemistry indicates an S_N1 process whereby a carbocation intermediate reacts with water at its less sterically hindered face.

Table 2.3. Reaction of styrene derivatives.[a]

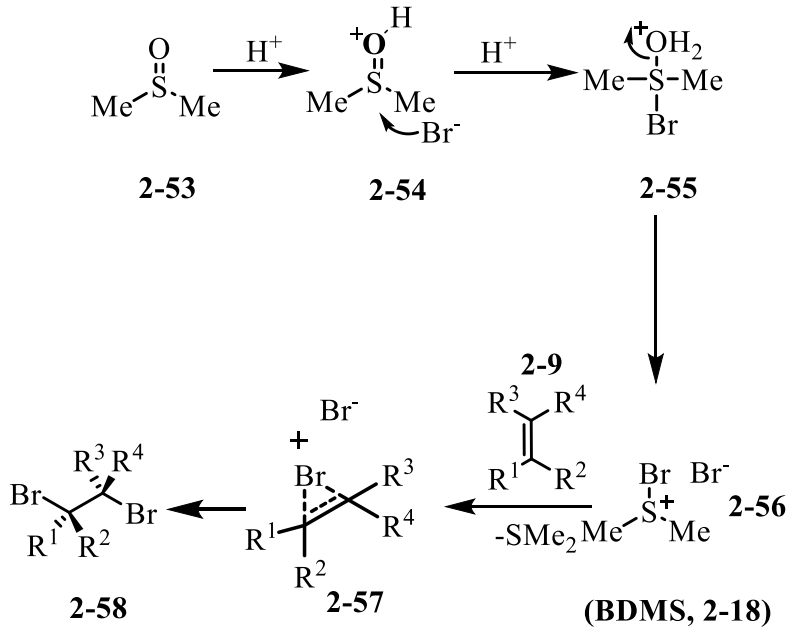


2-38 **2-39** **2-40**

Entry	Substrate	Major Product	Time (h)	Temp (°C)	Yield (%)[b]
1	 **2-41**	 **2-42**	12	65	61
2	 **2-43**	 **2-44**	24	65	65
3	 **2-45**	 **2-46**	12	65	61
4	 **2-47**	 **2-48**	3	65	93
5	 **2-49**	 **2-50**	12	65	72
6	 **2-51**	 **2-52**	12	65	65

[a] Reaction conditions: Substrate (0.5 mmol), HBr (5 equiv.), DMSO (0.5 mL); reaction workup with Et_2O/H_2O. [b] Isolated yield.

Scheme 2.9. below offers the proposed mechanism for the conversion of DMSO to BDMS **2-18** followed by subsequent olefin bromination.



Scheme 2.9. Mechanism of dibromination of olefins with HBr and DMSO

This methodology was not suitable for the bromination of α,β-unsaturated carbonyl derivatives. We also attempted to replace HBr with HCl for an analogous chlorination reaction without success. We must report that our work directly contradicts Yusobov et al. who have reported the oxidation of olefins to 1,2-diketones under identical conditions.[74]

Section 2.3. Summary

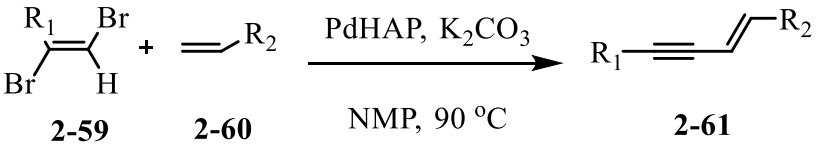
In summary, we have described a process for dibromination of olefins alkanes via oxidative bromination using aqueous hydrobromic acid paired with dimethyl sulfoxide, which serves as the oxidant as well as co-solvent. This methodology offers a simple, inexpensive, and mild alternative to the use of Br_2 or other more resource-intensive strategies. The substrate

scope includes 21 olefins brominated in good to excellent yields. Three of six styrene derivatives yielded bromohydrins under the reaction conditions.

Section 2.4. Incomplete Side Project Inspired by this Work

Section 2.4.1 Bromination of alkynes with HBr and DMSO

We have found that same reaction conditions can be applied to alkynes to yield 1,2-dibromoalkenes in a stereoselective fashion. 1,2-dibromoalkenes have been used as coupling partners in Heck reactions.[75] They have also been shown to be coupling partners with conjugated carboxylic esters under Pd catalysis to yield (*E*)-2-alkene-4-ynoate system (Scheme 2.10).[76]



2-59 **2-60** **2-61**

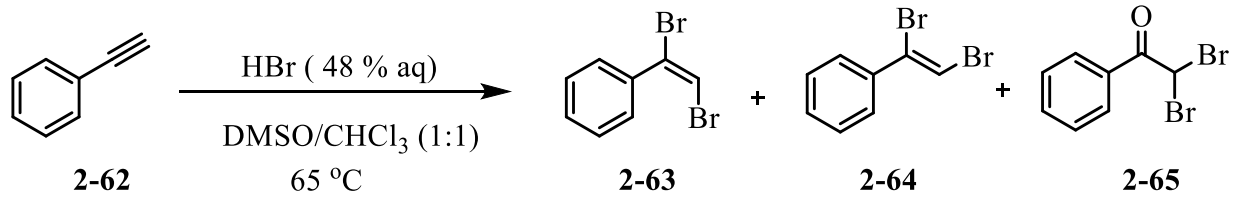
PdHAP: Hydroxyapatite-supported palladium

Scheme 2.10. Palladium catalyzed coupling of vicinal-dibromoalkanes with conjugated carboxylic esters.

This project remains under investigation in the lab and our observations to date are presented herein. We began by treating phenylacetylene **2-62** with our optimal condition for bromination of olefins (5 equiv. HBr in 1:1 DMSO/$CHCl_3$). We observed that in 16 h at 65 °C, we were able to isolate 48 % yield of (*E*)-1-(1,2-dibromovinyl)benzene **2-63**. However, 38 % of 2,2-dibromo-1-phenylethanone **2-65** was also formed. Following the initial success, we decided to optimize the reaction by varying the amount of HBr and DMSO, and time (Table 2.4). We found reaction went to 100 % conversion in 4 hours with 2.5 equiv. HBr and 0.5 mL DMSO, giving 83:17 ^{1}H NMR ratio of **2-63** to **2-65** (entry 2). Increasing the amount of HBr to

10 equiv. gave 90% of *E*-isomer **2-63** with respect to *Z*-isomer **2-64** and the 2,2-dibromo-1-phenylethanone **2-65** (entry 3).

Table 2.4. Initial optimization of bromination of alkynes [a]

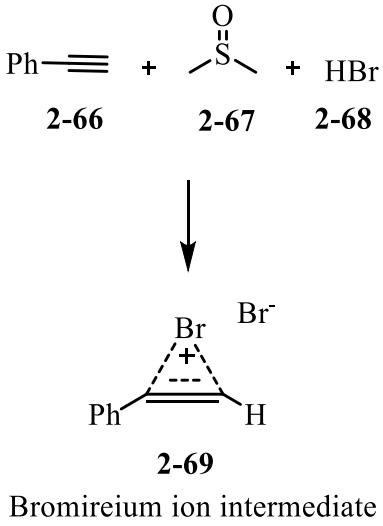


2-62 **2-63** **2-64** **2-65**

entry	HBr (equiv.)	DMSO (mL)	time (h)	ratio of **2-63** : **2-64** : **2-65** (^{1}H NMR)
1.	5	1	16	48[b]: 0: 38[b]
2.	2.5	0.5	4	83:0:17
3.	10	1	5	90: 6: 4
4.	10	1	8	91: 9: 0

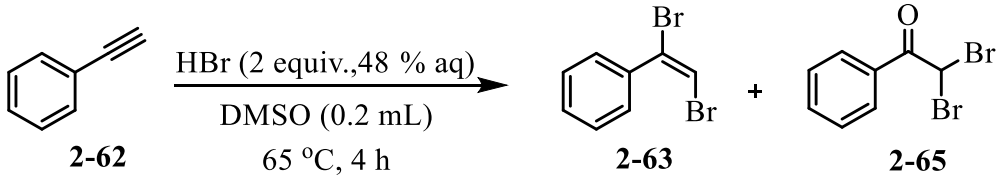
[a] Reaction conditions: Substrate (1 mmol), DMSO (1 mL); reaction workup with Et_2O/H_2O.
[b] Isolated yield

Formation of 2,2-dibromo-1-phenylethanone **2-65** could be attributed to attack of water present in aqueous HBr onto the three membered cyclic bromirenium ion **2-69** (Scheme 2.11). No **2-65** was formed when the reaction was heated at 65 °C for 8 hours with 10 equiv. HBr (entry 4). In this case we observed 91:9 ratio of *E*-isomer to corresponding *Z*-isomer **2-64**.



Scheme 2.11. Generation of bromirenium ion from phenylacetylene and HBr/DMSO

Table 2.5. Solvent Screening [a]



entry	solvent (0.5 mL)	ratio of **2-62** : **2-63** : **2-65** (^{1}H NMR)
1.	THF	10: 82: 8
2.	EtOAc	0: 90: 10
3.	MeOH	0: 56: 44
4.	Toluene	32: 51: 17
5.	DCM	0: 88: 12
6.	1,4-dioxane	0: 90: 10
7.	CH_3CN	0: 85: 15

[a] Reaction conditions: Substrate (1 mmol), HBr (2 equiv.), DMSO (0.2 mL); reaction workup with Et_2O/H_2O.

Table 2.5 shows a screen of co-solvents was performed in order to evaluate the effect of solvents on the chemoselectivity of the reaction with 2 equiv. HBr and in 0.2 mL DMSO. Bromination of phenylacetylene in tetrahydrofuran did not go to completion in 4 hours (entry 1). Reaction in methanol afforded ~ 1:1 mixture of compound **2-63** and **2-65** (entry 3). Ethyl acetate and 1,4-dioxane gave 90:10 ratio of **2-63** to **2-65** in 4 hours (entries 2 and 6 respectively).

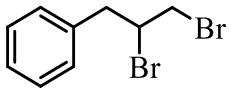
Further optimization of reaction condition is required for the stereoselective formation of *E* and *Z* isomer followed by exploration of substrate scope. This work will be continued by an undergraduate member of Dr. Magolan's lab.

Section 2.5 Experimental

General Considerations: Unless otherwise noted, commercially available reagents and solvents were used without further purification. Infrared spectra were obtained on a Thermo Scientific Nicolet 380 FT-IR spectrometer as thin films on ZnSe disks and peaks are reported in cm^{-1}. ^{1}H and ^{13}C NMR experiments were performed on a Bruker AVANCE 500 MHz instrument and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. MALDI-HRMS of compounds were recorded on a Q-TOF mass spectrometer using 2,5-dihydroxybenzoic acid as a matrix and mixture of polyethylene glycol (PEG 600) and (PEG 1000) as internal calibration standards. Elemental analyses were obtained on a CE0440 elemental analyzer (EAI Exeter Analytical). Reaction progress was monitored by thin-layer chromatography (TLC, EMD Chemicals Inc, Silica Gel 60 F254), visualized under UV light, and plates were developed using *p*-anisaldehyde or potassium permanganate stains. Flash

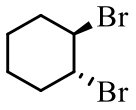
chromatography was performed using silica gel (Sorbent Technologies, particle size 40-63 µm). Melting points were determined using a Mel-Temp II apparatus and are uncorrected.

General Procedure for Dibromination Reaction: A solution of HBr (48 % aq., 5 equiv.) in DMSO (1 mL per mmol of substrate) is added to a reaction vial containing a magnetic stir bar and the alkene substrate (0.5 - 1.0 mmol) in $CHCl_3$ (1 mL per mmol of substrate). The reaction vial is capped and stirred at the specified temperature (rt or 65 °C) until complete disappearance of starting material is observed by TLC or ^{1}H NMR (TLC plates visualized using *p*-anisaldehyde or potassium permanganate stains). The reaction is transferred to a separatory funnel containing water and extracted with ether (3 x 30 mL). The combined organic extracts are dried over $MgSO_4$, and solvent removed *in vacuo.* The residue is purified by flash column chromatography on silica gel (gradient elution with EtOAc and hexanes). *Note: Flash chromatography effectively removes all trace DMSO that may remain after workup.*



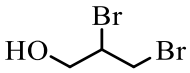
2-16

(2,3-Dibromopropyl) benzene (2-16): The standard procedure was used with allylbenzene **2-15** (132.5 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 12 hours of stirring at 65 ^{o}C, the reaction was worked up and purified as described above to yield compound **2-16** as oil (0.223 g, 80 % yield). R_F = 0.87 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.27 (m, 5H), 4.41 – 4.33 (m, 1H), 3.83 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.64 (dd, *J* = 10.4, 8.9 Hz, 1H), 3.51 (dd, *J* = 14.5, 4.8 Hz, 1H), 3.14 (dd, *J* = 14.5, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.9, 129.5, 128.5, 127.2, 52.4, 42.0, 36.0. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[77]



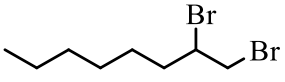
2-21

***trans*-1,2-Dibromocyclohexane (2-21):** The standard procedure was used with cyclohexene **2-20** (101 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 12 hours of stirring at room temperature, the reaction was worked up and purified as described above to yield compound **2-21** as a colorless liquid product (175 mg, 72 % yield). R_F = NA; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.45 (s, 2H), 2.57 – 2.31 (m, 2H), 1.96 – 1.74 (m, 4H), 1.57 – 1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.2, 32.1, 22.4. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[22]



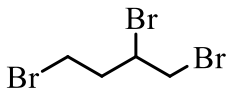
2-22

2,3-Dibromopropan-1-ol (2-22): The standard procedure was used with allyl alcohol (68 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). The reaction was stirred for 24 hours at room temperature. After workup and purification above compound **2-22** was obtained as a colorless liquid (196 mg, 90 % yield). R_F = 0.62 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.39 – 4.23 (m, 1H), 4.02 (d, *J* = 3.9 Hz, 2H), 3.88 – 3.74 (m, 2H), 1.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 64.2, 53.6, 31.5. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[78]



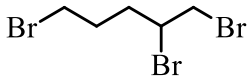
2-23

1,2-Dibromooctane (2-23): The standard procedure was used with 1-octene (78.5 µL, 0.5 mmol), HBr (48 % aq., 0.28 mL, 2.5 mmol), and DMSO (0.5 mL). After 12 hours of stirring at 65 °C, the reaction was worked up and purified as described above to yield compound **2-23** as a colorless liquid product (116.2 mg, 86 % yield); R_F = 0.65 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.25 – 4.09 (m, 1H), 3.85 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.63 (t, *J* = 10.0 Hz, 1H), 2.20 – 2.08 (m, 1H), 1.79 (dddd, *J* = 14.6, 10.1, 9.0, 4.6 Hz, 1H), 1.56 (dddd, *J* = 14.6, 13.2, 7.1, 3.7 Hz, 1H), 1.49 – 1.20 (m, 7H), 1.06 – 0.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.2, 36.4, 36.1, 31.6, 28.5, 26.7, 22.5, 14.0. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[20]



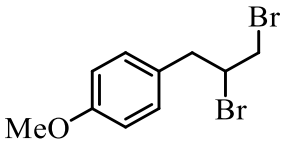
2-24

1,2,4-Tribromobutane (2-24): The standard procedure was used with 4-bromobut-1-ene (102 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 24 hours of stirring at 65 °C, the reaction was worked up and purified as described above to yield compound **2-24** as clear colorless oil (179 mg, 61 % yield); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.38 (tdd, *J* = 9.8, 4.3, 2.8 Hz, 1H), 3.90 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.72 – 3.51 (m, 3H), 2.68 (dddd, *J* = 15.5, 9.3, 6.4, 2.8 Hz, 1H), 2.26 (dddd, *J* = 15.5, 10.0, 5.5, 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 50.3, 39.2, 35.9, 30.4; IR (cm^{-1}): 2923.3, 1462.9, 736.8, 475.43; Elemental analysis: ($C_4H_7Br_3$, 294.81) Calcd: C, 16.3 %; H, 2.39 %. Found: C, 16.73 %; H, 2.07 %.



2-25

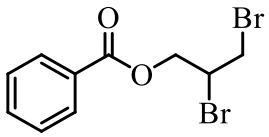
1,2,5-Tribromopentane (2-25): The standard procedure was used with 5-bromopent-1-ene (118.5 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 24 hours of stirring at 65°C, the reaction was worked up and purified as described above to yield compound **2-25** as oil (227 mg, 74 % yield); R_F = 0.66 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.18 (tdd, *J* = 9.8, 4.4, 3.0 Hz, 1H), 3.87 (dd, *J* = 10.3, 4.4 Hz, 1H), 3.63 (t, *J* = 10.1 Hz, 1H), 3.51 – 3.40 (m, 2H), 2.43 – 2.33 (m, 1H), 2.24 – 2.13 (m, 1H), 2.07 – 1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.43, 35.82, 34.71, 32.27, 30.02; IR (cm^{-1}): 2959.7, 1257.0, 1141.0, 563.8; Elemental analysis: ($C_5H_9Br_3$, 308.84) Calcd: C, 19.45 %; H, 2.94 %. Found: C, 19.71 %; H, 2.84 %.



2-26

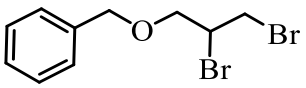
1-(2,3-Dibromopropyl)-4-methoxybenzene (2-26): The standard procedure was used with 1-allyl-4-methoxybenzene (153.4 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 12 hours of stirring at 65 °C, the reaction was worked up and purified as described above to yield compound **2-26** as colorless oil (276.6 mg, 90 % yield); R_F = 0.65 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 – 7.15 (m, 2H), 6.92 – 6.83 (m, 2H), 4.33 (dddd, *J* = 9.0, 7.4, 4.9, 4.2 Hz, 1H), 3.84 – 3.78 (m, 3H), 3.81 (s, 3H), 3.61 (dd, *J* = 10.5, 8.9 Hz, 1H), 3.42 (dd, *J* = 14.6, 4.9 Hz, 1H), 3.10 (dd, *J* = 14.7, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.8, 130.6, 128.8, 113.9, 55.2, 52.9, 41.1, 35.9; IR(cm^{-1}): 2929.8,

2833.6, 1610.4, 1509.9, 1463.1, 1430.4, 1242.7, 1176.3, 1031.6, 806.2, 594.5; Elemental analysis: ($C_{10}H_{12}Br_2O$, 308.01) Calcd: C, 38.99 %; H, 3.93 %. Found: C, 39.21 %; H, 3.84 %.



2-27

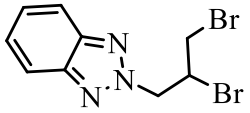
2,3-Dibromopropyl benzoate (2-27): The standard procedure was used with allyl benzoate (154 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 6 hours of stirring at 65 °C, the reaction was worked up and purified as described above to yield compound **2-27** as clear colorless oil (182 mg, 62 % yield); R_F = 0.35 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 – 8.04 (m, 2H), 7.63 – 7.56 (m, 1H), 7.51 – 7.45 (m, 2H), 4.77 (dd, *J* = 12.2, 4.5 Hz, 1H), 4.72 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.47 (ddt, *J* = 9.2, 5.3, 4.6 Hz, 1H), 3.88 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.83 (dd, *J* = 10.7, 9.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.8, 133.4, 129.8, 129.5, 128.5, 65.60, 47.0, 32.1; IR (cm^{-1}) 2950, 1720.6, 1602.1, 1451.92, 1377.2, 1267.7, 725.9, 707.04; APCI-HRMS Calcd for $C_{10}H_{11}Br_2O_2$ $(M+H)^+$: 320.9126. Found: 320.9115.



2-28

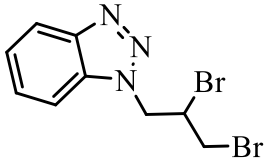
((2,3-Dibromopropoxy)methyl)benzene (2-28): The standard procedure was used with ((allyloxy)methyl)benzene (77.6 µL, 0.5 mmol), HBr (48 % aq., 0.28 mL, 2.5 mmol), and DMSO (0.5 mL). After 5 hours of stirring at 65 °C, the reaction was worked up and purified

as described above to yield compound **2-28** as clear colorless oil (100 mg, 65 % yield); R_F = 0.69 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, *J* = 4.8 Hz, 5H), 4.66 – 4.58 (m, 2H), 4.27 (dd, *J* = 8.3, 4.9 Hz, 1H), 3.92 – 3.79 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.5, 128.5, 127.9, 127.7, 73.5, 71.1, 49.1, 33.1; IR (cm^{-1}) 3028.9, 2859.7, 1495.3, 1452.4, 1360.0, 1072.6, 695.4, 573.9. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[79]



2-29

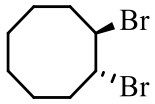
2-(2,3-Dibromopropyl)-2*H*-benzotriazole (2-29): The standard procedure was used with 2-allyl-2*H*-benzotriazole (125 mg, 0.79 mmol), HBr (48 % aq., 0.44 mL, 3.95 mmol), and DMSO (1 mL). After 24 hours of stirring at 65 ºC, the reaction was worked up and purified as described above to yield compound **2-29** as white solid (175 mg, 70 % yield); mp = 81-83 ºC; R_F = 0.79 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 – 7.79 (m, 2H), 7.41 (dd, *J* = 6.6, 3.1 Hz, 2H), 5.34 (dd, *J* = 14.1, 5.4 Hz, 1H), 5.13 (dd, *J* = 14.1, 7.1 Hz, 1H), 4.87 (tt, *J* = 7.3, 5.4 Hz, 1H), 3.99 – 3.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 126.9, 118.2, 59.9, 47.0, 33.4; IR (cm^{-1}): 3041.2, 2922.59, 1561.2, 1425.4, 1345.9, 1168.2, 751.2; ESI-HRMS Calcd for $C_9H_9Br_2N_3$ $(M+H)^+$: 317.9243. Found: 317.9243.



2-30

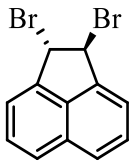
1-(2,3-Dibromopropyl)-1*H*-benzotriazole (2-30): The standard procedure was used with 1-allyl-1*H*-benzotriazole **2-19** (159 mg , 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and

DMSO (1 mL). After 24 hours of stirring at 65 ^{o}C, the reaction was worked up and purified as described above to yield compound **2-30** as white solid. (130 mg, 81 % yield); R_F = 0.85 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 – 8.07 (m, 1H), 7.64 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.41 (ddd, *J* = 8.4, 6.9, 1.0 Hz, 1H), 5.25 (dd, *J* = 14.9, 5.0 Hz, 1H), 5.05 (dd, *J* = 14.9, 6.9 Hz, 1H), 4.76 (dddd, *J* = 8.2, 6.9, 5.1, 4.5 Hz, 1H), 3.89 – 3.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.8, 133.6, 127.9, 124.2, 120.3, 109.4, 51.9, 47.8, 33.5, 29.7; IR (cm^{-1}): 2977.3, 1590.5, 1488.0, 1407.2, 1102.47, 728.77; ESI-HRMS Calcd for $C_9H_9Br_2N_3$ $(M+H)^+$: 317.9241. Found 317.9244.



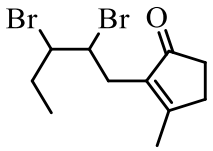
2-31

1,2-Dibromocyclooctane (2-31): The standard procedure was used with cyclooctene (130 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 24 hours of stirring at room temperature, the reaction was worked up and purified as described above to yield compound **2-31** as a colorless liquid product (268 mg, 99 % yield); R_F = 0.81 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.64 – 4.51 (m, 1H), 2.41 (dddd, *J* = 15.8, 8.9, 3.6, 1.3 Hz, 1H), 2.09 (dddd, *J* = 15.7, 7.8, 5.0, 2.7 Hz, 1H), 1.90 – 1.79 (m, 1H), 1.72 – 1.54 (m, 2H), 1.53 – 1.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 61.5, 33.2, 25.9, 25.4. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[80]



2-32

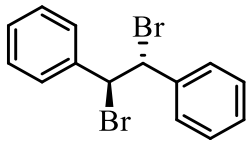
***trans*-1,2-Dibromoacenaphthene (2-32):** The standard procedure was used with acenaphthylene (100 mg, 0.66 mmol), HBr (48 % aq., 0.37 mL, 5 mmol), and DMSO (0.5 mL). After 32 hours of stirring at 35 ºC, the reaction was worked up and purified as described above to yield compound **2-32** as light brown solid (138 mg, 67 % yield); mp = 111-114 ºC; R_F = 0.83 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82 (dd, J = 7.5, 1.4 Hz, 2H), 7.70 – 7.56 (m, 4H), 6.01 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.5, 134.8, 131.0, 128.8, 125.9, 122.5, 54.9; ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[81]



2-33

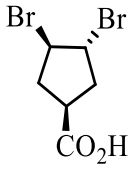
2-(2,3-Dibromobutyl)-3-methylcyclopent-2-enone (2-33): The standard procedure was used with *cis*-jasmone (170 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 24 hours of stirring at room temperature, the reaction was worked up and purified as described above to yield compound **2-33** as clear oil (151 mg, 50 % yield); R_F = 0.72 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.57 (td, *J* = 7.0, 2.3 Hz, 1H), 4.02 (ddd, *J* = 8.0, 5.5, 2.3 Hz, 1H), 2.88 (d, *J* = 7.0 Hz, 2H), 2.61 – 2.51 (m, 2H), 2.44 – 2.36 (m, 2H), 2.15 (s, 3H), 2.05 – 1.94 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.2, 173.7, 136.5, 62.0, 56.9, 34.2, 32.0, 32.0, 30.6, 17.8, 12.4; IR (cm^{-1}): 2967.6, 2912.6,

1690.9, 1644.6, 1432.9, 1382.5, 545.91.512.9; Elemental analysis: ($C_{11}H_{16}Br_2O$, 324.06) Calcd: C, 40.77 %; H, 4.98 %. Found: C, 40.95 %; H, 4.91 %.



2-34

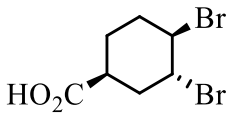
***meso*-1,2-Dibromo-1,2-diphenylethane (2-34):** The standard procedure was used with *trans*-stilbene (180 mg, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 40 hours of stirring at 65 °C, the reaction was worked up and purified as described above to yield compound **2-34** as white solid (295 mg, 87 % yield); mp = 236-238 °C; R_F = 0.78 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 – 7.49 (m, 4H), 7.45 – 7.34 (m, 6H), 5.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.0, 129.0, 128.8, 127.9, 56.1; Elemental analysis: ($C_{14}H_{12}Br_2$, 340.06) Calcd: C, 49.45 %; H, 3.56 %. Found: C, 49.7 %; H, 3.37 %. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[48]



2-35

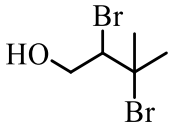
3,4-Dibromocyclopentanecarboxylic acid (2-35): The standard procedure was used with cyclopent-3-enecarboxylic acid (103 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 12 hours of stirring at 65 °C, the reaction was worked up and purified as described above to yield compound **2-35** as white powder (167 mg, 61 % yield); mp = 111-113

ºC; R_F = 0.51 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.63 (ddd, *J* = 4.8, 2.1, 1.2 Hz, 1H), 4.55 (dt, *J* = 6.2, 1.8 Hz, 1H), 3.45 – 3.33 (m, 1H), 3.11 – 2.97 (m, 2H), 2.68 – 2.57 (m, 1H), 2.49 (ddt, *J* = 15.0, 8.6, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.0, 56.2, 54.3, 40.5, 37.2, 37.1; IR (cm^{-1}) 2920.93, 1686.83, 1315.21, 914.17, 535.45; Elemental Analysis: ($C_6H_8Br_2O_2$, 271.94); Calcd: C, 26.50 %; H, 2.97 %; Found: C, 26.31 %; H, 2.88 %.



2-36

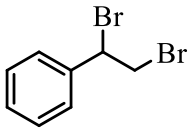
(1S,3R,4R)-3,4-dibromocyclohexanecarboxylic acid (2-36): The standard procedure was used with cyclohex-3-enecarboxylic acid (117 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 12 hours of stirring at 65 °C, the reaction was worked up and purified as described above to yield compound **2-36** as pale yellow solid (211.7 mg, 74 % yield); mp = 80-82 ºC; R_F = 0.59 (Hexanes/EtOAc 70:30 v/v); δ 4.70 (dd, 1H), 4.60 (dd, J = 3.3 Hz, 1H), 3.01 – 2.92 (m, 1H), 2.67 – 2.59 (m, 1H), 2.57 – 2.47 (m, 1H), 2.28 – 2.20 (m, 1H), 2.08 – 1.93 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.2, 51.9, 51.8, 37.4, 30.7, 28.2, 23.0; IR (cm^{-1}) 2929.89, 2605.09, 1701.33, 1451.40, 1283.43, 1026.09, 928.75, 889.46, 686.92, 541.99. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[82]



2-37

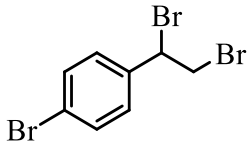
2,3-Dibromo-3-methylbutan-1-ol (2-37): The standard procedure was used with 3-methylbut-2-en-1-ol **(**102 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL). After 2 hours of stirring at 65 ºC, the reaction was worked up and purified as described

above to yield compound **2-37** as white crystals (162 mg, 66 % yield); mp = 38-39 ºC; R_F = 0.59 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.42 (dd, J = 8.2, 2.9 Hz, 1 H), 4.33 (d, *J* = 12.6, 2.9 Hz, 1 H), 3.98 (dd, *J* = 8.2, 12.5 Hz, 1 H), 1.98 (s, 3 H), 1.84 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 69.0, 66.1, 64.8, 35.5, 29.7; IR (cm^{-1}) 3243.76, 2972.09, 2953.23, 1376.92, 1093.64, 1067.70, 975.03, 548.19; Elemental analysis: ($C_5H_{10}Br_2O$, 245.94) Calcd: C, 24.42 %; H, 4.1 %. Found: C, 24.81 %; H, 4.01 %.



2-42

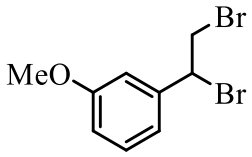
1,2-(Dibromoethyl)-benzene (2-42): The standard procedure was used with styrene **2-41** (57.5 µL, 0.5 mmol), HBr (48 % aq., 0.28 mL, 2.5 mmol), and DMSO (0.5 mL). After 12 hours of stirring at 65 ºC, the reaction was worked up and purified as described above to yield compound **2-42** as white solid (80 mg, 61 % yield); mp = 71-73 ºC; R_F = 0..79 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 – 7.32 (m, 3H), 5.15 (dd, *J* = 10.6, 5.4 Hz, 1H), 4.11 – 3.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.7, 129.2, 128.9, 127.7, 50.9, 35.0. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[54]



2-44

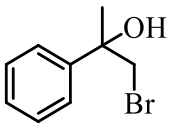
1-Bromo-4-(1,2-bromoethyl)benzene (2-44): The standard procedure was used with 4-bromostyene **2-43** (131 µL, 1.0 mmol), HBr (48 % aq., 0.56 mL, 5 mmol), and DMSO (1 mL).

After 24 hours of stirring at 65 ºC, the reaction was worked up and purified as described above to yield compound **2-44** as white solid (222 mg, 65 % yield); mp = 56-58 ºC; R_F = 0.82 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 – 7.50 (m, 2H), 7.30 – 7.26 (m, 2H), 5.09 (dd, *J* = 11.0, 5.1 Hz, 1H), 4.06 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.96 (dd, *J* = 11.0, 10.3 Hz, 1H);^{13}C NMR ($CDCl_3$, 500 MHz) δ 137.7, 132.1, 129.3, 123.2, 49.6, 34.6. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[83]



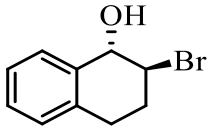
2-46

1-(1,3-Dibromoethyl)-3-methoxybenzene (2-46): The standard procedure was used with 3-methoxystyene **2-45** (69.4 µL, 0.5 mmol), HBr (48 % aq., 0.28 mL, 2.5 mmol), and DMSO (0.5 mL). After 12 hours of stirring at 65 ºC, the reaction was worked up and purified as described above to yield compound **2-46** as white solid (90 mg, 61 % yield); mp = 64-66 ºC; R_F = 0.61 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, *J* = 7.9 Hz, 1H), 6.99 (ddd, *J* = 7.8, 1.6, 0.8 Hz, 1H), 6.94 (t, *J* = 2.1 Hz, 1H), 6.88 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 5.11 (dd, *J* = 10.5, 5.4 Hz, 1H), 4.11 – 3.93 (m, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 140.1, 129.9, 119.9, 114.6, 113.5, 55.3, 50.8, 35.0; IR (cm^{-1}): 2917.1, 2833.9, 1600.22, 1490.4, 1462.29, 1434.1, 1047.0, 698.3; Elemental analysis: ($C_9H_{10}Br_2O$, 293.99) Calcd: C, 36.77 %; H, 3.43 %. Found: C, 36.44 %; H, 3.45 %.



2-48

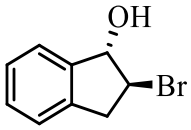
1-Bromo-2-phenylpropan-2-ol (2-48): The standard procedure was used with α-methylstyrene **2-47** (65 µL, 0.5 mmol), HBr (48 % aq., 0.28 mL, 2.5 mmol), and DMSO (0.5 mL). After 3 hours of stirring at 65 ºC, the reaction was worked up and purified as described above to yield compound **2-48** as colorless oil (100 mg, 93 % yield); R_F = 0.76 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 – 7.44 (m, 2H), 7.41 – 7.35 (m, 2H), 7.33 – 7.27 (m, 1H), 3.82 – 3.67 (m, 1H), 2.53 (s, 1H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.2, 128.4, 127.5, 124.9, 73.1, 46.3, 28.1; IR (cm^{-1}) 3437.57, 2975.72, 1492.64, 1445.88, 1373.48, 1064.98, 696.85. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[84]



2-50

***trans*-2-Bromo-1,2,3,4-tetrahydronaphthalen-1-ol (2-50):** The standard procedure was used with 1,2-dihydronaphthalene **2-49** (65.3 µL, 0.5 mmol), HBr (48 % aq., 0.28 mL, 2.5 mmol), and DMSO (0.5 mL). After 12 hours of stirring at 65 ºC, the reaction was worked up and purified as described above to yield compound **2-50** as white powder (82 mg, 72 % yield); mp = 108-110 ºC; R_F = 0.5 (Hexanes/EtOAc 90:10 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 – 7.49 (m, 1H), 7.27 – 7.20 (m, 2H), 7.15 – 7.08 (m, 1H), 4.91 (d, *J* = 7.0 Hz, 1H), 4.37 (ddd, *J* = 10.0, 7.0, 3.2 Hz, 1H), 3.04 – 2.87 (m, 3H), 2.51 (m, 2H), 2.29 (dddd, *J* = 13.7, 9.7, 8.4, 6.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.4, 135.0, 128.5, 128.03, 126.7, 74.2, 56.2, 29.8, 28.1. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[85]



2-52

***trans*-2-Bromo-1-indanol (2-52):** The standard procedure was used with indene **2-51** (57.8 µL, 0.5 mmol), HBr (48 % aq., 0.28 mL, 2.5 mmol), and DMSO (0.5 mL). After 12 hours of heating at 65 ºC, the reaction was worked up and purified as described above to yield compound **2-52** as white powder (69.3 mg, 65 % yield); mp = 120-122 ºC; R_F = 0.68 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 – 7.40 (m, 1H), 7.31 – 7.28 (m, 2H), 7.25 – 7.21 (m, 1H), 5.32 (d, *J* = 5.8 Hz, 1H), 4.29 (td, *J* = 7.3, 5.8 Hz, 1H), 3.59 (dd, *J* = 16.2, 7.3 Hz, 1H), 3.28 – 3.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.7, 139.7, 129.0, 127.6, 124.6, 124.1, 83.5, 54.5, 40.5; IR (cm^{-1}) 3211.77, 2908.20, 2849.39, 1477.19, 1461.02, 1438.36, 1343.48, 1289.79, 1183.46, 1063.85, 750.17, 729.86. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[36]

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Chapter 3: Discovery of High Iron Nontronite Clay as a Dehydrogenating Reagent

Section 3.1. Introduction

Section 3.1.1. Use of Heterogeneous reagents in the Magolan lab

Dr. Magolan's research lab is broadly engaged in developing chemical methods that reduce the environmental impact of organic chemistry, improve the productivity of synthetic chemists, reduce the burden of labor and associated cost of synthesis. These issues are addressed primarily with a focus on development of synthetic methods using heterogeneous reagents such as clays and aluminas.

The main benefit of heterogeneity stems from removal of catalysts or reagents from reaction products by filtration. Relative to other methods, filtration is an inexpensive, fast, and facile form of product purification. Furthermore, insoluble reagents are typically air stable and easy to weigh and handle. In the case of acids and bases, heterogeneous reagents do not require a quenching step or aqueous workup and thus produce no aqueous waste.[1] In terms of cost reduction and environmental impact, the benefits of heterogeneous catalysis are well documented.[2,3] Industrial scale gas-phase transformations catalyzed by heterogeneous materials are the most cost-efficient and waste-free reactions known.[4-6] One may argue that the benefits of heterogeneity are largely overlooked in routine laboratory-scale synthetic chemistry which is done almost exclusively in solution. Solution phase reactions are advantageous in terms mechanistic elucidation, reactivity, selectivity, and yield, but heterogeneous chemistry can often satisfy these criteria while reducing workload, expense, and environmental impact. These issues have been addressed by several authors. In his recent book, "Green Chemistry and Catalysis", Roger Sheldon attributes the original divide between synthetic chemistry and heterogeneous catalysts to the history of synthesis which developed in

academia and in isolation from the industrially-based science of catalysis.[7] In their 1997 review of reactions on alumina, Kabalka and Pagni state: "…the practice of carrying out reactions in solution may reflect tradition rather than actually being advantageous."[8] Excellent reviews of the subject of heterogeneous synthetic tools have been provided by Evelino Corma,[9-13] James Clark,[1,14,15] Steven Ley,[16-18] and Roger Sheldon.[3,19]

Section 3.1.2. Clays in Organic Chemistry

A clay is a layered crystalline material of very fine particle size (< 2 μm in diameter) composed primarily of silicon and aluminum oxides and often containing varying amounts of other oxides such as magnesium or iron. Clays are mined from various regions all over the world and have a wide range of uses including as reagents and catalysts for chemical reactions. The surface chemistry of many clays is characterized by Lewis and Bronsted acidity.[20] In the early 1930's acid-treated natural clays were used as solid catalysts by the petroleum industry for vapor phase isomerization and cracking of the large paraffin molecules in crude oil. They were subsequently replaced in such applications by synthetic zeolites with improved thermostability under the high-temperature catalytic cracking conditions.[21] In the 1970's clays and clay supported catalysts and reagents became incorporated by organic chemists for various synthetic transformations. The many examples of organic synthetic applications have been summarized in several large reviews on the subject by Nagendrappa,[22] Torok,[23] Varma,[21] Sudalai,[24] and others.[20,25]

The vast majority of clays used by organic chemists are based on the naturally occurring smectite clay, montmorillonite (also known as bentonite). Montmorillonite has an aluminosilicate structure characterized by a 2:1 crystalline sheet with two external tetrahedral

silica layers surrounding an internal octahedral alumina layer giving an overall tetrahedral-octahedral-tetrahedral (TOT) structure. There is a degree of isomorphous substitution of Al^{3+} in octahedral sites by Mg^{2+} and Fe^{2+}/Fe^{3+} resulting in the 2:1 silicate sheets retaining a residual negative charge.[26] Between these sheets is an interlamellar water layer that contains dissolved cations resulting in overall charge balance (Figure 3.1).

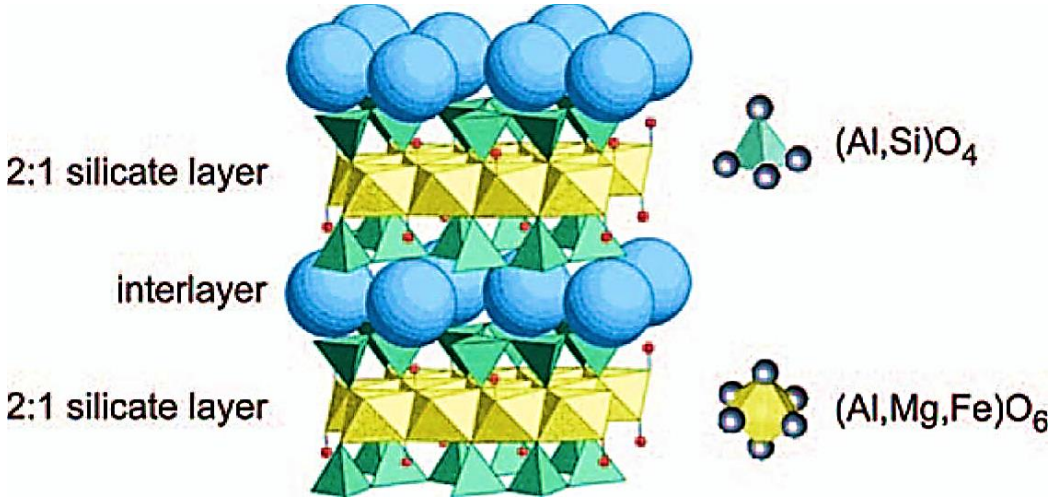
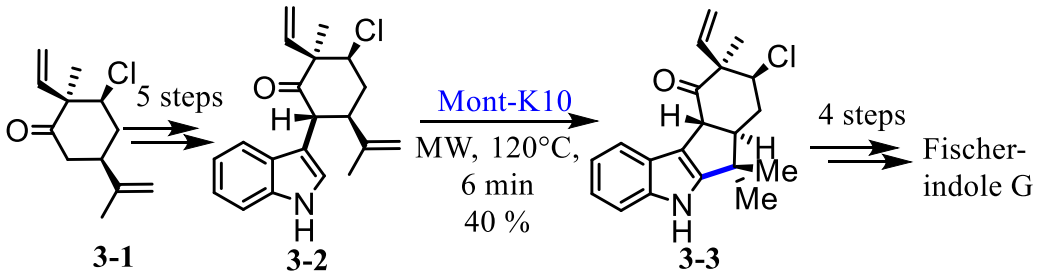


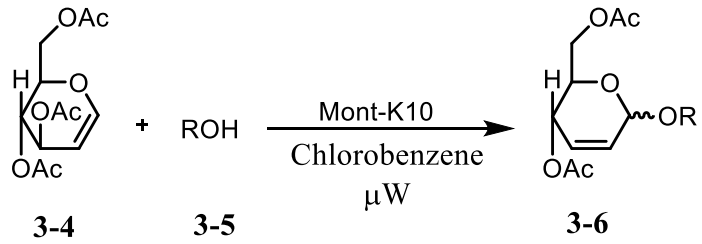
Figure 3.1 Schematic structure of montmorillonite clay.[27] Reproduced with permission from reference 27. Copyright Mineralogical Society of America.

The two most common clays used in organic synthesis are the K10 and KSF montmorillonites (Mont-K10, Mont-KSF). Both are natural montmorillonites modified by acid treatment under unspecified conditions. To our knowledge, the details of acid modification of natural clays (ie. nature of acid, temperature, time, etc.) are considered industrial trade secrets and are unpublished. Mont-K10, KSF and several other montmorillonites are available from many suppliers in large quantities. Several selected examples of the use of these clays in organic reactions are illustrated below.



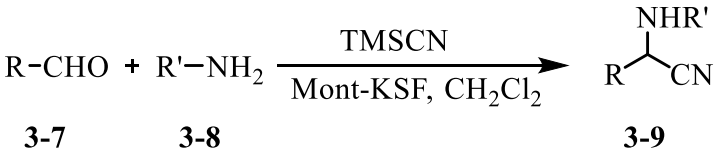
Scheme 3.1. Baran's synthesis of Fischerindole G using Mont-K10.[28]

In 2005, Baran and co-workers presented an efficient synthesis of Fischerindole G in which one of the key steps involved the Friedel-Crafts type cyclization of highly functionalized indole **3-2** to compound **3-3** using Mont-K10 (Scheme 3.1).[28]



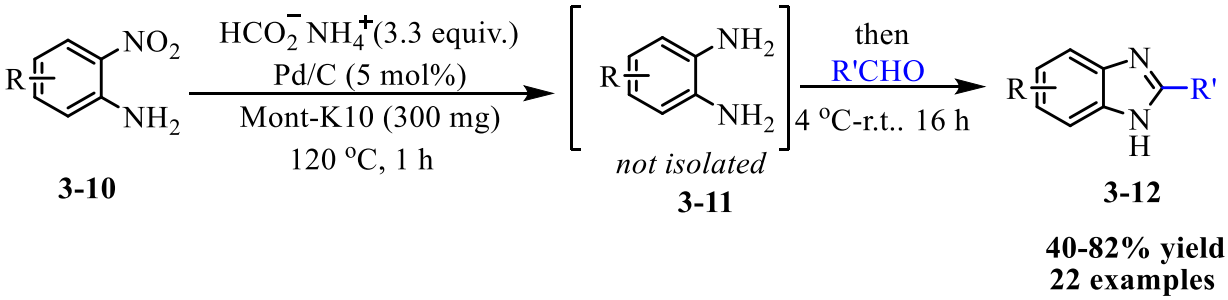
Scheme 3.2. Mont-K10 Catalyzed Ferrier Rearrangement.[29]

Mont-K10 was shown to catalyze the Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-galactal **3-4** in good yields under solvent-free microwave irradiation giving exclusively alkyl and aryl 2,3-dideoxy-d-*threo*-hex-2-enopyranosides **3-6** with very high α-selectivity via rapid glycosidation with allylic rearrangement (Scheme 3.2).[29]



Scheme 3.3. Mont-KSF clay catalyzed one-pot synthesis of α-aminonitriles.[30]

Another efficient application of montmorillonites was described by Yadav and co-workers who achieved a one-pot synthesis of α-aminonitriles via nucleophilic addition of trimethylsilylcyanide to aryl imines catalyzed on the surface of Mont-KSF (Scheme 3.3).[30]



3-10 **3-11** **3-12**

40-82% yield
22 examples

Scheme 3.4. Benzimidazoles synthesis methodology developed in the Magolan lab.[31]

In 2012, Dr. Magolan and co-workers developed an efficient one-pot synthesis of benzimidazoles **3-12** from *ortho*-nitroanilines **3-10** via one-pot transfer hydrogenation-condensation-dehydrogenation using a combination of Mont-K10 and Palladium-on-carbon (Pd/C), which is one of few heterogeneous reagents universally embraced by the synthetic community today (Scheme 3.4).[31] This idea was originally inspired by Torok and co-workers who had previously used Pd/C and montmorillonite clays for one-pot cyclization-dehydrogenation chemistry.[32,33]

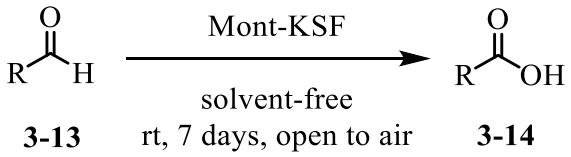
Section 3.1.3. Redox chemistry of structural iron in natural clays.

The project described in this chapter involves Fe^{3+}/Fe^{2+} redox chemistry on clays. To our knowledge this constitutes a new area of investigation in synthetic organic chemistry. Many clays, including montmorillonites contain substantial amounts of Fe^{3+} and Fe^{2+} oxides (typically 1-5 % for Montmorillonites). This clay mineral-bound Fe is relevant in environmental electron transfer reactions. Geologists studying the structure and properties of Fe-containing clay

minerals have investigated the manipulation of the oxidation state of Fe and found that the redox properties of structural Fe are affected by its bonding environment in the clay mineral's lattice which depends on: layer composition, ordering of cations, total Fe-content, and Fe oxidation state.[34] In this geological research, the structural Fe^{3+} in clay minerals has been reduced by sodium sulfide (Na_2S),[35] sodium dithionite ($Na_2S_2O_4$),[36-39] hydrazine, [36,37] tetraphenyl boron,[40,41] and microbial cultures.[42-44]

Oxidation of structural Fe^{2+} in clay minerals has been studied less than reduction of Fe^{3+} but re-oxidation has been done to evaluate the reversibility of structural changes caused by a previous reduction step.[38,45,46] In this context the most common oxidants are O_2 gas or air. More than 90 % of Fe^{2+} can be re-oxidized after exhaustive reduction and the reversibility of structural alterations can vary based on a number structural factors.[34] In their recent review of this subject, Hofstetter and co-workers admit that the characterization of the redox properties of structural Fe in clay minerals have been challenging and some of the most fundamental properties are only poorly understood.[34] These include the fraction of total structural Fe available for reduction/oxidation and estimates of structural Fe^{3+}/Fe^{2+}-reduction potentials.[47]

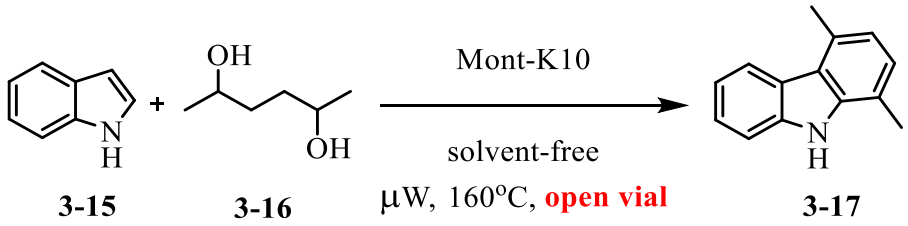
As a practically useful resource, it has been proposed that structural Fe present in clay minerals may act as a renewable source of redox equivalents in soils and sediments for the degradation of pollutants at contaminated sites.[47] To our knowledge no research group has previously considered clay-bound Fe as a potentially valuable reagent in the context of organic synthetic chemistry. However we are aware of two recent publications that describe 'aerobic' oxidative transformations on the surface of clays. In both cases, the authors did not consider the potential that clay-bound iron may be involved in the oxidative process.



3-13 3-14

Scheme 3.5. Oxidation of aliphatic aldehydes on Mont-KSF shown by Dintzner.[48]

The first of these was the solvent-free aerobic oxidation of aliphatic aldehydes catalyzed by Mont-KSF clay to corresponding carboxylic acids shown by the Dintzner group in 2010 (Scheme 3.5).[48] As stated above, it appears that Dnitzner and co-workers did not consider the possibility that Fe^{3+} present in the clay may be involved in the oxidation process. It was implied that the substrates were directly oxidized by O_2 in the air.



3-15 3-16 3-17

Scheme 3.6. Torok's Mont-K10 catalyzed Friedel-Crafts alkylation and electrophilic annulation of indoles.[33]

In 2009, Torok and co-workers, who have worked extensively with clay-catalyzed reactions, showed that Mont-K10 catalyzed a double Friedel-Crafts annulation of indole **3-15** with 1,4-diol **3-16** directly to the aromatic carbazole **3-17** under microwave irradiation open to the air (Scheme 3.6).[33] In this case the formation of an aromatic product required that an oxidation had taken place. Torok briefly states that the oxidation was an aerobic process occurring on the surface of clay. In this case, the authors did not mention the potential of Fe-involvment.

In 2012, we became intrigued by the potential role of montmorillonite-bound Fe in the oxidative aromatization chemistry reported by Torok (Scheme 3.6). We therefore explored the extent of reactivity of this clay in dehydrogenation reactions.

Dehydrogenation is an important transformation in organic chemistry. Despite its usefulness in syntheses, there is a scarcity of recyclable, inexpensive dehydrogenating reagents that do not produce hazardous waste and are effective at moderate temperature conditions (< 120 ^{o}C). Since the initial discoveries of quinone derivatives such as chloranil, and 2,3-dichloro-5,6-dicyanobenzoquinone as dehydrogenating agents 60 years ago,[49] substantial progress has been made by the synthetic community to develop alternatives. Promising catalyst driven methods have been developed such as catalytic gallium nitride mediated non-oxidative aromatization of light alkanes,[50] the bis(phosphine) transition metal pincer catalyst systems for dehydrogenation of cyclic, linear alkanes,[51] and heterocycles,[52] rhodium catalyzed light-driven dehydrogenation of alkanes to olefins,[53,54] *o*-quinone with co-catalyst Co(salen) system for the oxidative dehydrogenation of tetrahydroisoquinolines.[52] More traditional methods include dehydrogenation over Pd/C,[55] MnO_2,[56] dichlorodicyanoquinone (DDQ).[57-59]

Section 3.2. Results and Discussion

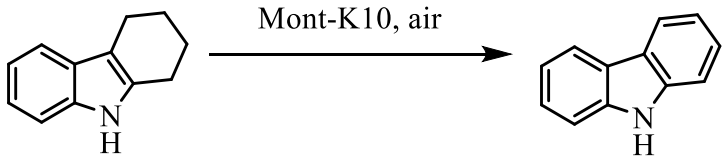
Section 3.2.1. Montmorillonite Clay-Based Dehydrogenation

This project was initiated by using 1,2,3,4-tetrahydrocarbazole **3-18** as the model substrate for its dehydrogenation to carbazole **3-19** using Mont-K10.

Presented in Table 3.1 below are our observations of a straightforward initial reaction whereby 1,2,3,4-tetrahydrocarbazole, **3-18,** was ground together with Mont-K10 and heated at 100 ^{o}C in an oven for 2 hours. We observed a 4 % ^{1}H NMR yield of carbazole **3-19** with 55%

conversion to products. High conversion and such low yield of carbazole could be due to the decomposition of the substrate **3-18** on the surface of acidic Mont-K10.

Table 3.1. Initial studies of 1,2,3,4-tetrahydrocarbazole dehydrogenation with Mont-K10[a]



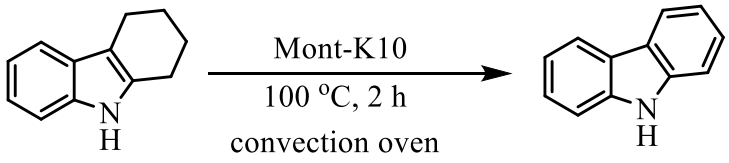
3-18 **3-19**

entry	temp (°C)	time (h)	conversion [b] (%)	yield [b] (%)
1.	80	2	38	2
2.	100	2	55	4
3.	120	2	100	3
4.	140	2	100	0
5.	160	2	100	0

[a]Reaction conditions: 1,2,3,4-tetrahydrocarbazole **3-18** (0.5 mmol), Mont-K10 (200 wt%), convection oven. Water-EtOAc work up.* [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2.
**See experimental section for details.*

Control experiments done under argon atmosphere and in the absence of clay suggested that a combination of clay and air was necessary for these results (Table 3.2).

Table 3.2. Control experiments[a]



3-18 **3-19**

entry	atmosphere	Mont-K10 (wt %)	Conversion [b] (%)	Yield [b] (%)
1.	Air	200	55	4
2.	Air	0	10	0
3.	Argon	200	5	0

[a]Reaction conditions: 1,2,3,4-tetrahydrocarbazole **3-18** (0.5 mmol), Mont-K10 (200 wt%), convection oven. Reaction workup: Water-EtOAc.* [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2.

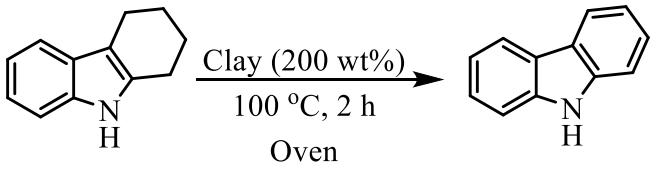
**See experimental section for details.*

Section 3.2.2. Screening of clays towards dehydrogenation of 1,2,3,4-tetrahydrocarbazole.

Since the reaction yielded a very small amount of carbazole **3-19** with Mont-K10 (Table 3.2, entry 1), we decided to screen a variety of other clays for the dehydrogenation of 1,2,3,4-tetrahydrocarbazole **3-18** at 100 ^{o}C in the oven (Table 3.3). Clays under investigation were divided into three categories: (1) processed natural montmorillonites purchased from chemical suppliers (Sigma Aldrich, Alfa Aesar, Acros) (2) natural clays purchased from The Clay Minerals Society, and (3) synthetic clays prepared in the geological sciences department at the University of Idaho in Dr. Leslie Baker's laboratory.

These reactions were set up by grinding 200 wt % of clay with 0.086 g of the 1,2,3,4-tetrahydrocarbazole **3-18** using a mortar and pestle. The reaction mixture was then placed in a convection oven and heated for 2 hours at 100 ^{o}C. ^{1}H NMR yields were determined using dibromomethane as internal standard.

Table 3.3. Screening of clays towards dehydrogenation of 1,2,3,4-tetrahydrocarbazole **3-18**[a]



3-18 **3-19**

entry	clay used	yield [b] (%)
	Processed natural clays purchased from chemical suppliers	
1.	Natural Montmorillonite*	0
2.	Mont-K10*	4
3.	Montmorillonite K30*	0
4.	Mont-KSF (Obtained from Acros)*	0
5.	Mont -KSF (Obtained from Aldrich)*	0
6.	Mont -KSF (Obtained from Alfa Aesar)*	0
	Natural Clays purchased from Clay Minerals society	
7.	Illite (Imt-1)*	0
8.	SYn-1*	0
9.	Nontronite Green (NAu -1)*	1
10.	Nontronite Brown (NAu-2)*	2
	Synthetic Clays Made at the U of I	
11.	Allophane I (Al:Si =1:3)*	7
12.	Allophane II (Al:Si =1:1)*	2
13.	Allophane III (Al:Si =2:1)*	0
14.	Allophane III (Al:Si =1:1; Fe =1 %)*	2
15.	2- line Ferrihydrite*	1
16.	6- line Ferrihydrite*	2
17.	Lepidocrocite*	0
18.	Nontronite Precursor*	1
19.	Nontronite*	8
20.	High iron nontronite (Fe-non)*	30

[a]Reaction conditions: 1,2,3,4-tetrahydrocarbazole **3-18** (0.5 mmol), Clay (200 wt%). [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2. * *see experimental section for characterization*

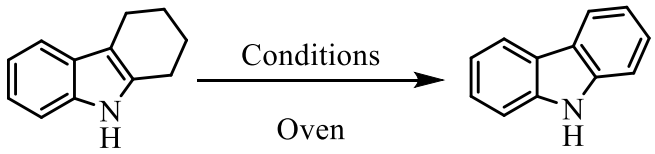
As shown in Table 3.3 four different commercially available montmorillonite clays purchased from chemical suppliers were tested for their ability to catalyze dehydrogenation of 1,2,3,4-tetrahydrocarbazole **3-18** to carbazole **3-19.** Only Mont-K10 offered trace amount of carbazole **3-19** (4 % NMR yield) after 2 h at 100 °C in the oven (entry 2). Mont-KSF clays obtained from three different sources of chemical suppliers yielded no carbazole **3-19** (entries 4-6). We next screened five natural clays purchased from The Clay Minerals Society. We hoped that iron-rich nontronite green (NAu-1) and nontronite brown (NAu-2) would offer an improvement over Mont-K10. However, we were disappointed to find that none of these nontronites were better than Mont-K10 (entries 9 and 10). The final category of clays tested towards the dehydrogenation of 1,2,3,4-tetrahydrocarbazole **3-18** were synthetic clays prepared in Dr. Leslie Baker's lab in the department of Geological Sciences at the University of Idaho. With these clays we began to see some more promising results. Out of the four allophane-type clays examined towards this dehydrogenation, allophane I (Al:Si =1:3) gave 7 % NMR yield of carbazole **3-19** (entry 11). Ferrihydrite clays, which are essentially hydrated ferric iron gave 1% and 2 % yields (entry 15 and 16 respectively). Synthetic nontronite gave 8 % yield of carbazole **3-19** (entry 19). Notably, Allophane I and synthetically prepared nontronite had similar chemical composition with respect to ratio of aluminum and silicon content present in these clays. A breakthrough result came with a synthetic clay that we called 'high iron nontronite' or 'Fe-non' (*characterization details below*) which gave 30 % NMR yield of carbazole **3-19** under these conditions.

Section 3.2.3. Reaction Optimization with Fe-Non

Based on the successful result that we obtained with synthetic Fe-non for the dehydrogenation of tetrahydrocarbazole, we began the reaction optimization. We varied the following reaction parameters: amount of Fe-non, time and temperature (Table 3.4). The ^{1}H NMR yield of carbazole **3-19** from 1,2,3,4-tetrahydrocarbazole **3-18** was improved to 40 % by increasing the amount of Fe-non to 400 wt % (entry 5) at 100 ^{o}C. We also observed that amount of Fe-non can be reduced to 200 wt % by increasing the temperature to 120 ^{o}C, giving 40 % yield of carbazole **3-19** (entry 7). Leaving the reaction mixture for 2 hours at 120 ^{o}C reduced the ^{1}H NMR yield to 11 % (entry 8). Increasing the amount of clay as well as the temperature did not offer any improvement in the product yield (entry 11). Using 800 wt % of Fe-non at 120 ^{o}C improved the yield to 50 % (entry 13). However, since there was only 10 % increase in the carbazole **3-19** yield when we switched from 400 wt %/100 ^{o}C (entry 5) to 800 wt %/120 ^{o}C (entry 13), we decided to continue with 400 wt %/100 ^{o}C for further optimization studies.

The use of *p*-toluenesulfonic acid monohydrate ($TsOH.H_2O$) as an additive in the dehydrogenation of 1,2,3,4-tetrahydrocarbazole **3-18** did not lead to any considerable increase in the yield (entry 12).

Table 3.4. Reaction Optimization Part I[a]



3-18 **3-19**

entry	Fe-non (wt %)	temp (°C)	time (h)	conversion[b] (%)	yield[b] (%)
1.	50	100	2	82	6
2.	100	100	2	86	10
3.	200	100	2	90	30
5.	400	100	2	100	40
6.	200	120	0.5	90	30
7.	200	120	1	92	40
8.	200	120	2	99	11
9.	300	100	2	100	18
10.	300	120	2	100	23
11.	400	120	1	100	38
12.	400[c]	120	1	100	35
13.	800	120	1	100	50

[a]Reaction conditions: 1,2,3,4-tetrahydrocarbazole **3-18** (0.5 mmol). Reaction workup: Water-EtOAc.* [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2.

**See experimental section for details.*

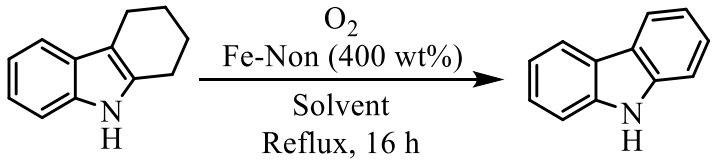
[c]0.01 equiv. TsOH was added to the reaction mixture.

The maximum yield of carbazole obtained under dry conditions with Fe-non was 50 %. At this point we decided to screen this reaction in a series of organic solvents. Initial solvent screening was done in a variety of different aromatic hydrocarbon solvents, polar protic solvents, and polar aprotic solvents with a wide boiling point range and under an O_2 atmosphere (Table 3.5). We were delighted to find that dehydrogenation proceeded to complete conversion with good yields in toluene, chlorobenzene, and *p*-xylene (enteries 5-7). We selected toluene as

our preferred reaction solvent medium over chlorobenzene and *p*-xylene, because it has the lowest boiling point and is, therefore, most convenient to remove *in vacuo*.

Based on the successful results obtained in solvents with Fe-non, we decided to repeat the similar reaction with Mont-K10, nontronite green (NAu-1) and iron oxide (Fe_2O_3) in refluxing toluene, negligible amount of carbazole 3-19 was observed in all the cases (1% yield) (entries 10-12).

Table 3.5. Reaction Optimization Part II - Solvent studies with Fe-non. [a]



3-18 **3-19**

entry	solvent	temp (°C)	conversion[b] (%)	yield[b] (%)
1.	Benzene	80	76	23
2.	Acetonitrile	82	68	2
3.	Nitromethane	101	82	8
4.	1,3-dioxane	101	20	5
5.	Toluene	110	100	60 (55)[c]
6.	Chlorobenzene	132	100	61
7.	*p*-Xylene	138	100	61
8.	Dimethylformamide	153	30	0
9.	2-methoxyethylether	162	82	15
10.	Toluene (Mont-K10)	110	28	1
11.	Toluene (NAu-1)	110	26	1
12.	Toluene (Fe_2O_3)	110	16	1

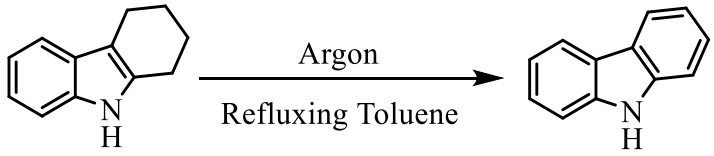
[a]Reaction conditions: 1,2,3,4-tetrahydrocarbazole **3-18** (0.5 mmol), Fe-non (400 wt%). Reaction workup: Fitration.* [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2. [c]Isolated yield after column chromatography.

**See experimental section for details.*

Since the crude ^{1}H NMR spectrum obtained for the reaction done in toluene under O_2 atmosphere was qualitatively 'messy' indicating formation of some unidentifiable side products (entry 5), we performed the same reaction under atmospheres of argon and air. These reactions were set up with 1,2,3,4-tetrahydrocarbazole **3-18,** 400 wt % of Fe-non in refluxing toluene for 16 hours under argon and open to the air. ^{1}H NMR data revealed that reaction under air gave a similar result to that of O_2 (94 % conversion; 62 % yield) with intractable side products. The reaction done under an argon atmosphere however afforded 59 % of carbazole **3-19** with only 90 % conversion and in this case the ^{1}H NMR spectrum of the crude reaction mixture was notably cleaner with very few observable signals other than substrate and product.

Table 3.6 shows the data for the optimization study of dehydrogenation of 1,2,3,4-tetrahydrocarbazole **3-18** to carbazole **3-19** by varying the amount of Fe-non, time and temperature under argon atmosphere.

Table 3.6. Reaction Optimization for dehydrogenation of 1,2,3,4-tetrahydrocarbazole **3-18.** [a]



3-18 **3-19**

entry	Fe-non (mg/mmol)	time (h)	conversion[b] (%)	yield[b] (%)
1.	400	8	40	24
2.	400	12	42	33
3.	400	24	82	59
4.	400	48	96	76
5.	600	48	100	96[c]

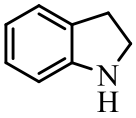
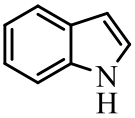
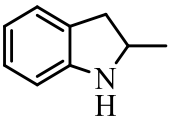
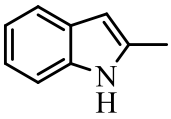
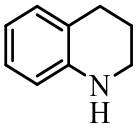
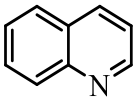
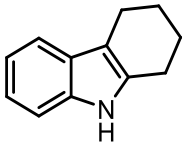
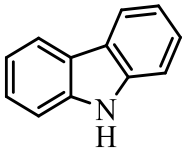
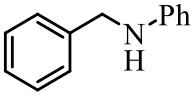
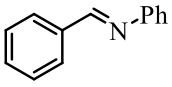
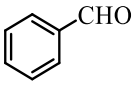
[a]Reaction conditions: 1,2,3,4-tetrahydrocarbazole **3-18** (0.2 mmol), Toluene (5 mL). [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2. [c]Isolated yield after chromatography.

We obtained a yield of 24 % of carbazole **3-19** with 400 mg/mmol of Fe-non in refluxing toluene for 8 hours under Argon atmosphere (entry 1). The yield of carbazole **3-19** was improved to 33 %, 59 %, and 76 % by extending the reaction time to 12, 24, and 48 hours respectively (entries 2, 3 and 4). By increasing the amount of Fe-non to 600 mg/mmol, we obtained 100 % conversion and 96 % isolated yield of the dehydrogenated product **3-19** (entry 5).

Section 3.2.4. Substrate Scope

The substrate scope of this dehydrogenation methodology was evaluated with indoline, 2-methylindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydrocarbazole, *N*-phenylbenzyamine, (Table 3.7).

Table 3.7. Substrate Scope[a]

entry	substrate	Fe-non (mg/ mmol)	time (h)	product	isolated yield (%)
1.	 **3-20**	400	10	 **3-21**	84
2.	 **3-22**	600	24	 **3-23**	72
3.	 **3-24**	600	48	 **3-25**	66
4.	 **3-18**	600	48	 **3-19**	96
5.	 **3-26**	600	48	 **3-27**  **3-28**	64[b] 6[b]

[a]Reaction conditions: Substrate (0.2 mmol), Toluene (3 mL), reflux, Ar atmosphere. [b]NMR yield with CH_2Br_2 as internal standard.

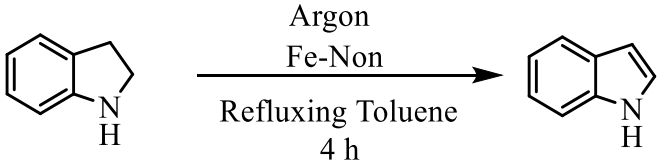
Indoline **3-20** was converted to indole **3-21** in 83% yield in 10 hours with 400 mg/mmol Fe-non. 2-Methylindoline **3-22** was dehydrogenated in 24 hours in refluxing toluene with 600 mg/mmol Fe-non to yield the corresponding 2-methylindole **3-23** in 72 % isolated yield. A

reaction time of 48 hours was required for complete conversion of 1,2,3,4-tetrahydroquinoline **3-24** to quinoline **3-25**, which was obtained as pale yellow liquid in 66 % yield in 48 hours. 1,2,3,4-Tetrahydrocarbazole **3-18** was dehydrogenated to give carbazole **3-19** in 96 % isolated yield. Reaction of *N*-phenylbenzylamine **3-26** went to 73 % conversion with 72 % yield in 24 hours. Complete conversion to *N*-benzylideneaniline **3-27** was observed in 48 hours with 64 % ^{1}H NMR yield with CH_2Br_2 as internal standard. Compound **3-27** was not isolated *via* column chromatography as imines tend to hydrolyze on silica. Some fraction of benzaldehyde **3-28** formation was observed due to *in situ N*-benzylideneaniline **3-27** hydrolysis.

Section 3.2.5. Studies on Re-usability of Fe-Non

Table 3.8 shows a series of recycling experiments performed with synthetic Fe-non using indoline 3-20. Complete conversion to indole **3-21** with 85 % yield was achieved in 4 hours in refluxing toluene with 1g/mmol of Fe-non under Argon atmosphere. We adopted this as our optimal reaction condition for all the recycling experiments shown in Table 3.8 below. We observed that used clay dried at room temperature for 24 hours retained its efficiency to dehydrogenate indoline **3-20** in the second run with 100% conversion and 90% yield. When this clay was reused for the third time, we observed a decrease in conversion and yield (%). Heating used clay in an oven at 150 ^{o}C and 200 ^{o}C open to the air substantially reduced its efficiency as the oxidant towards dehydrogenation of indoline **3-20** in the second run giving 56 % and 52 % yields respectively. Drying the used clay at 100 ^{o}C for 12 hours gave 100 % conversion and 85 % yield in the second cycle. However, third run of reaction set up with this clay gave lower yield (71%) of product **3-21**. Recycling experiments are currently ongoing in Dr. Magolan's lab and will be continued by other students.

Table 3.8. Recycling experimental studies of Fe-non.[a]



3-20 **3-21**

entry	no recharging	rt for 1 day	Drying at 100 °C	Drying at 150 °C	Drying at 200 °C
		% Yield (% Conversion) based on ^{1}H NMR [b]			
Cycle 2	32 (72)	90 (100)	86 (100)	56 (60)	52 (68)
Cycle 3		76 (76)	71 (70)	42 (67)	28 (30)
Cycle 4			34 (32)		

No recharging: After the completion of first reaction, wet clay was immediately used for the second run.

rt for 1 day: Clay was dried at rt for 24 hours prior to its use in the second cycle.

Drying at 100 °C: Clay dried at 100 °C for 12 h prior to its use in the second cycle.

Drying at 150 °C: Clay dried at 150 °C for 12 h prior to its use in the second cycle.

Drying at 200 °C: Clay dried at 200 °C for 12 h prior to its use in the second cycle

[a] Reaction conditions: Indoline **3-20** (0.1 mmol), Fe-non (100 mg), Toluene (3 mL); Reaction work up: Filtration with dichloromethane. [b]NMR conversions and yields with CH_2Br_2 as internal standard.

Section 3.2.6. Structural Characterization of High Iron Nontronite

Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) studies were performed on synthetic nontronite clay samples by fusing it with lithium metaborate and were analyzed on a Thermo Electron iCAP inductively coupled plasma spectrometer (ICP-AES) (Thermo Scientific, Waltham, Massachusetts, USA) for bulk composition analyses. The fusion data averaged to 81.59 mol % SiO_2, 17.53 mol % FeO, 0.72 mol % Na_2O. The chemical composition obtained from ICP experiments revealed that the synthetic Fe-non contains slightly higher content of Si compared to natural nontronite.[60]

FTIR and SEM experiments were performed on: 1) synthetic high iron nontronite clay, 2) a sample of this clay after a dehydrogenation reaction with indoline **3-20** (spent nontronite), and 3) a sample of natural nontronite obtained from UI-Garfield. These experiments are discussed below.

First, the three samples were analyzed using diffuse reflectance Fourier-transform infrared spectroscopy (FTIR). The FTIR analyses were carried out on a Perkin-Elmer System 2000 (Thermo Scientific, Waltham, Massachusetts, USA), using a mixture of 3 wt % nontronite and 97 wt % optical-grade KBr. Spectra were processed using the Kubelka-Munk algorithm provided in the Perkin Elmer Spectrum 2.0 software (Thermo Scientific, Waltham, Massachusetts, USA). The FTIR and ICP-AES data for natural nontronite samples (UI-Garfield) were obtained from the previous work done in Dr. Leslie Baker's laboratory for its comparison with synthetic nontronite.[60]

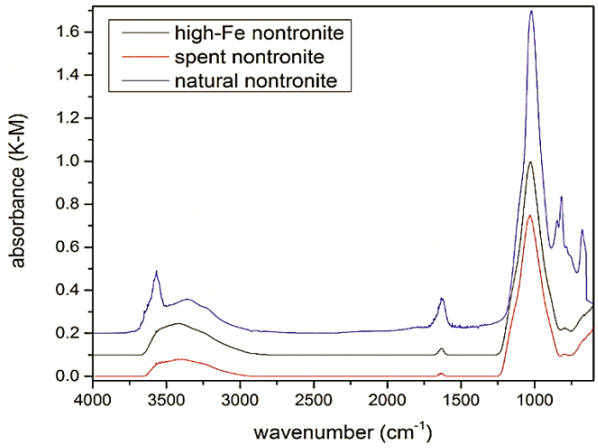


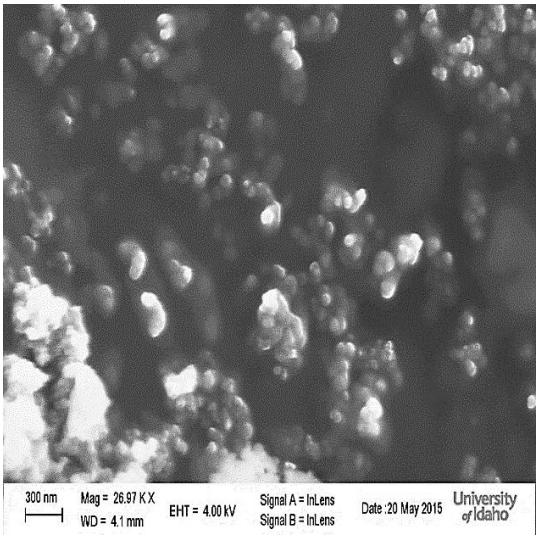
Figure 3.2. Comparison of IR spectra of UI-Garfield nontronite with synthetic high iron nontronites.

Figure 3.2. shown above directly compares the IR data for the UI-Garfield natural nontronite with the synthetic high iron nontronite and the spent high iron nontronite. In the Garfield nontronite sample, typical nontronite IR peaks were observed;[61] Fe–Fe–OH stretching

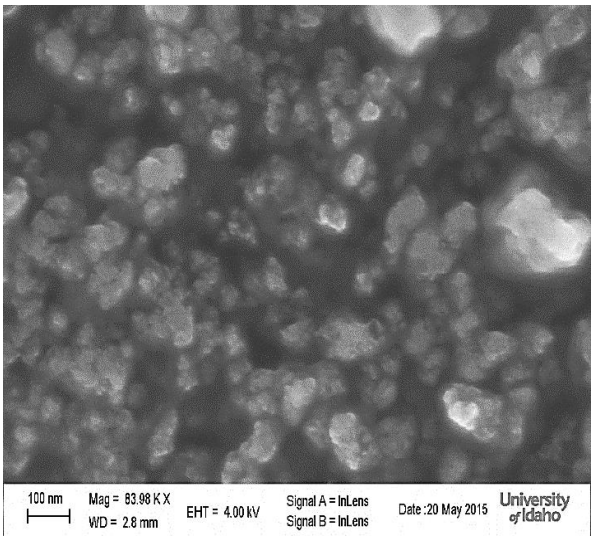
peak at 3565 cm^{-1}, the Fe–Si–O stretched at a range of frequencies centered near 1000 cm^{-1}, the Fe–Al–OH bend near 855 $cm^{-1}$and Fe-Fe-OH bend near 815 cm^{-1}, and an out-of-plane bending vibration corresponding Si–O–Fe bend at 675 cm^{-1}.

Samples of high iron nontronite and spent nontronite showed similarities in the IR peak pattern. No sharp peak for Fe–Fe–OH stretch at 3565 cm^{-1} was observed in the case of synthetic nontronite gels. Instead, a shoulder peak at 3565 cm^{-1} was rather observed in the case of both fresh Fe-non and the spent nontronite. Inflection at 1640 cm^{-1} represented structural water present in the clay. The broadening and absence of characteristic spectral peaks in the synthetic high iron nontronites suggested that they were less crystalline than the naturally obtained nontronite.

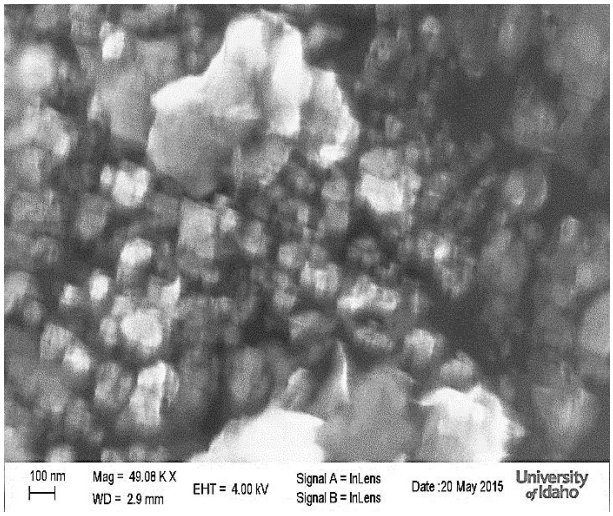
Figure 3.3 illustrates the data obtained from SEM experiments performed on three different samples: (1) synthetic high iron nontronite (Figure 3.3a), (2) ‘spent’ high iron nontronite (Figure 3.3b), (3) natural nontronite sample obtained from UI-Garfield (Figure 3.3c). SEM experiments were performed on JEOL 2010J 200 kV Analytical TEM/STEM machine. The SEM image for natural nontronite showed that the clay particles were aggregated in clumps with an approximate particle size of 50 nm. In contrast the synthetic high iron nontronite SEM image showed clay particles as smaller spheres with particle size of approximately 20-30 nm.



(a) SEM image of synthetic high iron nontronite



(b) SEM image of 'spent' synthetic high iron nontronite



(c) SEM image of natural UI-Garfield nontronite

Figure 3.3. (a) SEM image of synthetic high iron nontronite; SEM image of 'spent' synthetic high iron nontronite; (c) SEM image of natural UI-Garfield nontronite

Section 3.3. Summary

In the above sections, we have described the initial discovery of a new oxidant which is a synthetic iron-rich clay that we have called high iron nontronite or Fe-non. Our initial application of this clay is the oxidative dehydrogenation of *N*-heterocyclic compounds such as

indolines, tetrahydrocarbazole to their corresponding aromatic derivatives. This methodology offers a mild, procedurally simple and high yielding synthesis of pharmaceutically relevant heterocycles such as indoles, carbazoles, and quinolines. Partial structural characterization of synthetic high iron nontronite was discussed. Further characterization of this clay is currently underway and includes characterization by X-ray absorption spectroscopy at the Stanford Synchrotron Radiation Laboratory (SSRL). This work presently continues with several members of Dr. Magolan's research group engaged in further work with this new oxidant.

There are many potential synthetic applications of this new oxidant yet to be investigated. Below is a summary of two projects that are presently under development.

Section 3.4. Other Project Inspired by This Work

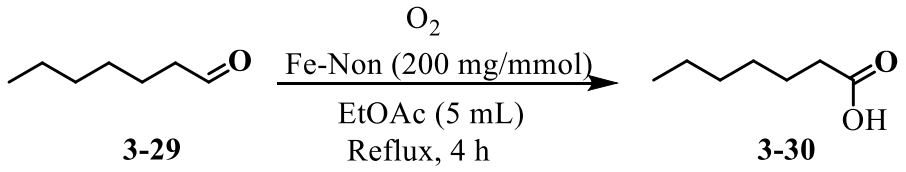
To explore the potential of high iron nontronite towards other oxidation reactions, we decided to treat a variety of substrates with Fe-non in refluxing solvent conditions. Results are summarized below.

Section 3.4.1. Oxidation of Aliphatic Aldehydes to Carboxylic Acids

Another potential reaction methodology that is currently ongoing in Dr. Magolan's lab is the use of synthetic high iron nontronite as the oxidant in the oxidation of aliphatic and aromatic aldehydes to corresponding carboxylic acids. To date, the most common method used in synthetic labs for the oxidation of aldehydes to carboxylic acid is undoubtedly, the Pinnick oxidation.[62] Since then, a number of successful new methods have been published for this oxidation by various scientific groups[63-69] to avoid the use toxic metal and hazardous compounds such as potassium permanganate,[63,70] chromates,[71] and chlorites.[72] Most of these

methods suffered from limitations such as preparation of supported catalysts, excessive use of oxidants, and generation of metal waste.

Our approach uses synthetic clay as the oxidant for the oxidation of aldehydes to acids. We initiated this project by treating heptanal **3-29** with 200 mg/mmol of high iron nontronite in refluxing EtOAc for 4 hours. We were delighted to find that the reaction went to 98 % conversion with 85 % yield of heptanoic acid **3-30 (Scheme 3.7)**.



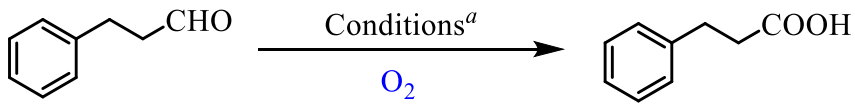
[1]Conversion and yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Scheme 3.7. Oxidation of heptanal **3-29** to heptanoic acid **3-30** using Fe-non.

Use of low boiling heptanal **3-29** as the model substrate posed problem in the calculation of percentage conversion based on internal standard/^{1}H NMR due to its evaporation on rotary evaporator. Therefore, we decided to switch to hydrocinnamaldehyde **3-31** as the substrate of choice for the optimization studies of this methodology. The evaluation of scope and limitations for this oxidative process will be continued by an undergraduate researcher Jake Dalton. Tables 3.9-3.11 show preliminary efforts towards reaction optimization. No product formation was observed in refluxing ethanol (Table 3.9, entry 9). Reaction in reluxing toluene gave just 5 % yield of hydrocinnamic acid **3-32**. Low yields were obtained for reactions done in acetone and DCM, 28 % and 31 % respectively (entries 1 and 4 respectively). We observed that reactions done in ethyl acetate and acetonitrile gave comparable results at both room temperature and under refluxing conditions (entries 2, 3, 6, 7). When EtOAc was used as the solvent, the

oxidation of heptanal **3-31** went to 100 % conversion in 12 hours giving 69 % yield (entry 3). Based on these observations, we chose ethyl acetate as the optimal solvent for this reaction methodology.

Table 3.9. Reaction Optimization: Solvents screen at different temperatures. [a]



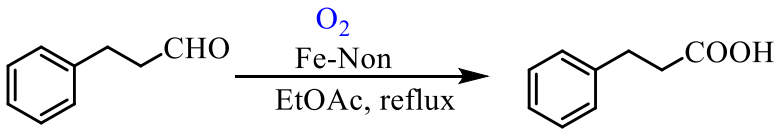
3-31 **3-32**

entry	Fe-non (Amt)	solvent	temperature (°C)	time (h)	conversion[b] (%)	yield[b] (%)
1.	200 mg/mmol	acetone	rt	18	84	28
2.	200 mg/mmol	EtOAc	rt	18	84	41
3.	100 mg/mmol	EtOAc	reflux	12	100	69
4.	200 mg/mmol	CH_2Cl_2	rt	18	66	31
5.	200 mg/mmol	chlorobenzene	rt	18	98	42
6.	200 mg/mmol	CH_3CN	rt	18	78	42
7.	100 mg/mmol	CH_3CN	reflux	12	96	73
8.	200 mg/mmol	tetrahydrofuran	rt	18	86	11
9.	200 mg/mmol	EtOH	rt	18	26	0
10.	200 mg/mmol	toluene	rt	18	42	5

[a]Reaction conditions: Hydrocinnamaldehyde **3-31** (0.5 mmol), Solvent (5 mL). [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2.

Table 3.10. shows the results obtained from three reactions done with 200 mg/mmol Fe-non in refluxing ethyl acetate under O_2 atmosphere for different reaction times.

Table 3.10. Optimization parameter: Reaction time[a]



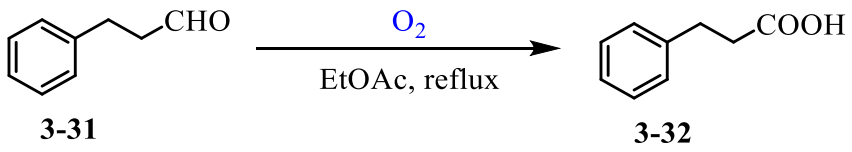
3-33 **3-34**

entry	time (h)	conversion[b] (%)	yield[b] (%)
1.	4	74	40
2.	8	96	62
3.	12	100	69

[a]Reaction conditions: Hydrocinnamaldehyde **3-31** (0.5 mmol), Fe-non (200mg/mmol), EtOAc (5 mL). [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2.

On comparing the results of reactions done for 12 hours with 200 mg/mmol (Table 3.10, entry 3) and 100 mg/mmol (Table 3.9, entry 3) of Fe-non, we found that both the reactions went to 100 % conversion giving 69 % ^{1}H NMR yields. These observations prompted us to do optimization of this reaction with respect to the amount of Fe-non loading. We anticipated that further lowering of clay to sub stoichiometric or catalytic level was possible under these conditions (Table 3.11).

Table 3.11. Optimization parameter: Clay loading[a]



3-31 **3-32**

entry	Fe-non (Amt)	time (h)	conversion[b] (%)	yield[b] (%)
1.	100 mg/mmol	12	92	62
2.	50 mg/mmol	12	94	51
3.	50 mg/mmol	24	98	85

[a]Reaction conditions: Hydrocinnamaldehyde **3-31** (0.5 mmol), EtOAc (5 mL). [b]^{1}H NMR conversion and yield based on internal standard CH_2Br_2.

To date, we have been able to lower the clay loading down to 50 mg/mmol giving 98 % conversion and 85 % yield in refluxing ethyl acetate for 24 hours under O_2 (entry 3). These are the best reaction conditions we have found so far. Future work on this project includes: recharging of the clay, experiments to gain mechanistic insight, and exploration of substrate scope will be continued in Dr. Magolan's lab.

Section 3.5. Experimental

General

^{1}H and ^{13}C NMR experiments were performed on a Bruker AVANCE 300 MHz instrument, and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C) or DMSO-d_6 (referenced to 2.5 ppm for ^{1}H and 40.45 ppm for ^{13}C). Coupling constants (J) are reported in hertz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All other reagents and solvents were used as purchased from Aldrich, AKSci, and VWR. Reaction progress was monitored by thin layer chromatography (TLC, EMD Chemicals, Inc., silica gel

60 F254), visualized under UV light, and plates were developed using *p*-anisaldehyde or potassium permanganate stains. Flash chromatography was performed using silica gel (Sorbent Technologies, particle size 40−63 μm).

Section 3.5.1. Synthesis and Physical/Chemical Data for the Clays used in Table 3.3

Section 3.5.1.1. Source Clay Data obtained from The Clay Minerals Society (http://www.clays.org)

Barasym SSM-100 Syn-1

Origin: Synthetic, trade name: Barasym SSM-100, synthetic mica-montmorillonite (NL industries); Date of manufacture: 1972; Chemical composition (%): SiO_2: 49.7 Al_2O_3: 38.2, TiO_2: 0.023, Fe_2O_3: 0.02, MgO: 0.014, Na_2O: 0.26, K_2O: <0.01, Li_2O; 0.25, F: 0.76, P_2O_5: 0.001,S: 0.10; Cation Exchange Capacity (CEC): Barium method ca.70 meq/100g; ammonium method ca. 140 meq/100g; Surface area: N2 area: 133.66 +/- 0.72 m^2/g.

Illite IMt-1

Origin: Silver Hill, Montana, USA; Chemical Composition (%):SiO_2: 49.3 Al_2O_3: 24.25, TiO_2: 0.55, Fe_2O_3:7.32, FeO: 0.55, MnO: 0.03, MgO: 2.56, CaO: 0.43, Na_2O: 0, K_2O: 7.83, P_2O_5: 0.08, LOI: 8.02

Nontronite NAu-1

Origin: South Australia; Chemical Composition (%): SiO_2: 53.33, Al_2O_3: 10.22, Fe_2O_3: 34.19, MgO: 0.27, CaO: 3.47, Na_2O: 0.08, K_2O: 0.03; Structure: $(M^+_{1.0})[Si_{7.00}\ Al_{1.00}][Al_{.58}Fe_{3.38}Mg_{.05}]$

Nontronite NAu-2

Origin: South Australia; Chemical Composition (%): SiO_2: 56.99, Al_2O_3: 3.4, Fe_2O_3: 37.42, MgO: 0.34, CaO: 2.67, Na_2O: 0.11, K_2O: 0.02; Structure: $(M^+_{.97})[Si_{7.57}Al_{.01}Fe_{.42}][Al_{.52}Fe_{3.32}Mg_{.7}]O_{20}(OH)_4$

Section 3.5.1.2. Clays Obtained from Chemical Suppliers

Montmorillonite Mont-KSF (Chemical Supplier: Acros Organics)

Physical Form: Yellow-gray to gray powder; Bulk Density apparent bulk density: 800g/L; Loss on Ignition: 15 % (1000°C, 2 hrs.); Particle Size: Sieve analysis of the dry powder:> 63µm: < 50 %; Surface Area: 10 m^2/g; Fe_2O_3: 5.2 % (dried at 110°C, 2 hrs); Al_2O_3: 17.0 % (dried at 110°C, 2 hrs), CaO: 1.5 % (dried at 110°C, 2 hrs), MgO: 2.5 % (dried at 110°C, 2 hrs), K_2O: 1.5 % (dried at 110°C, 2 hrs), SiO_2: 54 % (dried at 110°C, 2 hrs), Na_2O: 0.4 % (dried at 110°C, 2 hrs).

Montmorillonite Mont-KSF (Chemical Supplier: Sigma Aldrich)

Physical Form: Yellow-gray to gray powder; surface area 20-40 m^2/g

Montmorillonite K 30 (Chemical Supplier: Fluka Analytical)

Physical Form: Gray powder; surface area: ~330 m^2/g; pH: 2.8-3.8

Montmorillonite K 10 (Chemical Supplier: Sigma Aldrich)

Physical Form: Cream or grey to pale brown; Bulk density 385 ± 55 kg/m^3; Free moisture ≤ 5 %; pH: 3.4 ± 0.7; Particle Size: ≤ 25 wt % is > 0.063mm (+230mesh)

Montmorillonite, naturally occurring mineral (Chemical Supplier: Alfa Aesar)

Physical Form: gray powder; Approximate formula: $R^+_{0.33}Al_2SiO_4O_{10}(OH)_2 \bullet XH_2O$, where R^+ includes one or more of the cations Na^+,K^+

Section 3.5.1.3. Clays Synthesized in Dr. Leslie Baker's lab at the University of Idaho

2-line Ferrihydrite

A solution of 0.1 M NaOH was titrated at a rate of 1.3mL/min into a 250 mL aliquot of 0.1M $Fe(NO_3)_3$ under constant stirring until the solution reached a pH of 7, using a total of 750 mL of NaOH. The precipitate from this procedure was centrifuged for 15 minutes and dialyzed in deionized water and was freeze dried for 3 days.

6-line Ferrihydrite

A solution of 0.01 M NaOH was titrated at a rate of 1.3mL/min into a 125 mL aliquot of 0.01M $Fe(NO_3)_3$. $9H_2O$ under constant stirring until the solution reached a pH of 7, using a total of 3.878 L of NaOH altogether. The precipitate from this procedure was centrifuged for 10 minutes and dialyzed in deionized water for 48 hours followed by freeze-drying for 3 days.

Allophanes

Allophanes were synthesized at different Al:Si ratios (Table 3.12) using the method described by Baker and Strawn (2012).[73] 0.1 M $FeCl_3$ was added to a solution of 0.1 M $AlCl_3$ and tetraethyl ortho silicate was added to this solution in order to reach Al/Si ratios equal to 1:3, 1:1, 2:1, 1:1. This solution was then subjected to titration with 0.1 M NaOH at the rate of 1.3 mL/min. The precipitate from this procedure was centrifuged for 10 minutes and dialyzed in deionized water for 48 hours followed by freeze-drying for 3 days.[74]

Allophane	Al:Si	Fe % of Al	
1	1:3	10	2.5 % Fe
2	1:1	5	2.5 % Fe
3	2:1	1	0.66 % Fe
4	1:1	1	0.5 % Fe

Table 3.12. Composition of different allophanes and content of Fe in it.

Lepidocrocite

A 0.1 M mixture of $FeCl_2$. $4H_2O$ and $Al(NO_3)_3$ solution was adjusted to pH 8 with NH_3/NH_4Cl buffer (0.2 M NH_3 + 0.2 M NH_4Cl; 1:19), followed by oxidation with CO_2-free air at uniform flow rate of 0.5 liter/min. The pH of the solution was maintained at 8 by adding NH_3 solution dropwise. The initial greenish black precipitate turned orange after 30 minutes which was centrifuged for 10 minutes and dialyzed in deionized water for 48 hours followed by drying in air.[75]

Nontronite Precursor

0.1 M $FeCl_2$ and 0.1 M $AlCl_3$ were mixed with 16.6 mL tetraethyl orthosilicate and one drop of hydrazine, and stirred rapidly on a magnetic stir plate. A solution of 0.1 M NaOH was titrated into the solution at a rate of 1.3 mL/min under rapid stirring, forming a dark blue-green gel. The final pH of this gel suspension was 7.6 after titration. The resulting suspension of clay in water was centrifuged and decanted, followed by dialysis for 2 days and freeze-drying for 3 days.

Note: Nontronite precursor gel was synthesized using a method slightly modified from the nontronite synthesis by Baker and Strawn (2014).[60] The Fe:Al molar ratio of this gel was 1:1 and Si:(Fe,Al) molar ratio was 3:1.

High Iron Nontronite (Fe-non)

0.1 M $FeCl_2$ was mixed with 66.52 mL tetraethyl orthosilicate, and stirred rapidly on a magnetic stir plate. A 3 L solution of 0.1 M NaOH was titrated into the $FeCl_2$ solution at a rate of 1.3 mL/min under rapid stirring, forming a dark green gel. The final pH of this gel suspension was 7.6 after titration. The precipitate from this procedure was centrifuged for 10 minutes to collect the gel which was transferred to the dialysis tubing and dialyzed in deionized water for 48 hours followed by freeze-drying for 3 days. Clay was dried under vacuum prior to use.

Section 3.5.2. Typical Procedure for Reactions Done in a Convection Oven (Table 3.1-3.4)

1,2,3,4-Tetrahydrocarbazole **3-18** (0.5 mmol) was ground with clay using a mortar and pestle and heated at the specified temperature in the oven for 2 hours (unless otherwise stated). The reaction mixture was cooled to room temperature and was poured into a mixtue of 20 mL water and 10 mL ethyl acetate. This mixture was rapidly stirred for 15 minutes after which it was filtered using a Buchner funnel. The resulting solution was poured into a separatory funnel and the organic extract was dried with $MgSO_4$. The solvent was removed *in vacuo*. Conversion (%) and yield (%) were determined using dibromomethane (0.5 mmol) as internal standard. The methylene peak in CH_2Br_2 appears at δ 4.93 in the ^1H NMR spectrum in $CDCl_3$.

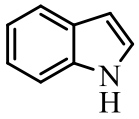
Section 3.5.3. Typical Procedure for Reactions Done in Solvent (Table 3.5)

To a mixture of 1,2,3,4-tetrahydrocarbazole **3-18** (0.5 mmol) and synthetically prepared high iron nontronite (400 wt %), solvent (5 mL) was added and was refluxed under O_2 atmosphere. After 16 hours of refluxing, the reaction was cooled to room temperature and was

filtered using a fritted glass funnel and the clay was washed with dichloromethane. The reaction mixture was concentrated by rotary evaporation, and analyzed by ^{1}H NMR using CH_2Br_2 (0.5 mmol) as internal standard. The methylene peak in CH_2Br_2 appears at δ 4.93 in the ^{1}H NMR spectrum in $CDCl_3$. (In case of high boiling solvents such as dimethyl formamide and methoxymethyl ether, after filtering out the clay, the reaction was transferred to a separatory funnel containing water and extracted with ether (3 x 30 mL), dried over $MgSO_4$).

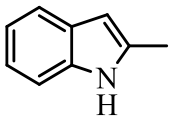
Section 3.5.4. General Procedure for Substrate Scope (Table 3.8)

A mixture of substrate (0.2 mmol) and high iron nontronite clay (400 or 600 mg/mmol) was refluxed in toluene (5 mL) under Argon atmosphere until complete disappearance of the starting material was observed by ^{1}H NMR. The reaction was cooled to room temperature and was filtered *in vacuo* using a fritted glass funnel. The clay was washed with dichloromethane (10 mL). The solvent was removed *in vacuo.* The residue was purified by flash column chromatography on silica gel (gradient elution with EtOAc and hexanes).



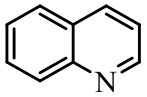
3-21

Indole (3-21) The standard procedure was used with indoline **3-20** (22.4 μL, 0.2 mmol), high iron nontronite (400 mg/mmol) and toluene (5 mL). After refluxing for 10 h, the reaction was worked up and purified as described above to yield compound **3-21** as white crystals (19.7 mg, 84 % yield): Rf = 0.77 (hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.26 – 7.07 (m, 3H), 6.57 (d, J = 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0, 127.9, 124.1, 122.0, 120.7, 119.8, 111.0, 102.7. ^{1}H NMR and ^{13} C NMR spectral data match with an authentic samples.



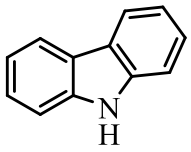
3-23

2-methylindole (3-23) The standard procedure was used with 2-methylindoline **3-22** (26 μL, 0.2 mmol), high iron nontronite (600 mg/mmol) and toluene (5 mL). After refluxing for 24 h, the reaction was worked up and purified as described above to yield compound **3-23** as colorless liquid (19 mg, 72.4 % yield): Rf = 0.63 (hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (s, 1H), 7.58 – 7.48 (m, 1H), 7.33 – 7.24 (m, 1H), 7.17 – 7.03 (m, 2H), 6.23 (s, 1H), 2.45 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 135.0, 129.1, 120.9, 119.6, 110.2, 100.4, 29.7, 13.7. ^{1}H and ^{13}C NMR spectral data are consistent with previously reported values.[76]



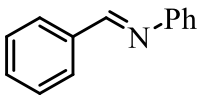
3-25

Quinoline (3-25) The standard procedure was used with 1,2,3,4-tetrahydroquinoline **3-24** (25 μL, 0.2 mmol), high iron nontronite (600 mg/mmol) and toluene (5 mL). After refluxing for 48 h, the reaction was worked up and purified as described above to yield compound **3-25** as yellow oil (17 mg, 66% yield): Rf = 0.5 (hexanes/EtOAc 70:30 v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.91 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.20 – 8.07 (m, 2H), 7.80 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 148.7, 136.0, 129.4, 129.4, 128.3, 127.7, 126.5, 121.0. ^{1}H NMR and ^{13} C NMR spectral data match with the authentic samples.



3-18

Carbazole (3-18) The standard procedure was used with 1,2,3,4-tetrahydrocarbazole **3-17** (34 mg, 0.2 mmol), high iron nontronite (600 mg/mmol) and toluene (5 mL). After refluxing for 48 h, the reaction was worked up and purified as described above to yield compound **3-18** as white powder (32 mg, 96% yield): Rf = 0.83 (hexanes/EtOAc 70:30 v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.11 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.44 – 7.34 (m, 2H), 7.22 – 7.10 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.6, 126.3, 123.3, 121.0, 119.3, 111.8. ^{1}H NMR and ^{13} C NMR spectral data match with the authentic samples.



3-27

***N*-benzylideneaniline (3-27)** The standard procedure was used with *N*-phenylbenzylamine **3-26** (34.5 μL, 0.2 mmol), high iron nontronite (600 mg/mmol) and toluene (5 mL). After refluxing for 48 h, the reaction was worked up as described above and ^{1}H NMR conversion and yield (%) were determined with CH_2Br_2 (0.5 mmol) as internal standard.

^{1}H NMR Conversion: 100 %; ^{1}H NMR Yield **(*N*-benzylideneaniline (3-27)): 64 %**; ^{1}H NMR ($CDCl_3$, 300 MHz) **(*N*-benzylideneaniline (3-27)):** δ 8.49 (s, 1H), 7.98 – 7.91 (m, 2H), 7.54 – 7.39 (m, 5H), 7.30 – 7.18 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 152.1, 136.2, 131.3, 129.1, 128.8, 128.7, 125.9, 120.8. ^{1}H and ^{13}C NMR spectral data is consistent with previously reported values.[77] ^{1}H NMR Yield **(benzaldehyde (3-28)):** 6 %.

Section 3.5.5. General Procedure for Optimization Reactions for the Oxidation of Aldehydes to Carboxylic Acids

A mixture of aldehyde (0.5 mmol) and high iron nontronite clay was stirred at the specified temperature (rt or reflux) for the given time in the solvent (5 mL) under O_2 atmosphere. The reaction was cooled to room temperature and was filtered using a fritted glass funnel. The clay was washed with the same solvent (10 mL) used in the reaction. After the clay was filtered off, the reaction mixture was concentrated *in vacuo*, and analyzed by ^{1}H NMR using CH_2Br_2 (0.5 mmol) as internal standard.

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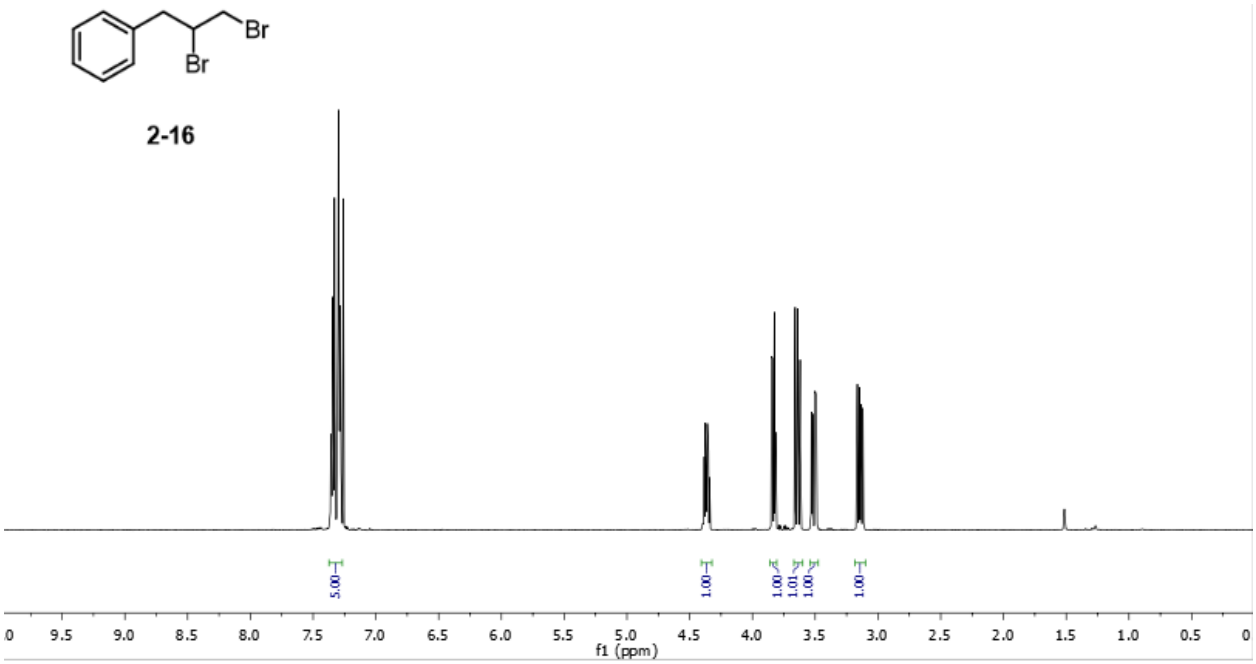
Appendix I

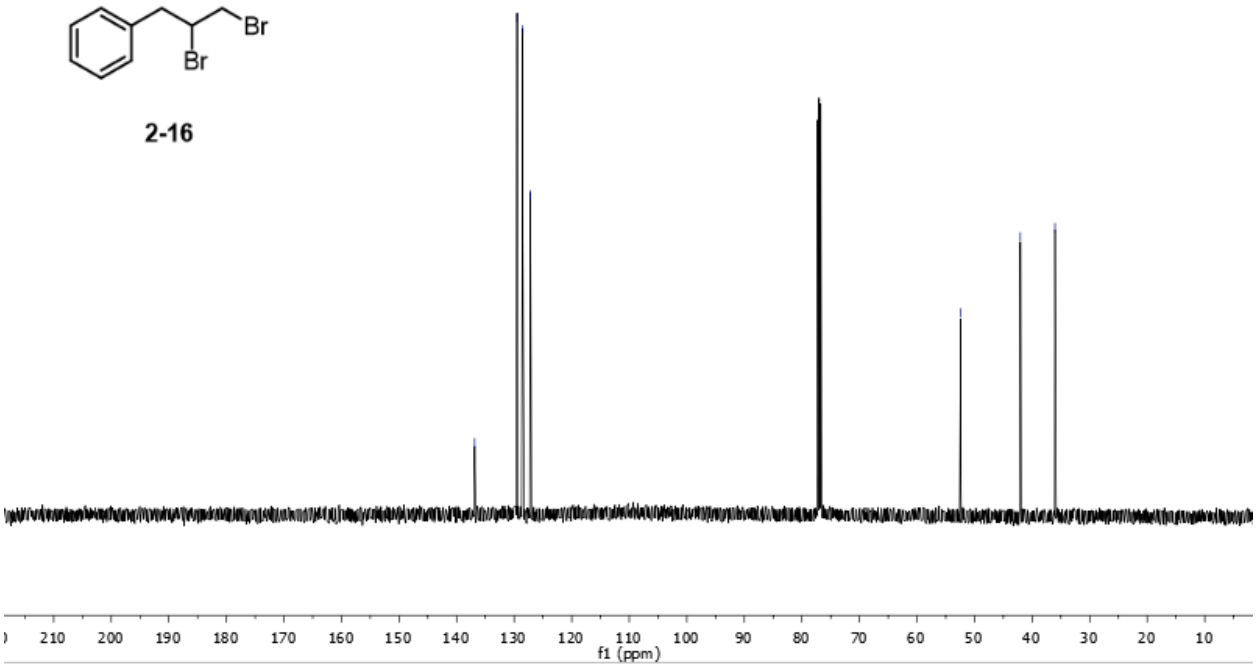
^{1}H and ^{13}C NMR spectra

Chapter 2

^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



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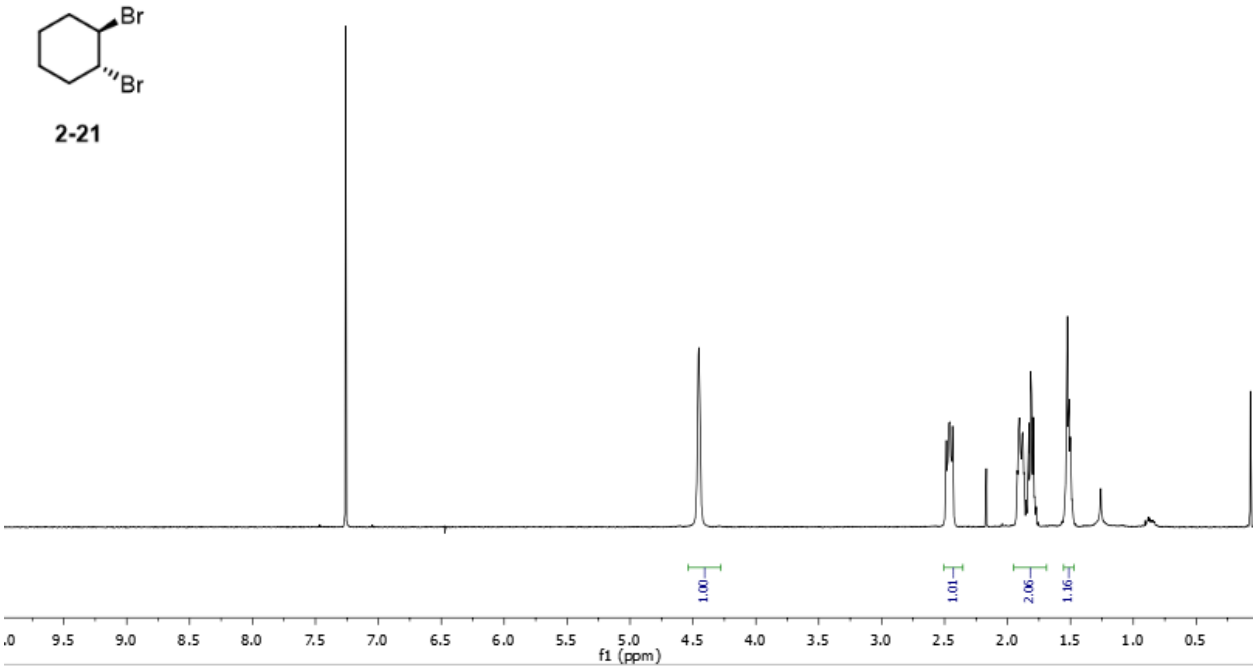

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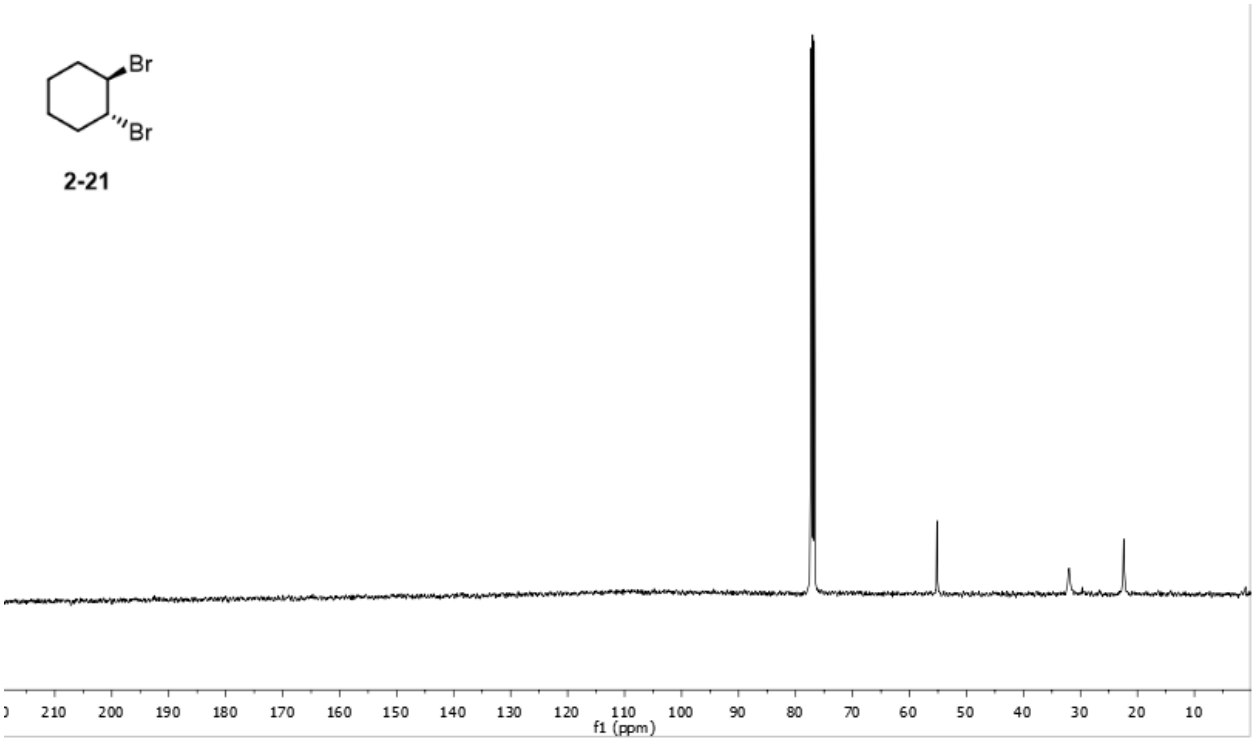

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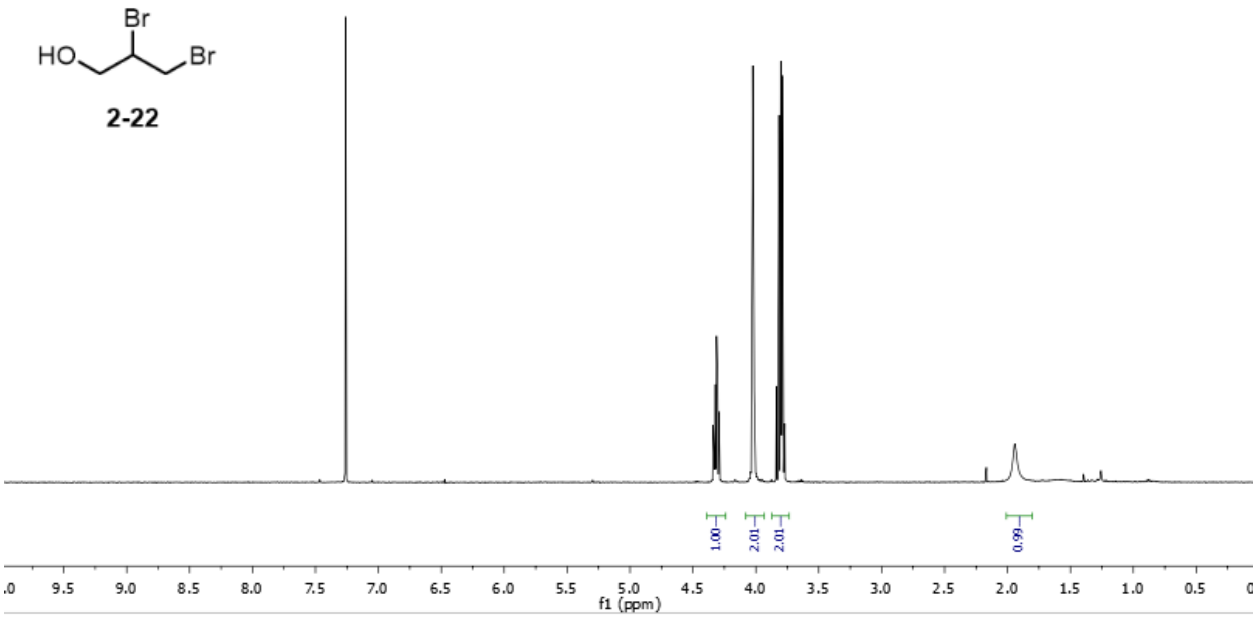

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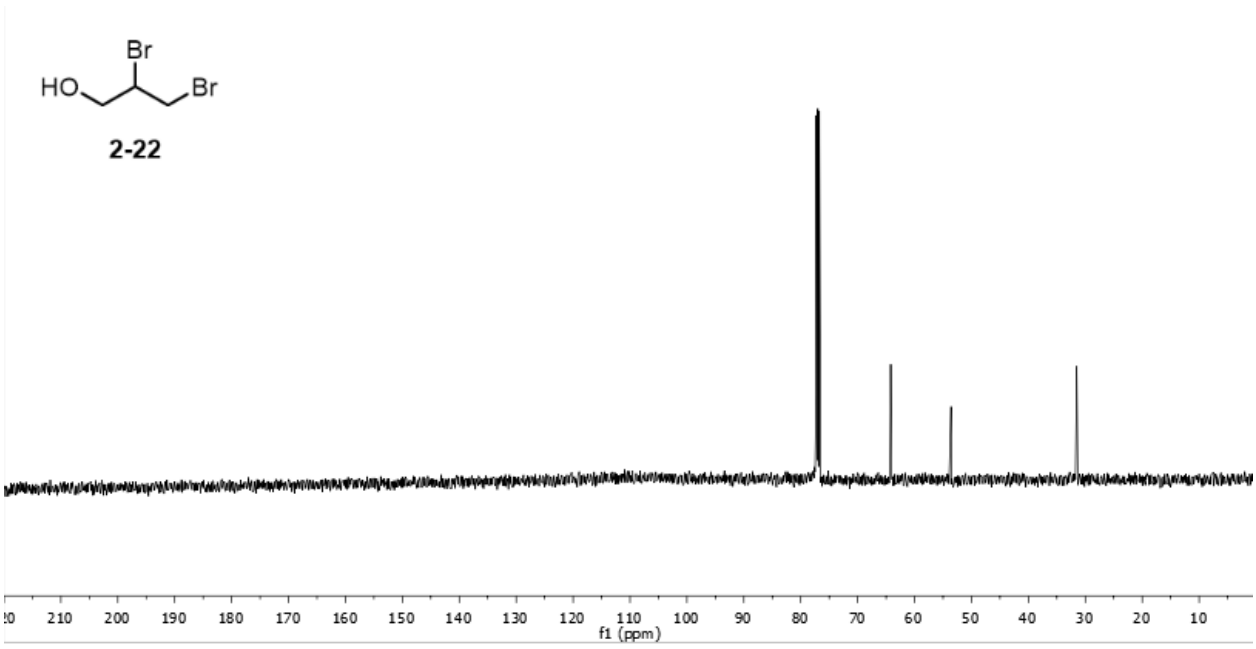

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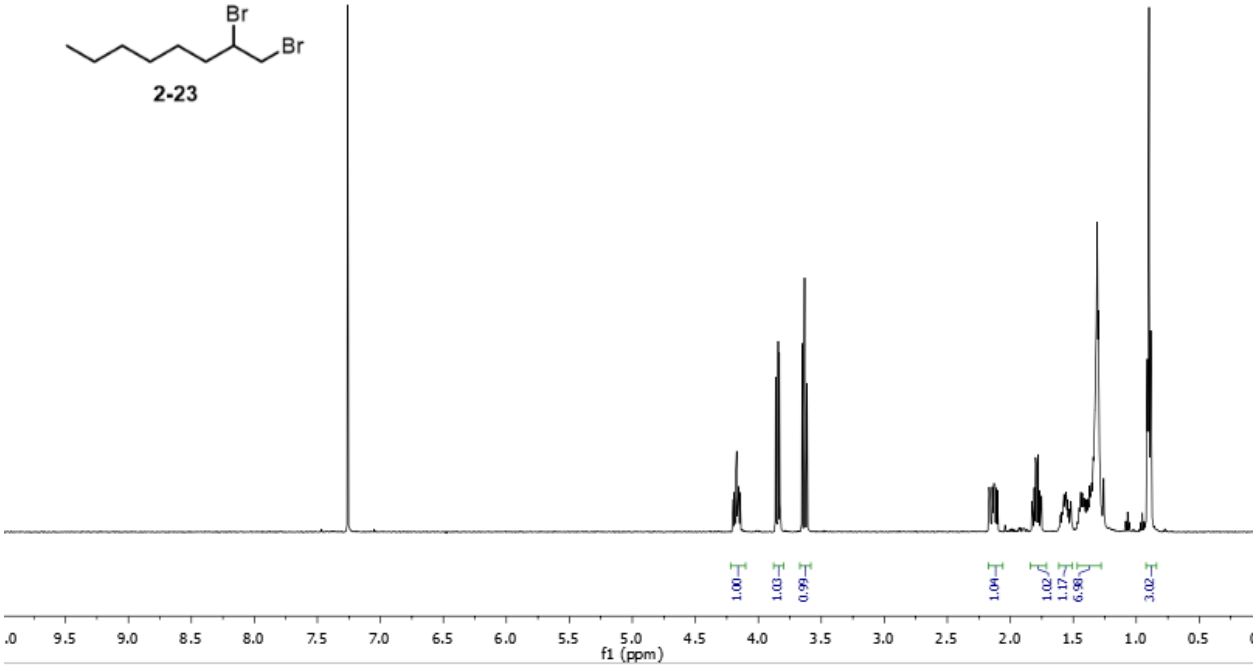

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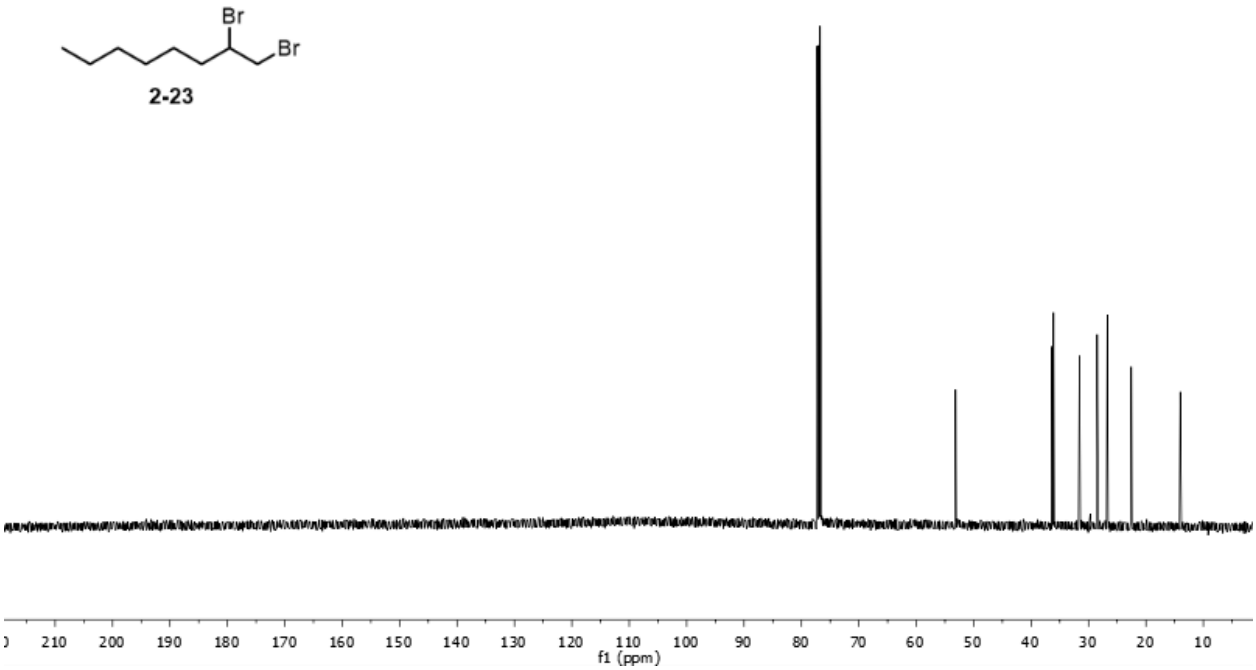

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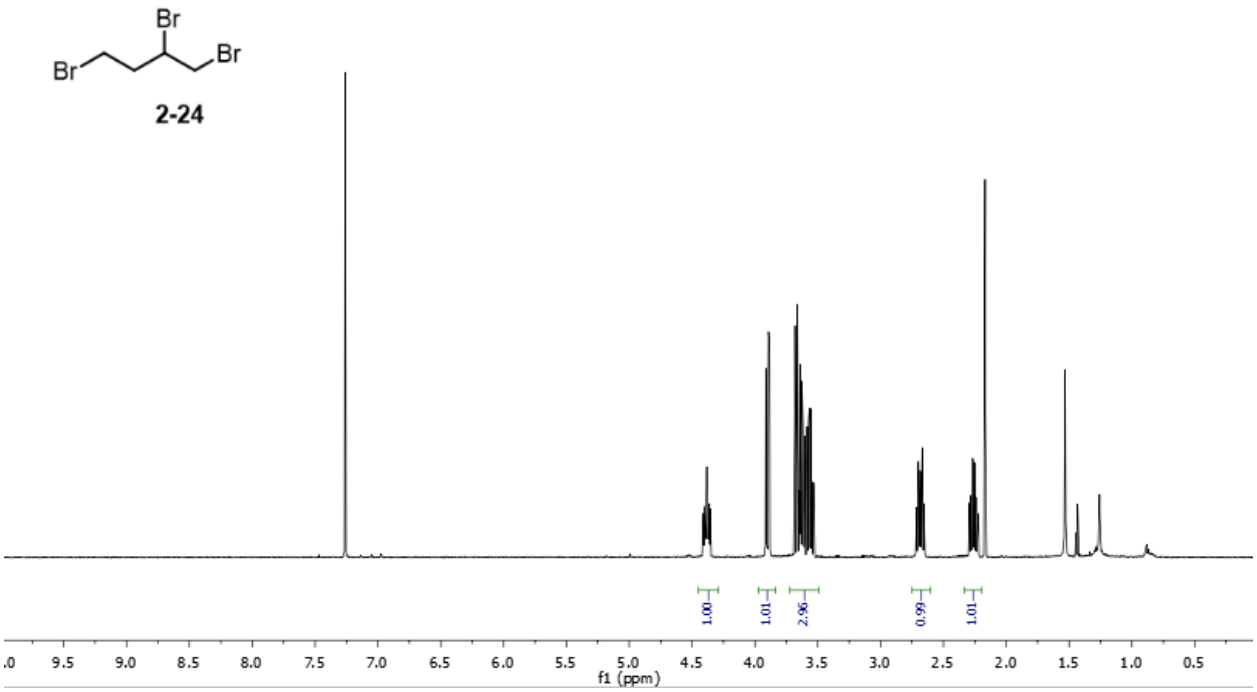

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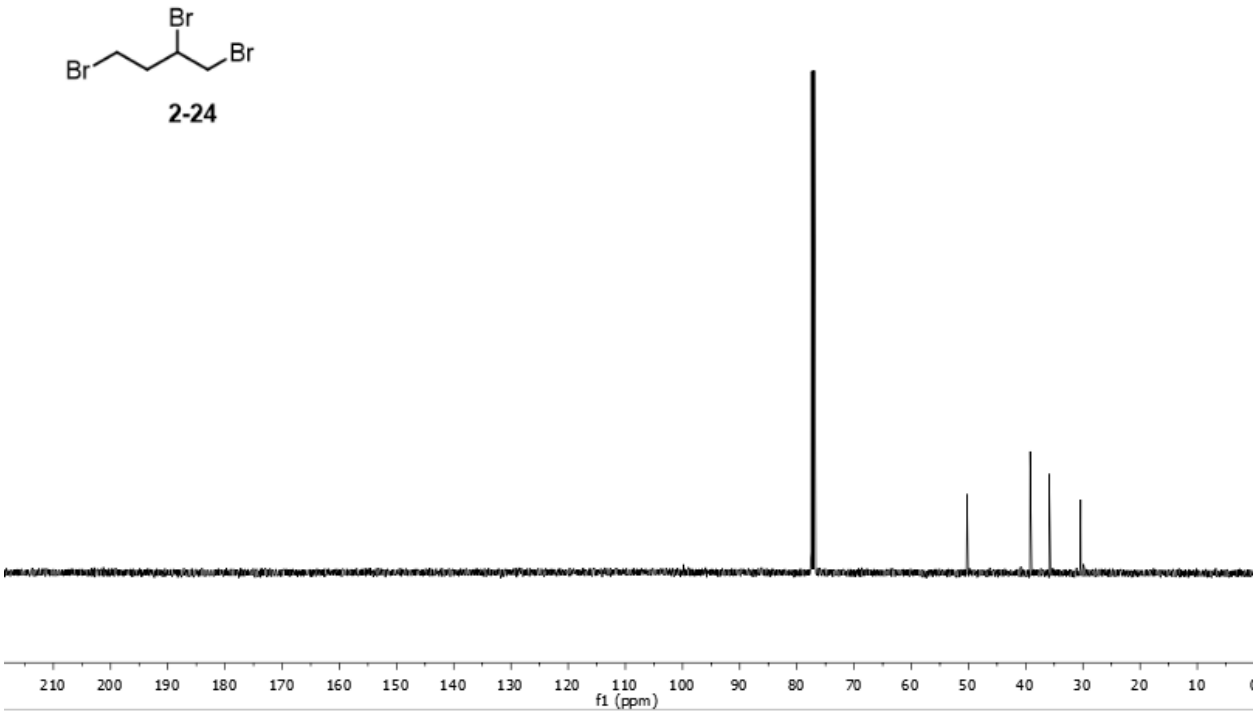

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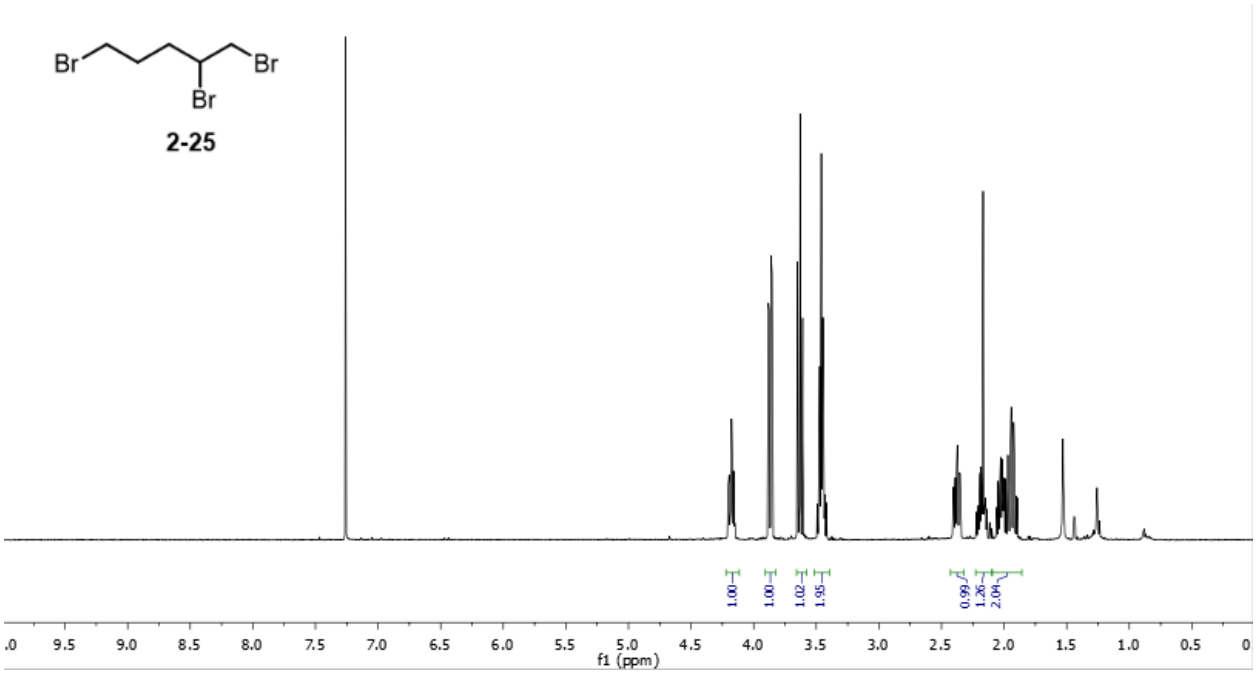

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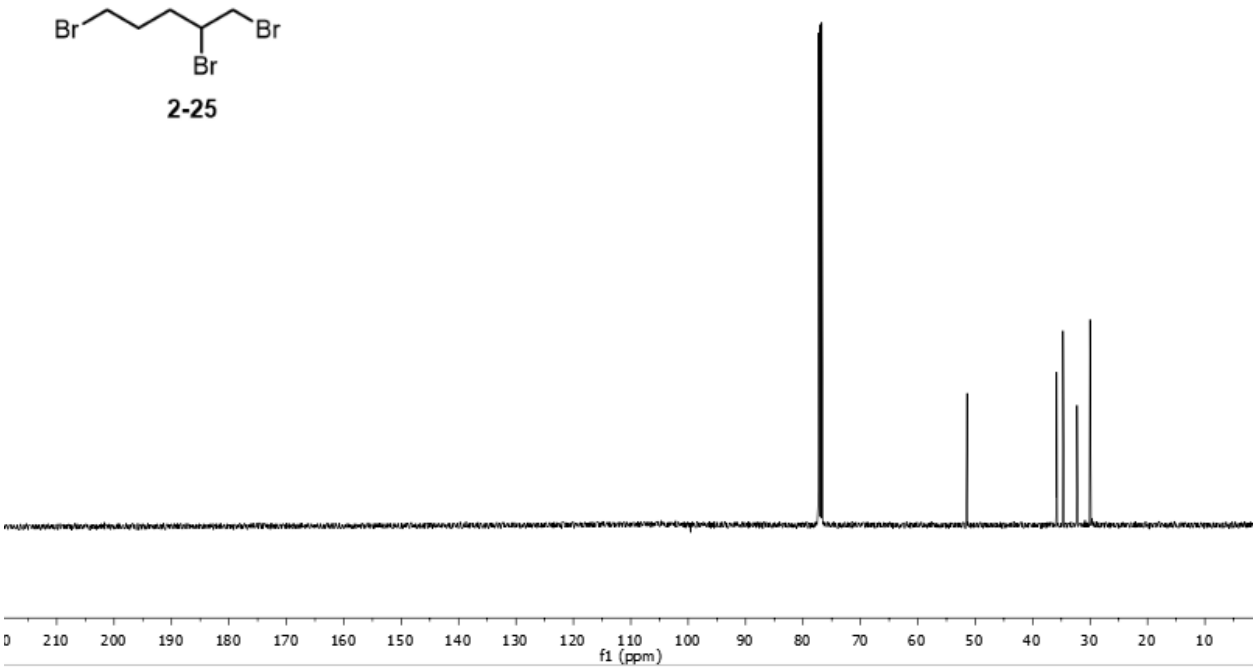

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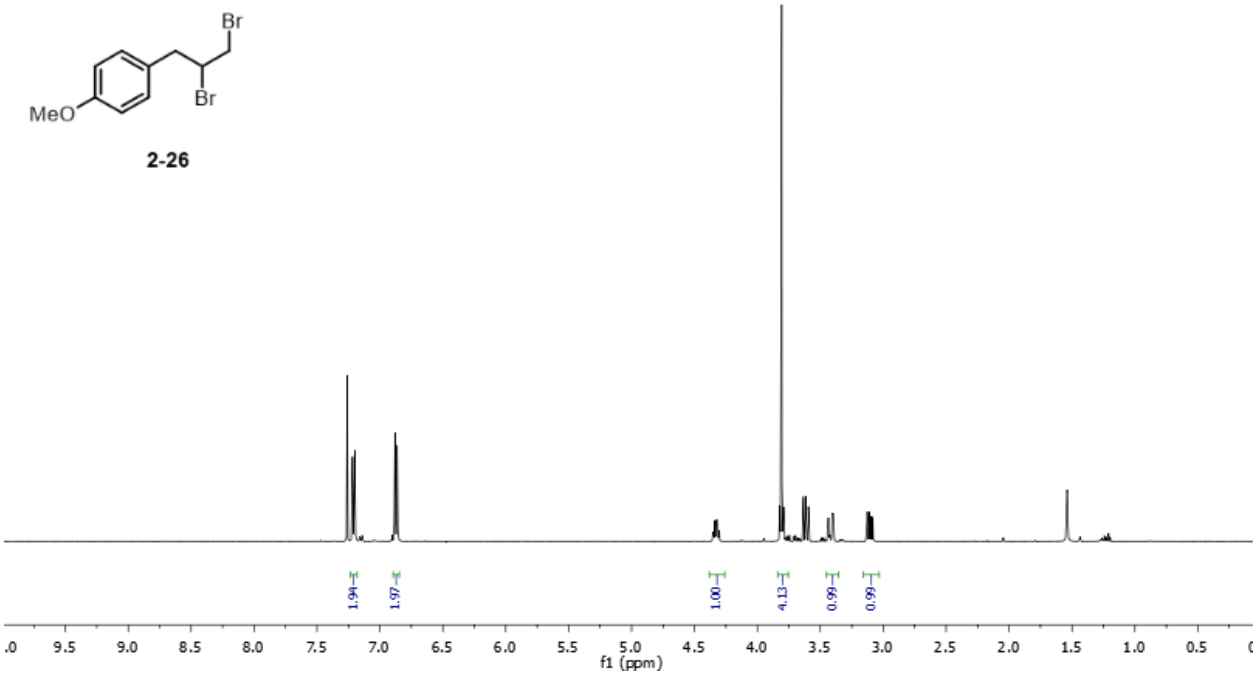

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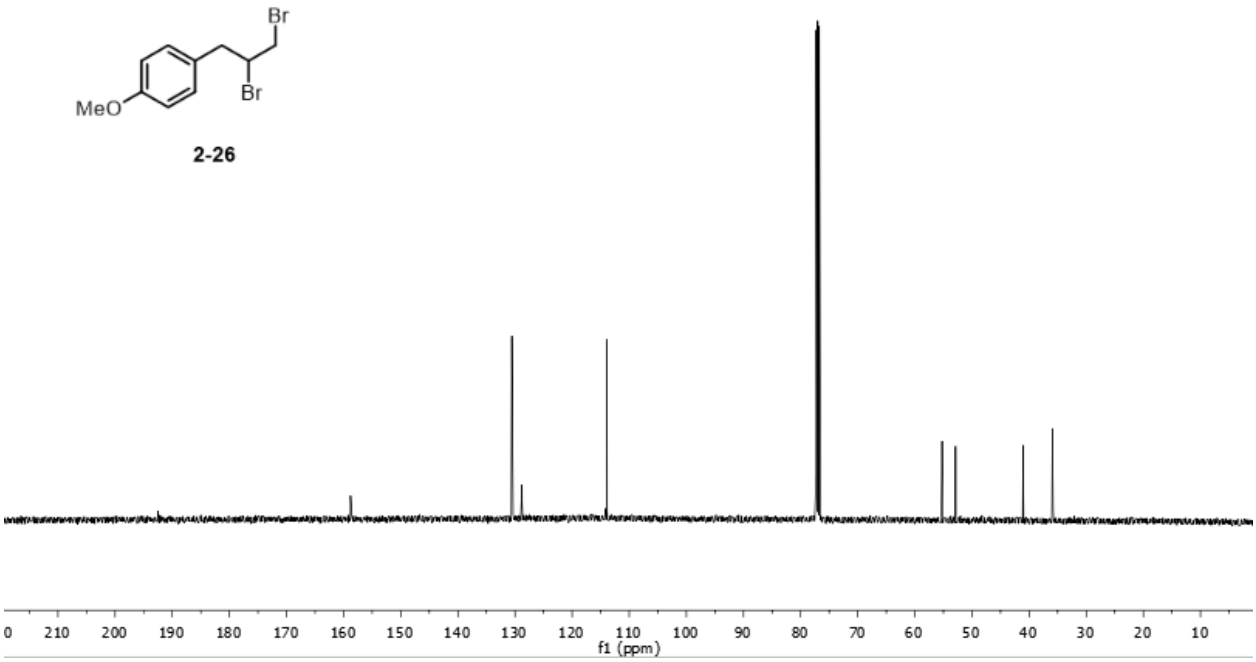

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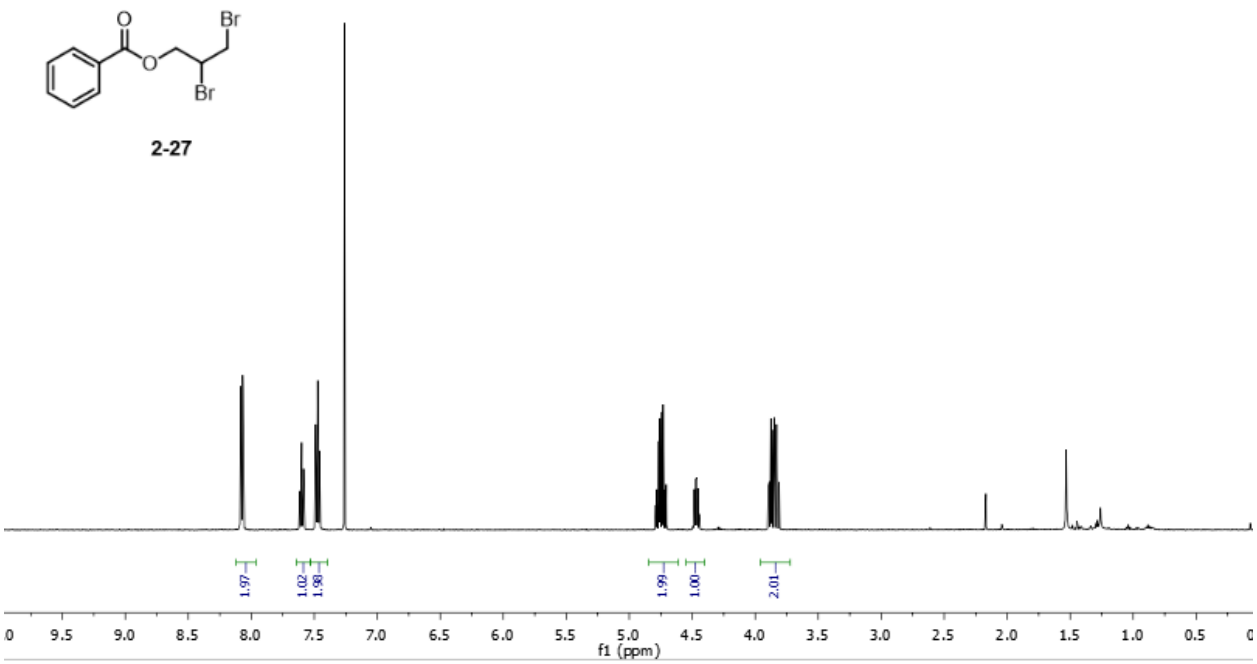

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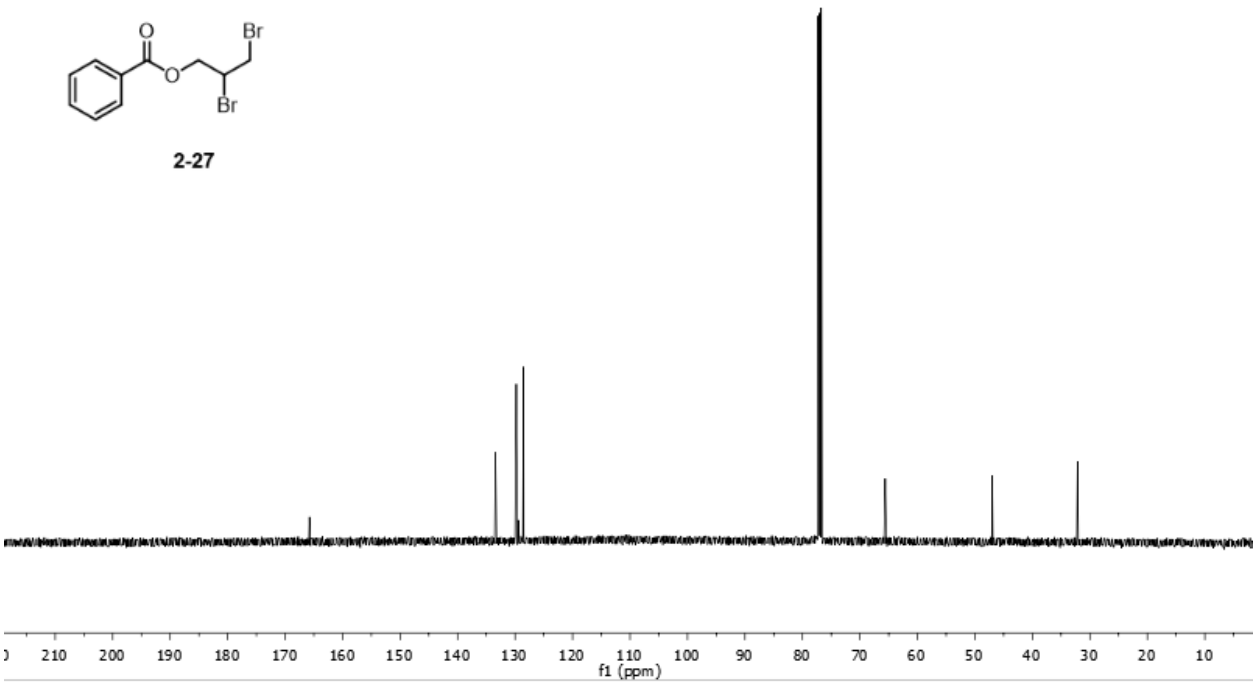

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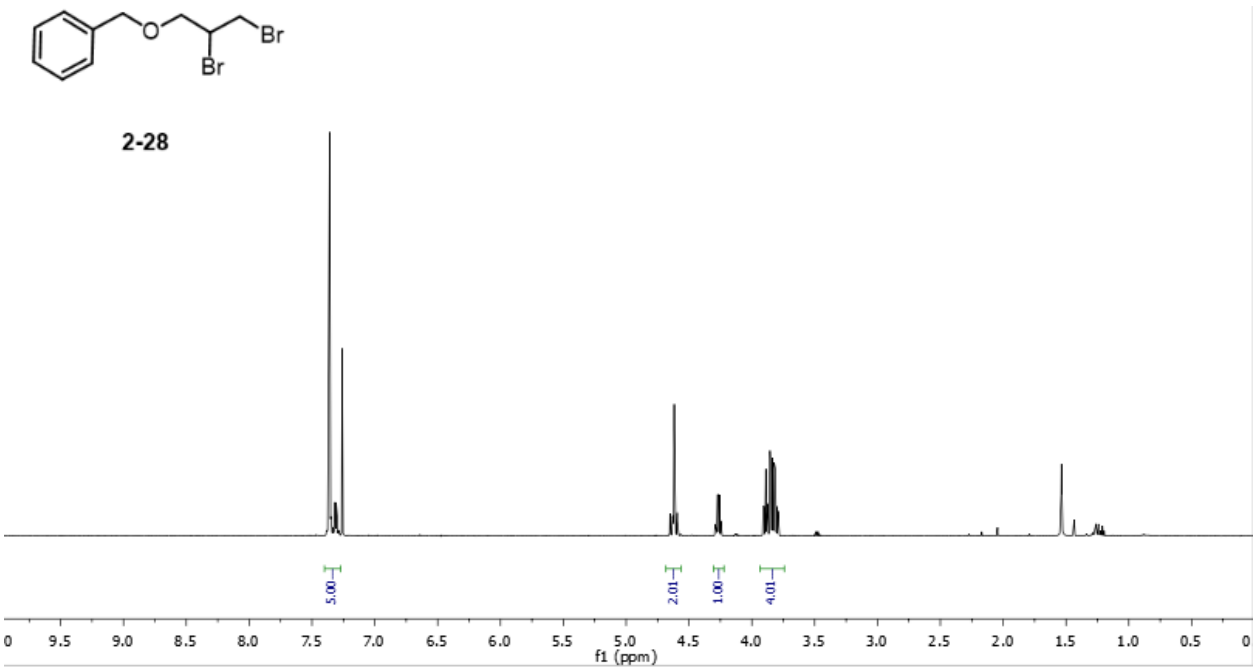

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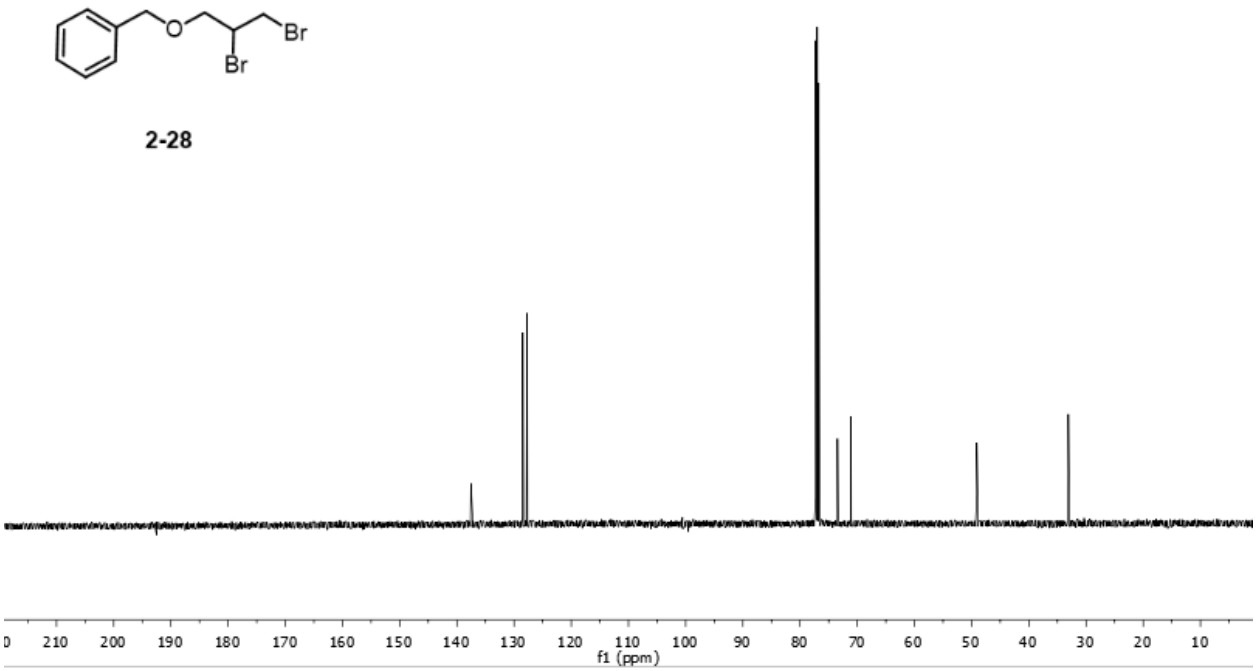

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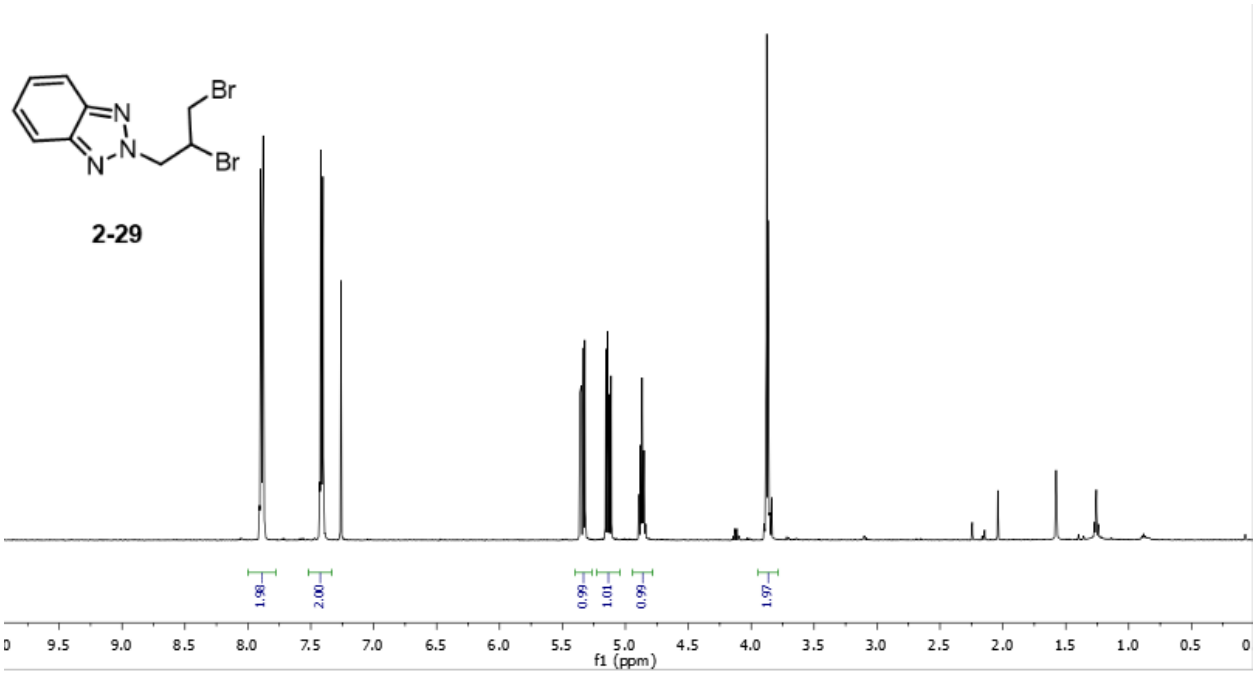

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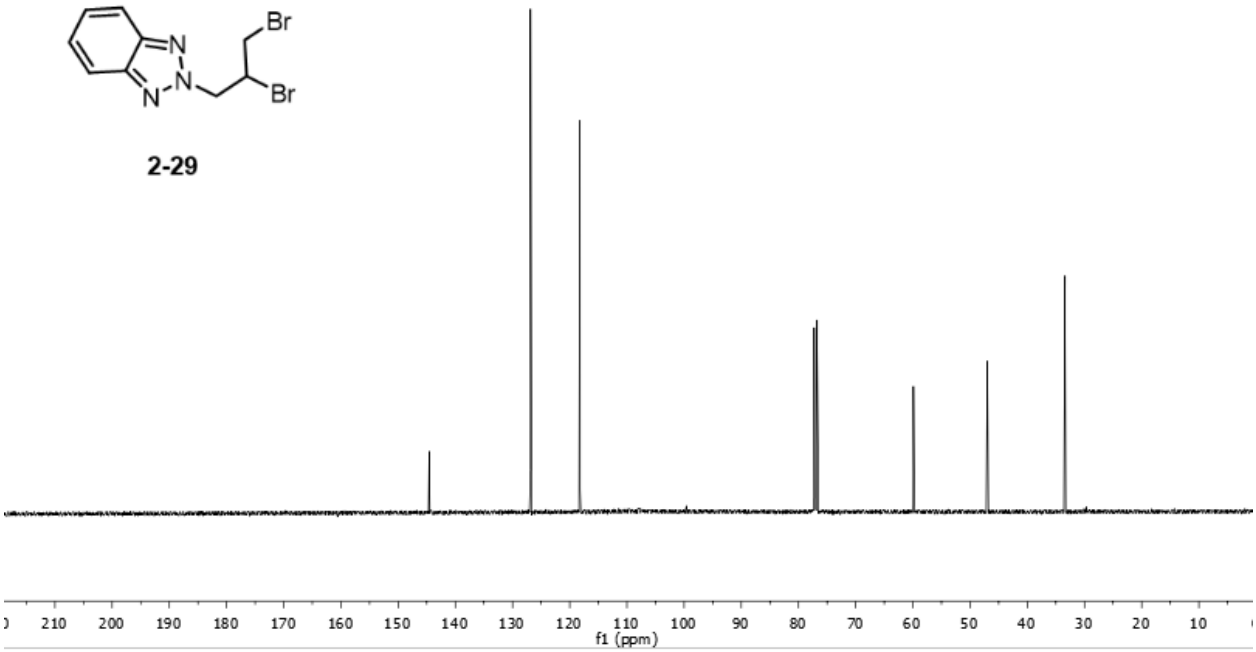

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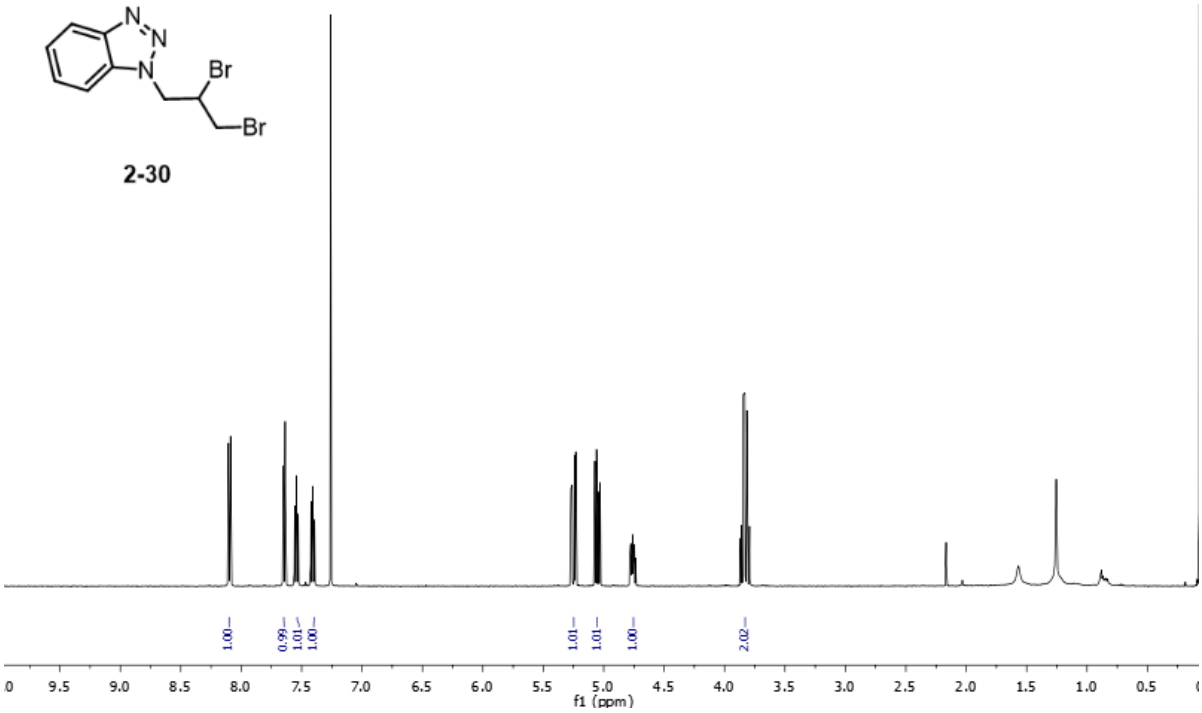

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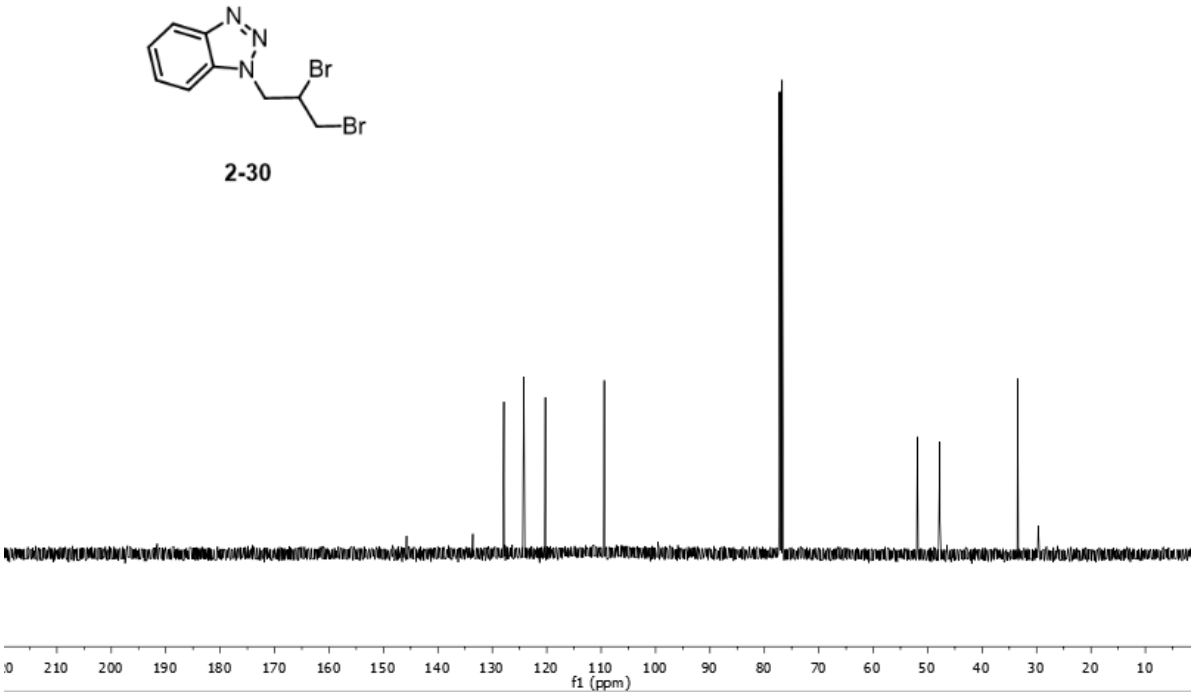

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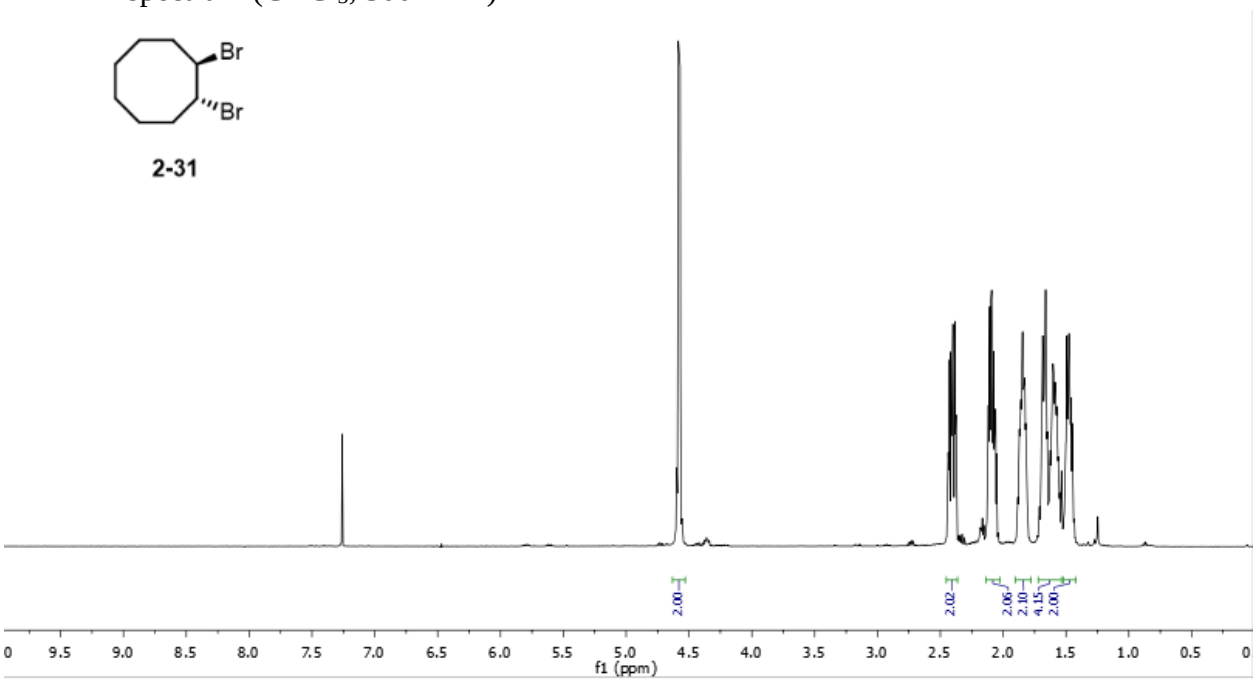

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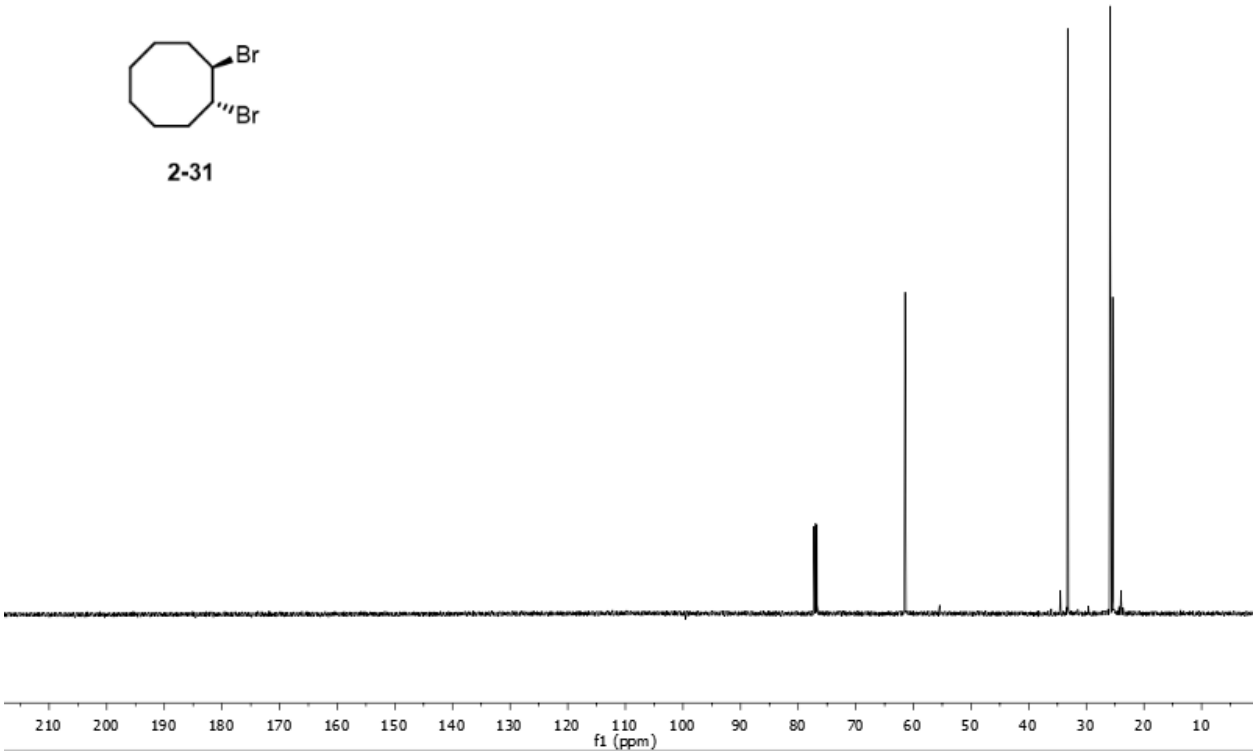

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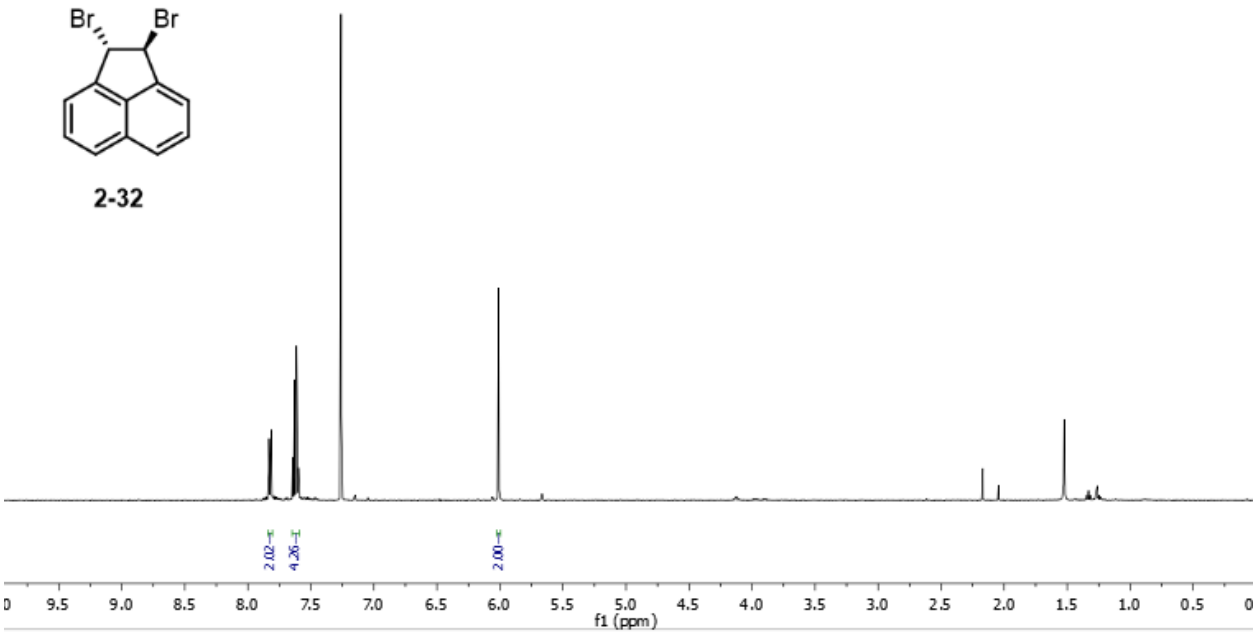

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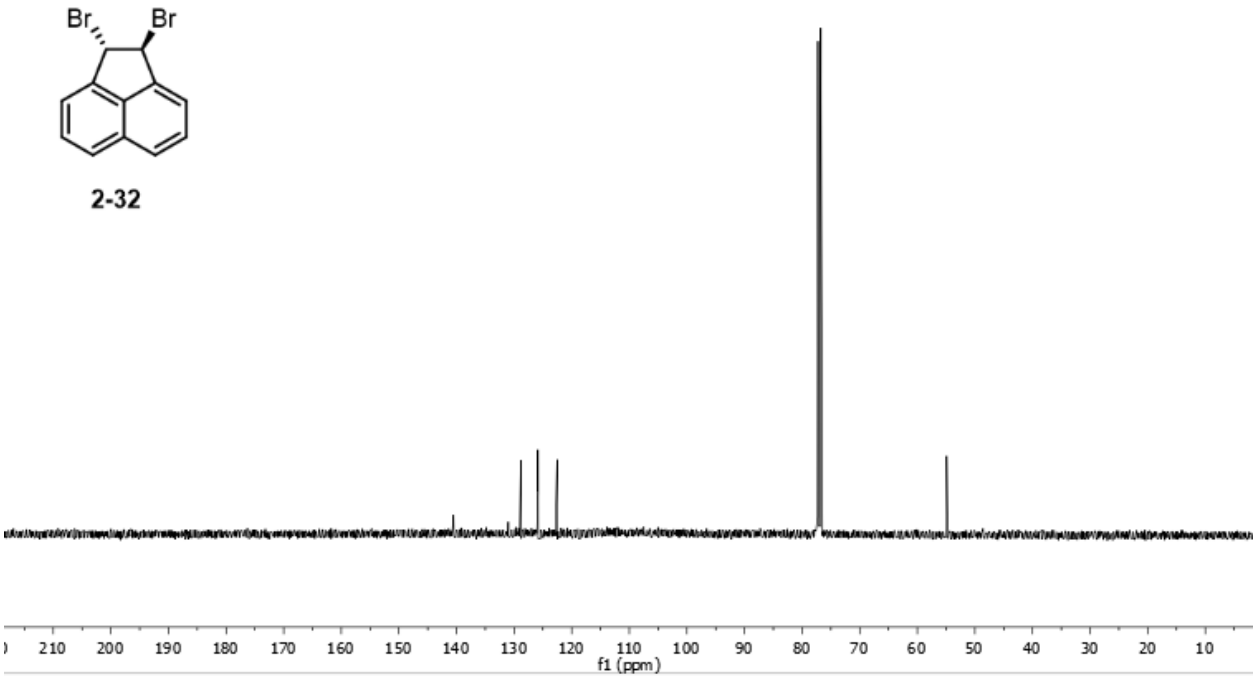

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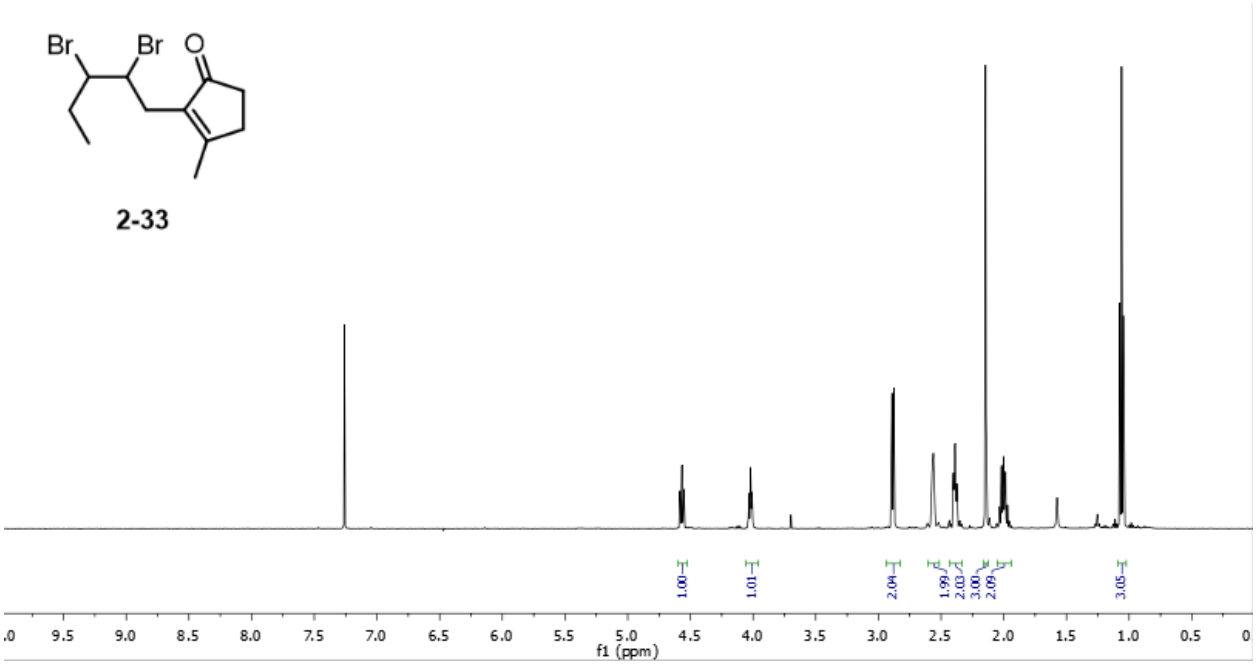

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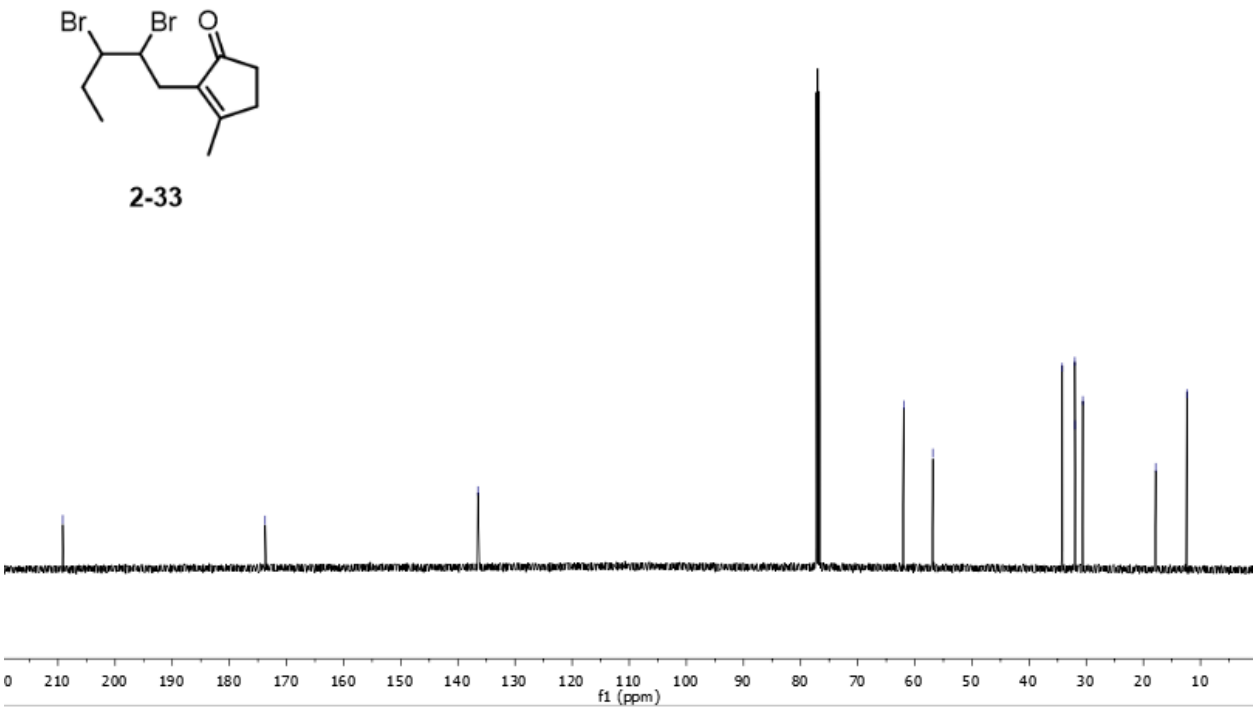

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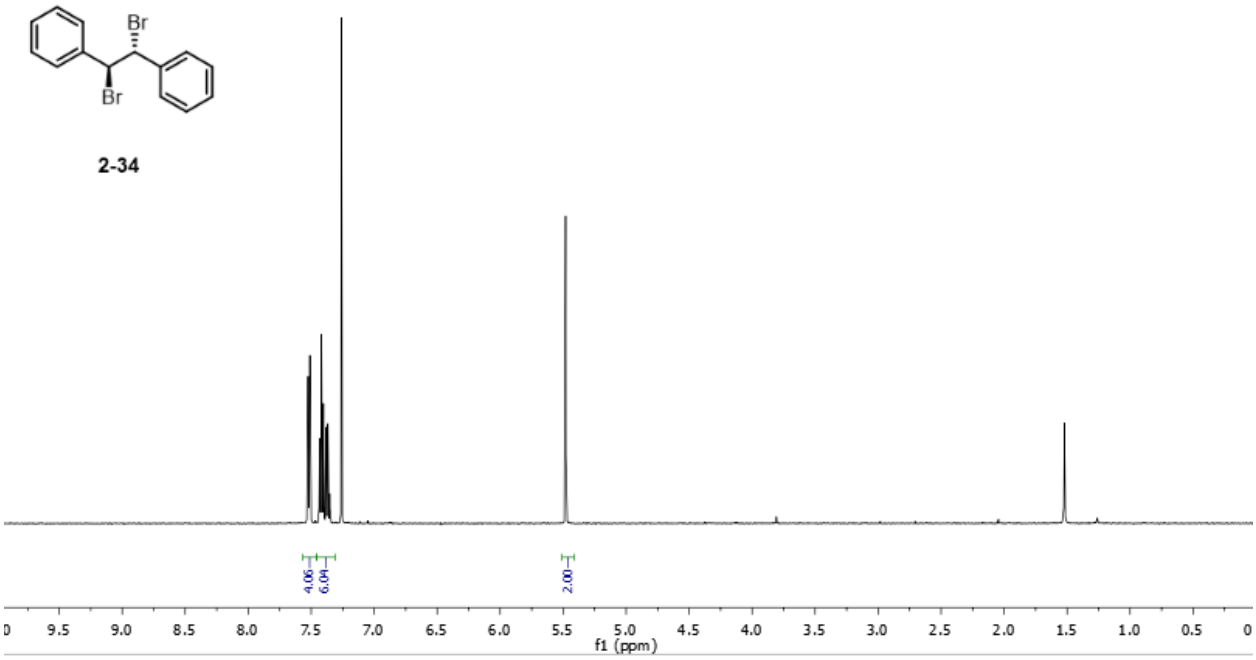

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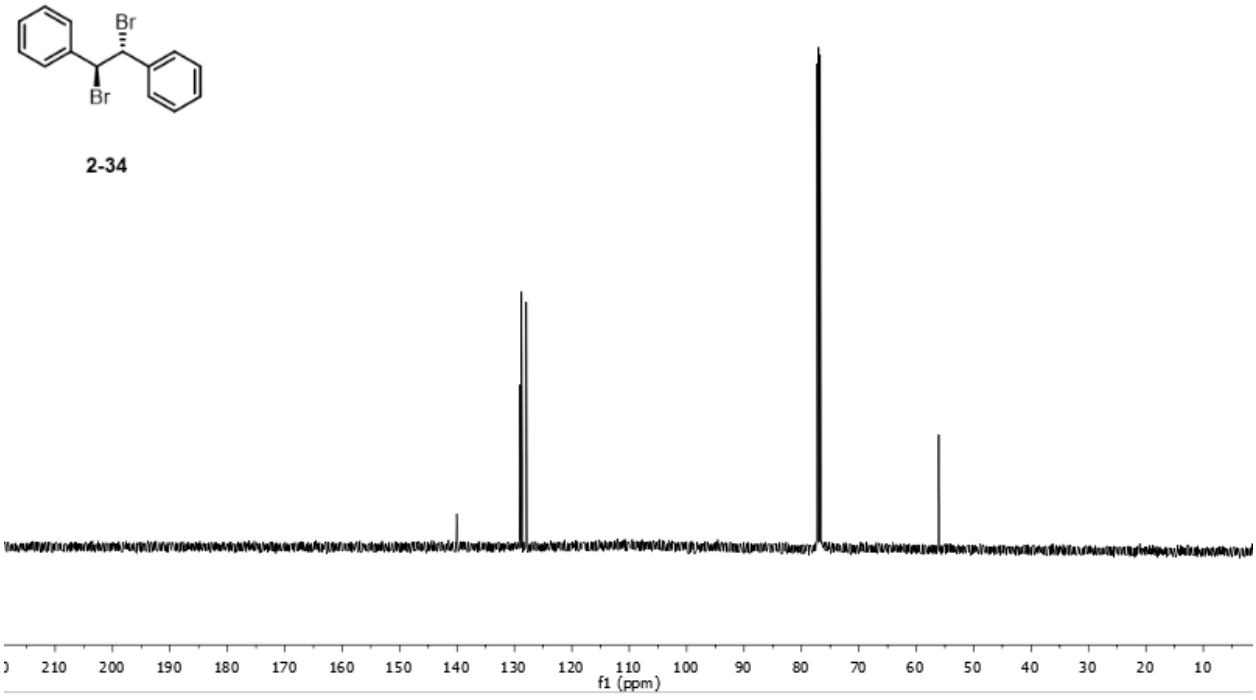

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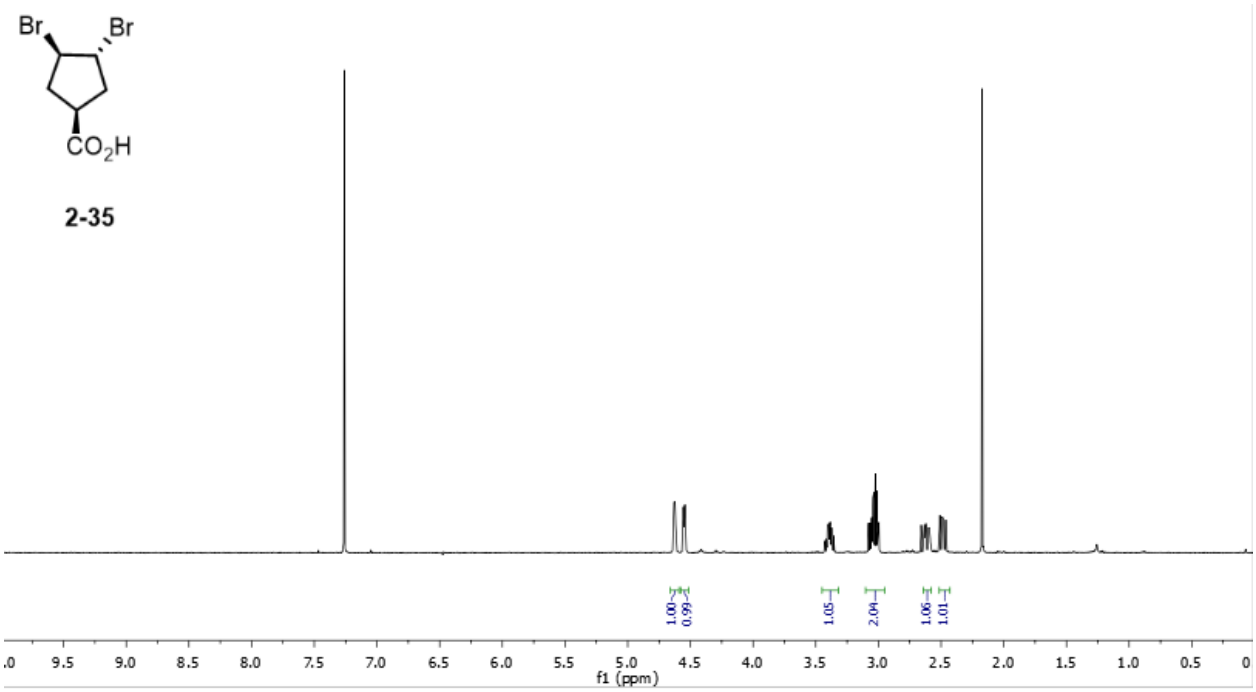

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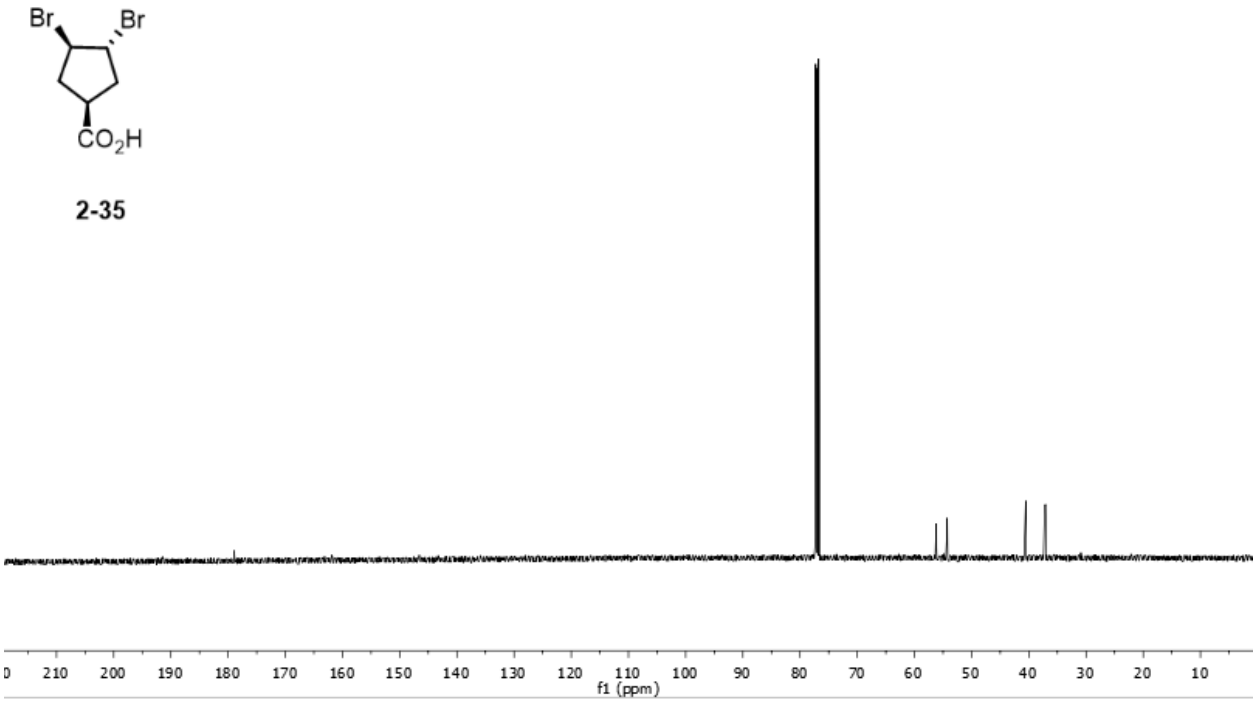

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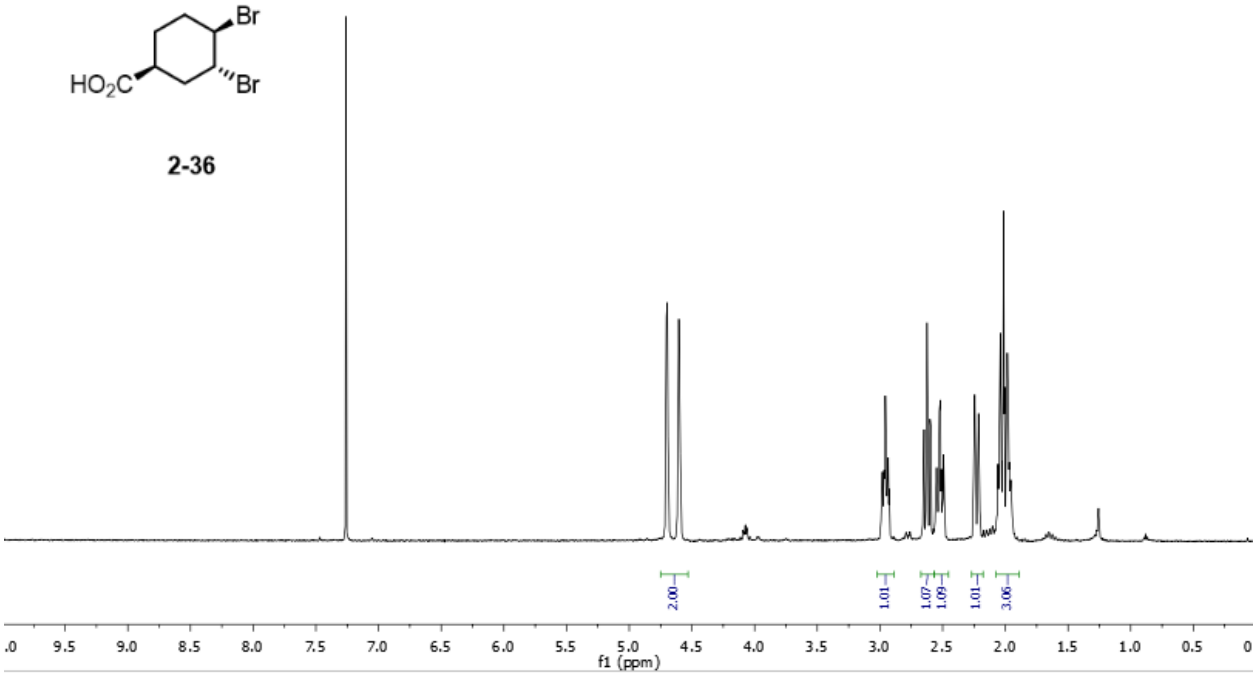

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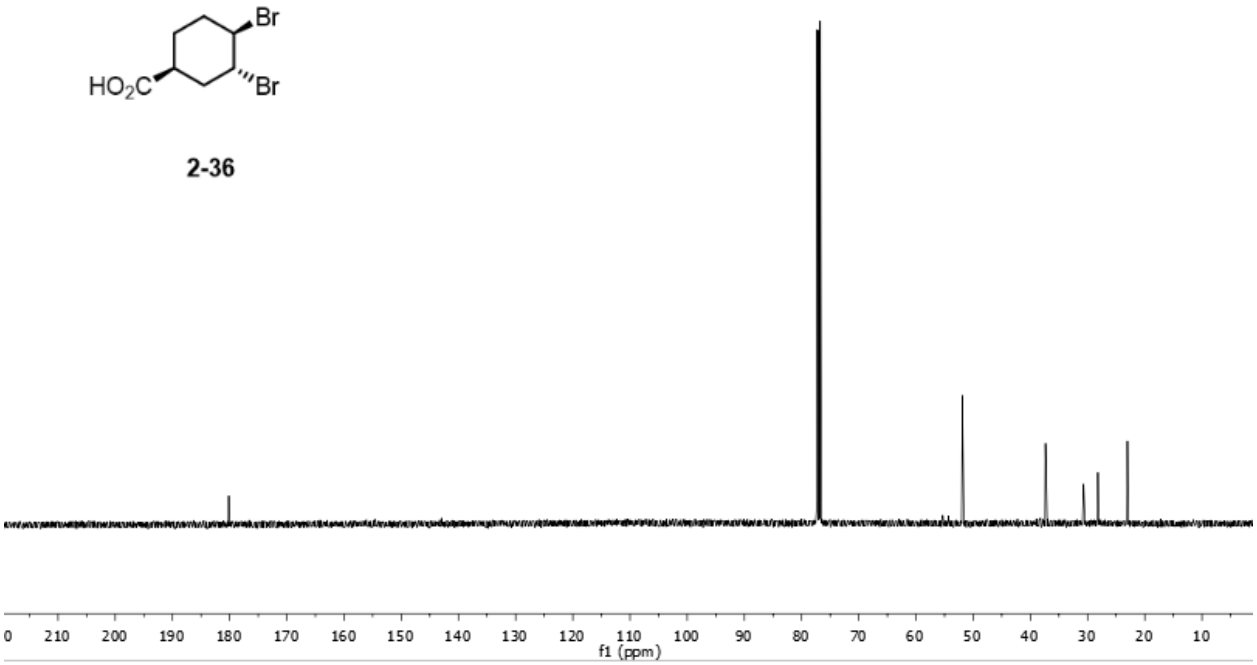

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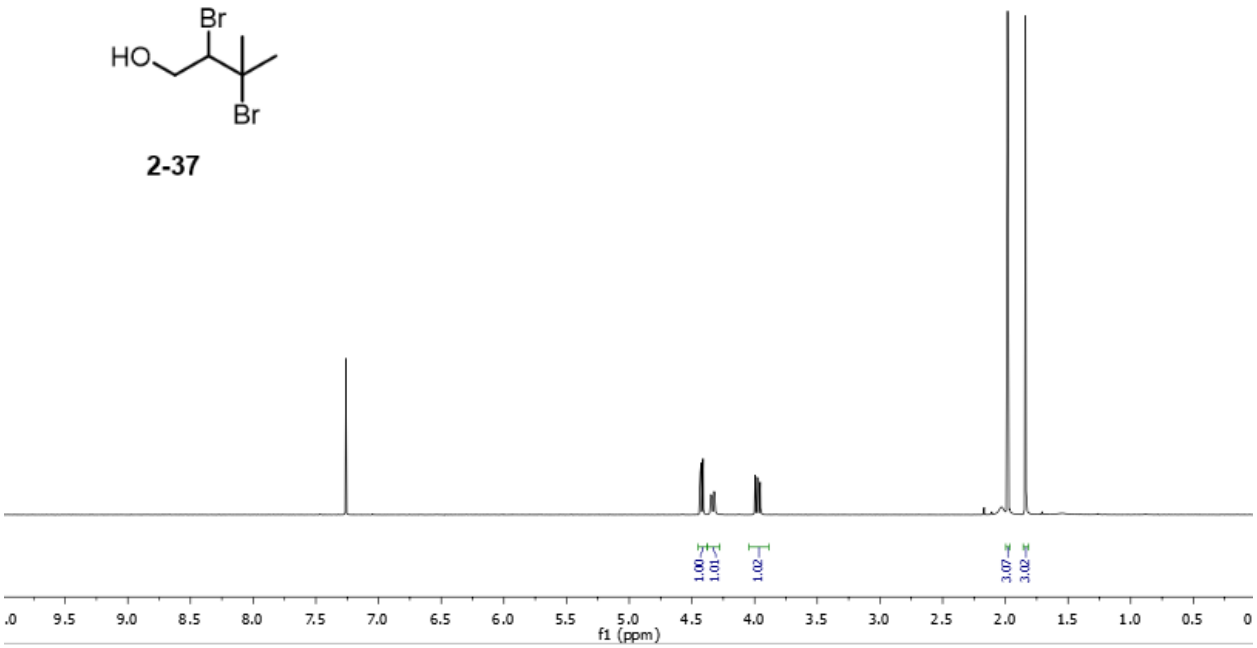

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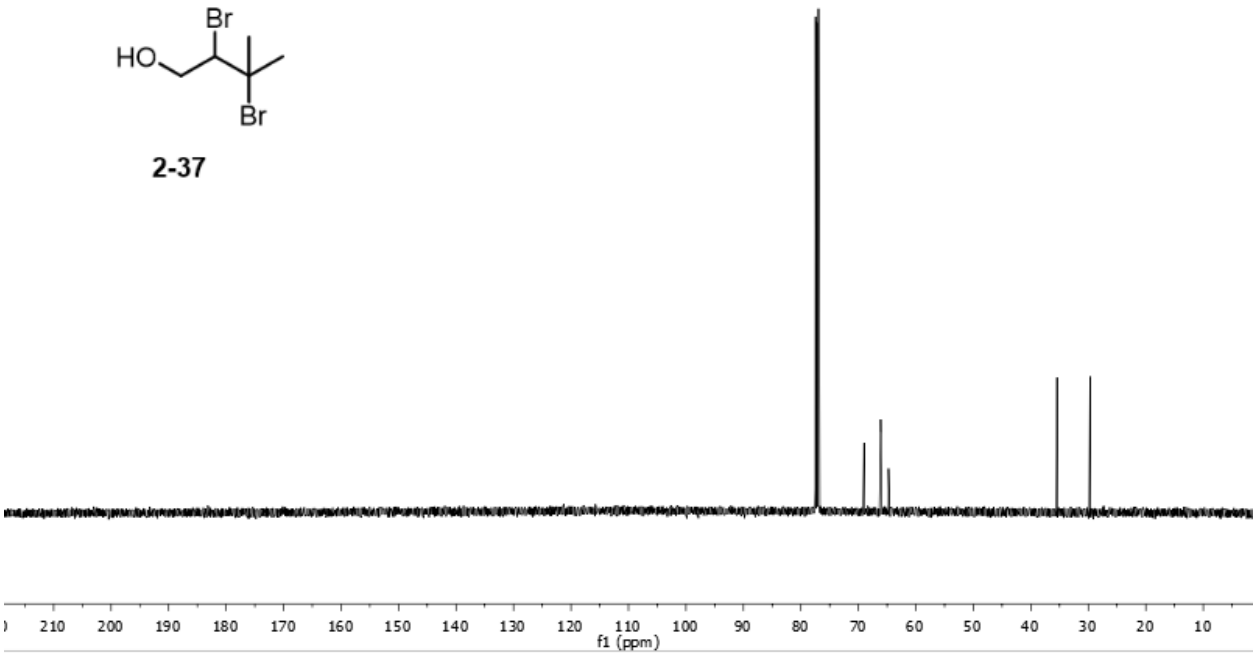

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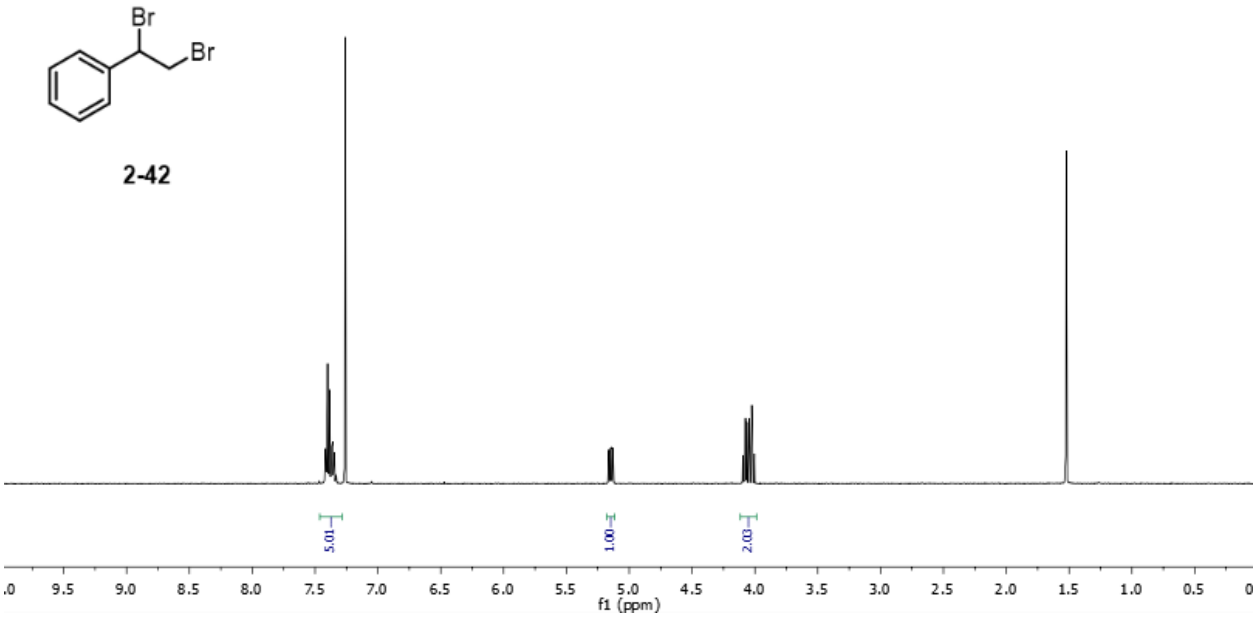
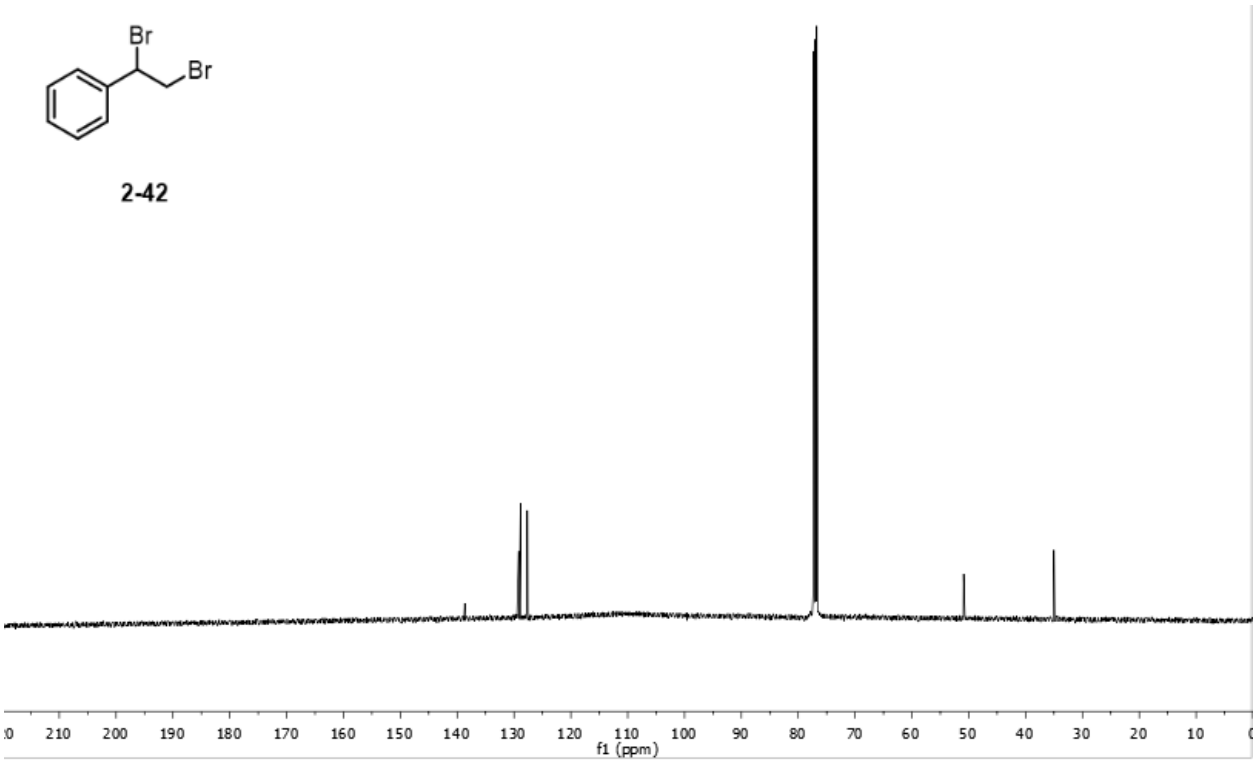
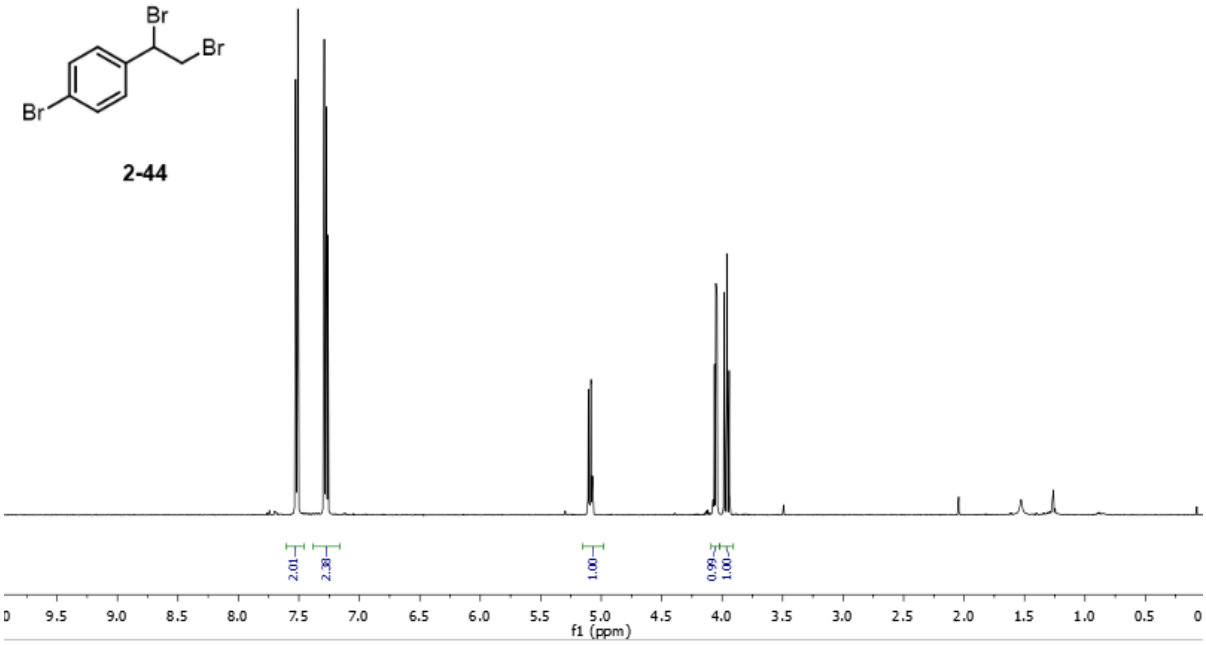


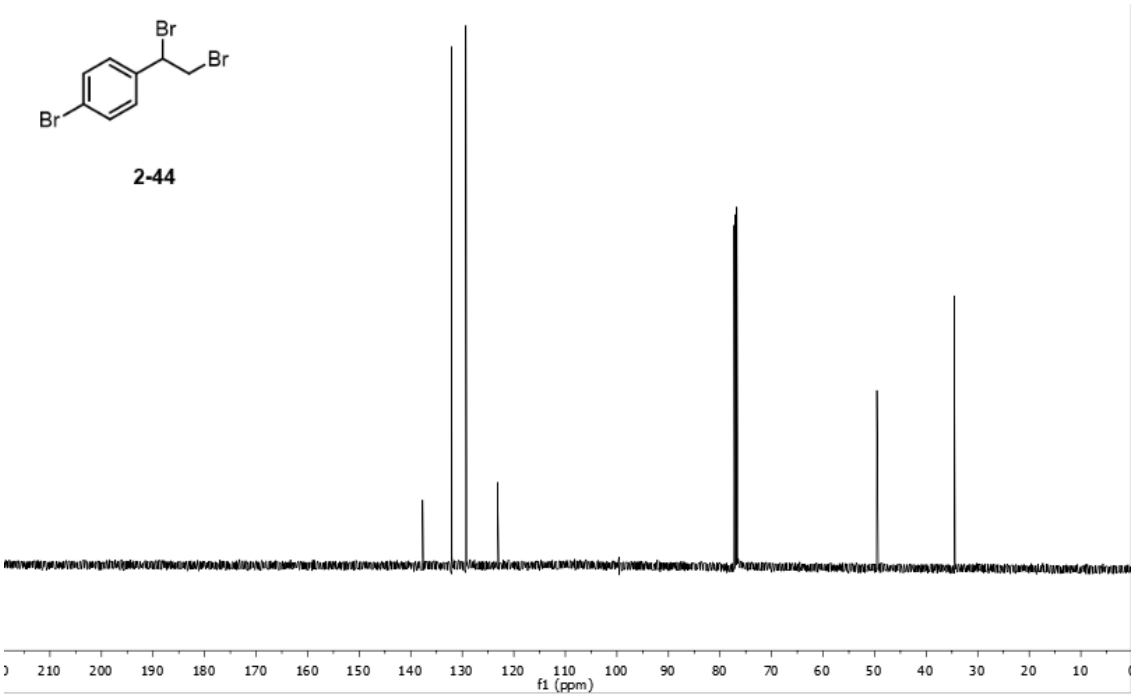
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



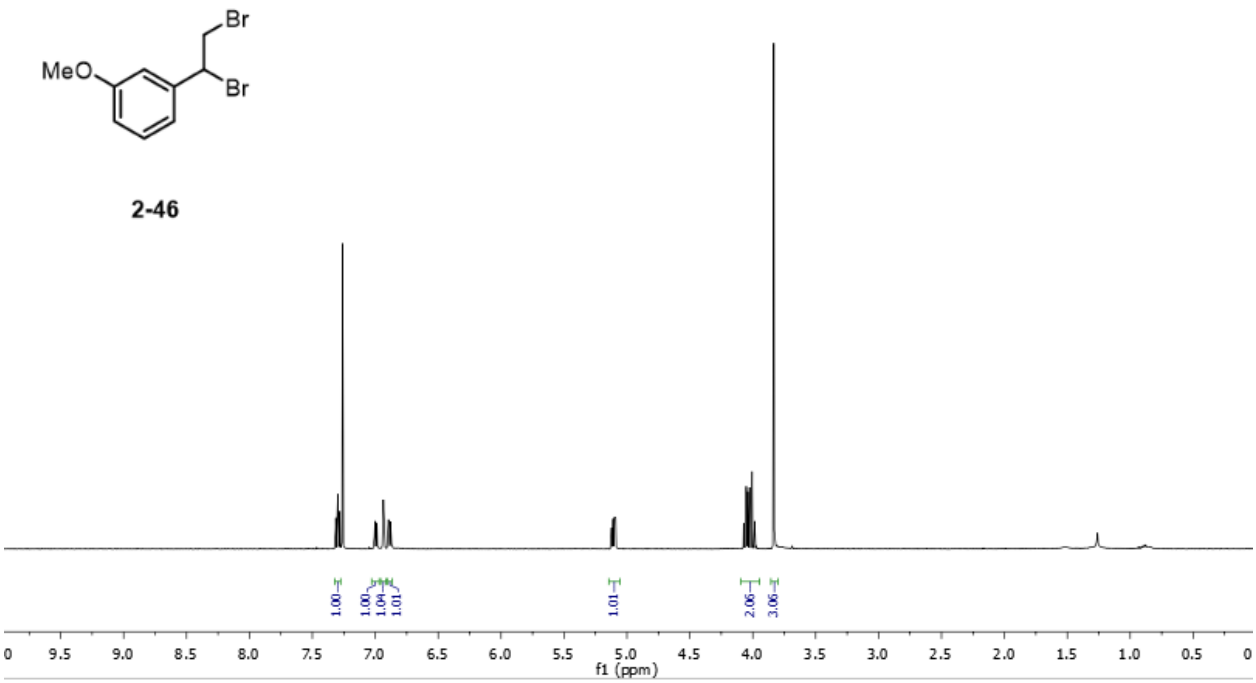
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



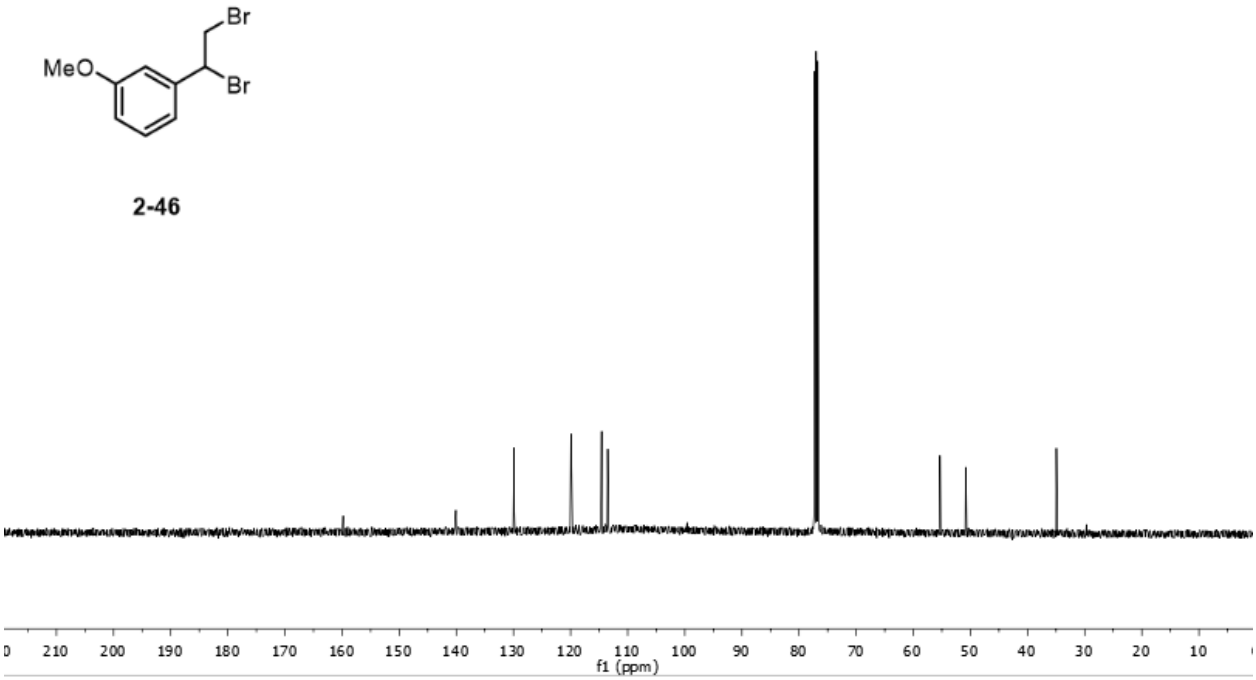
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



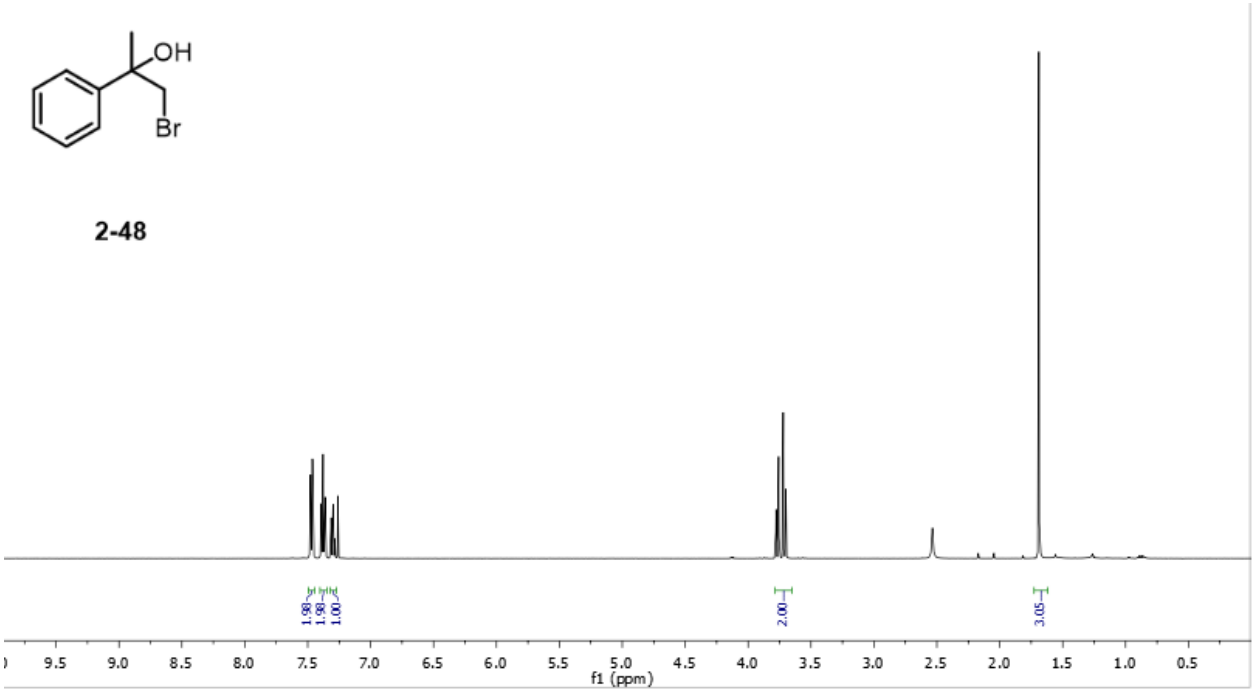
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



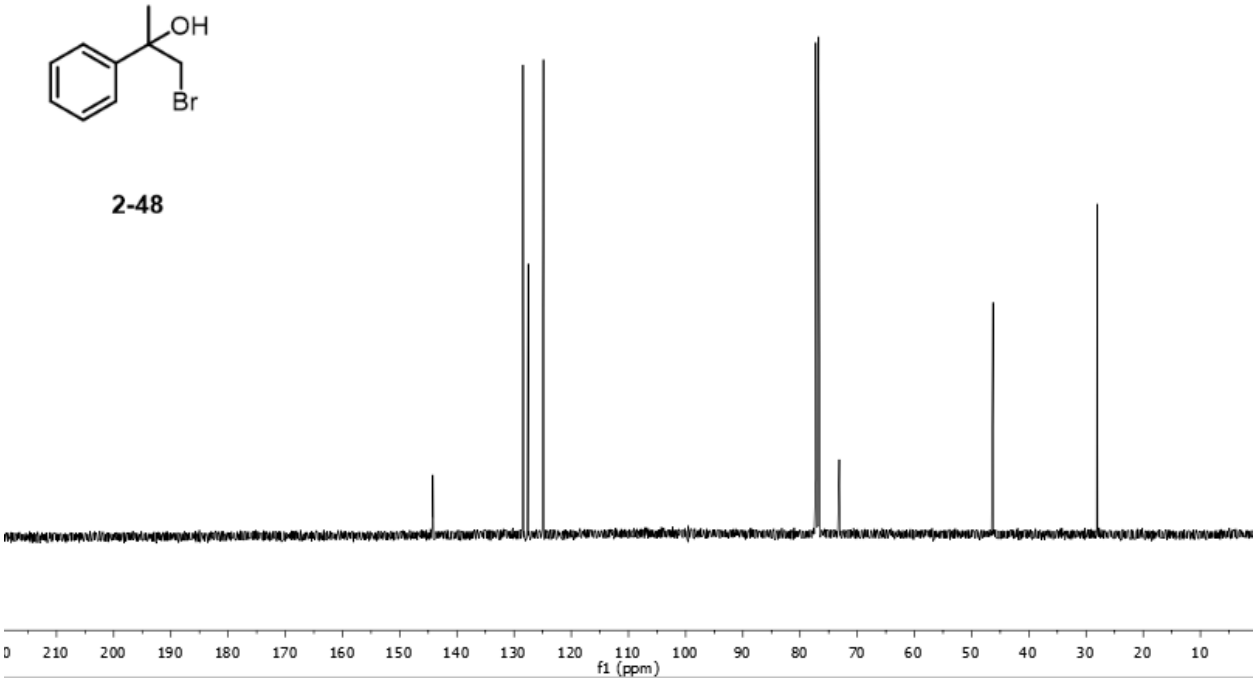
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



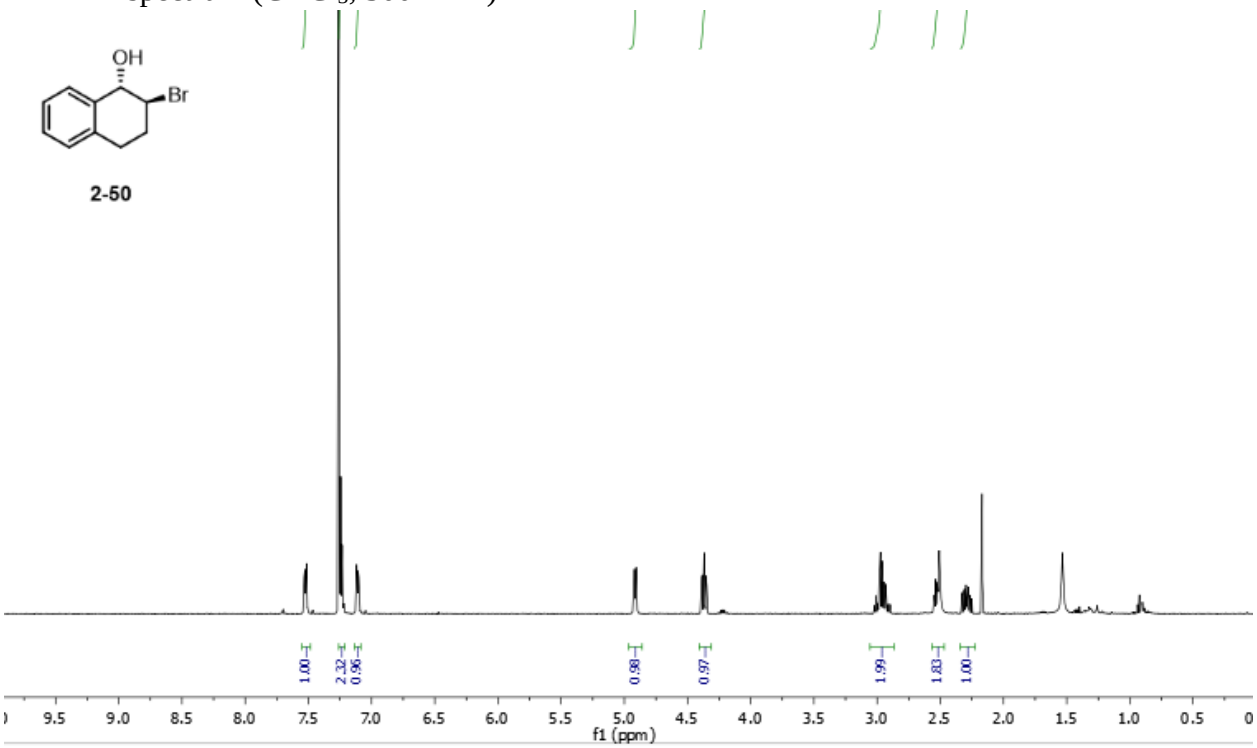
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



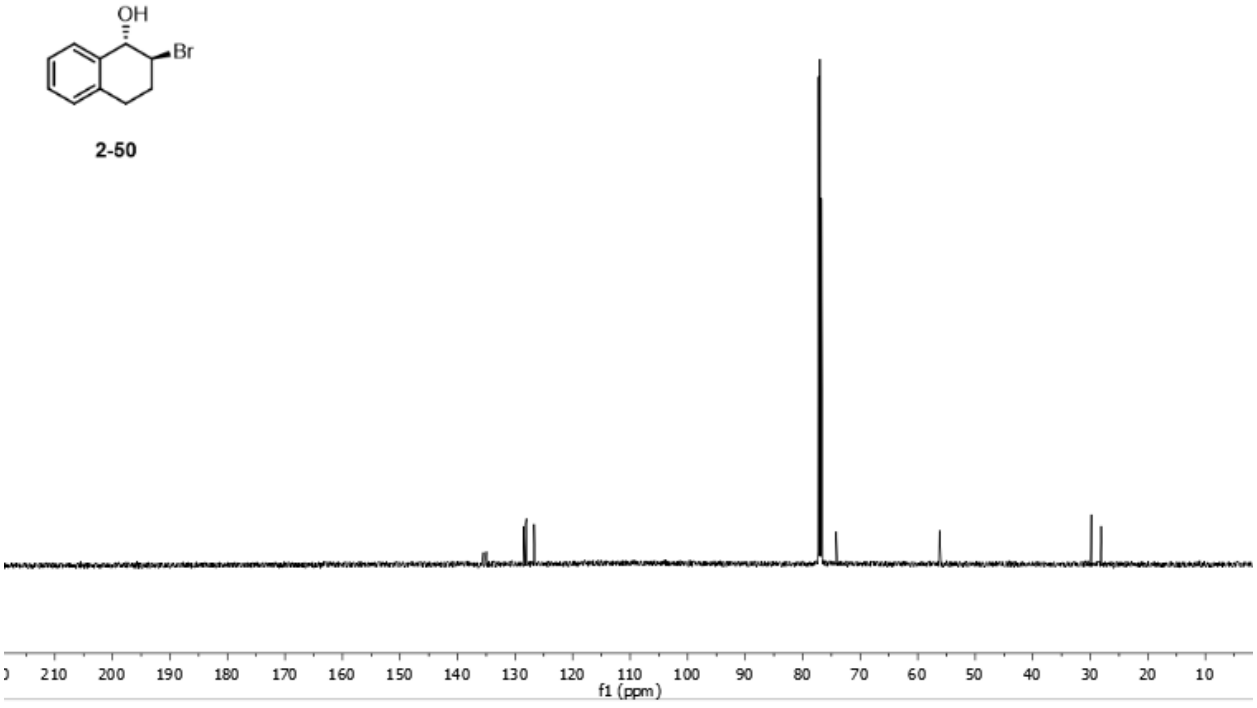
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



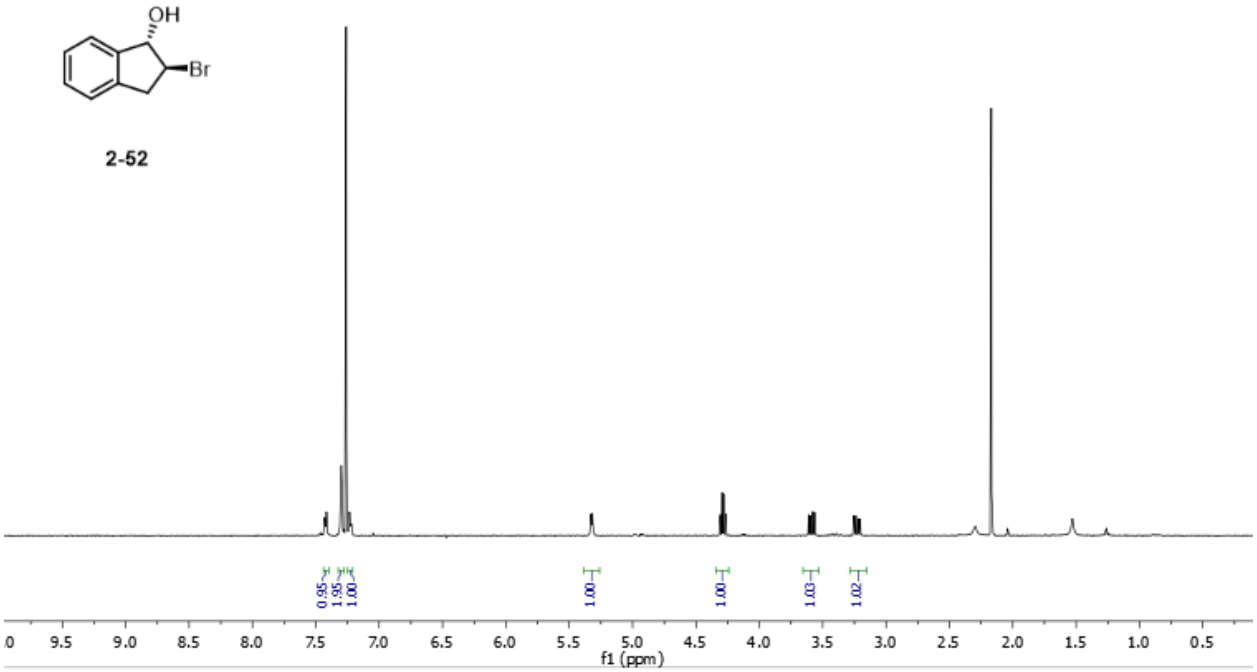
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



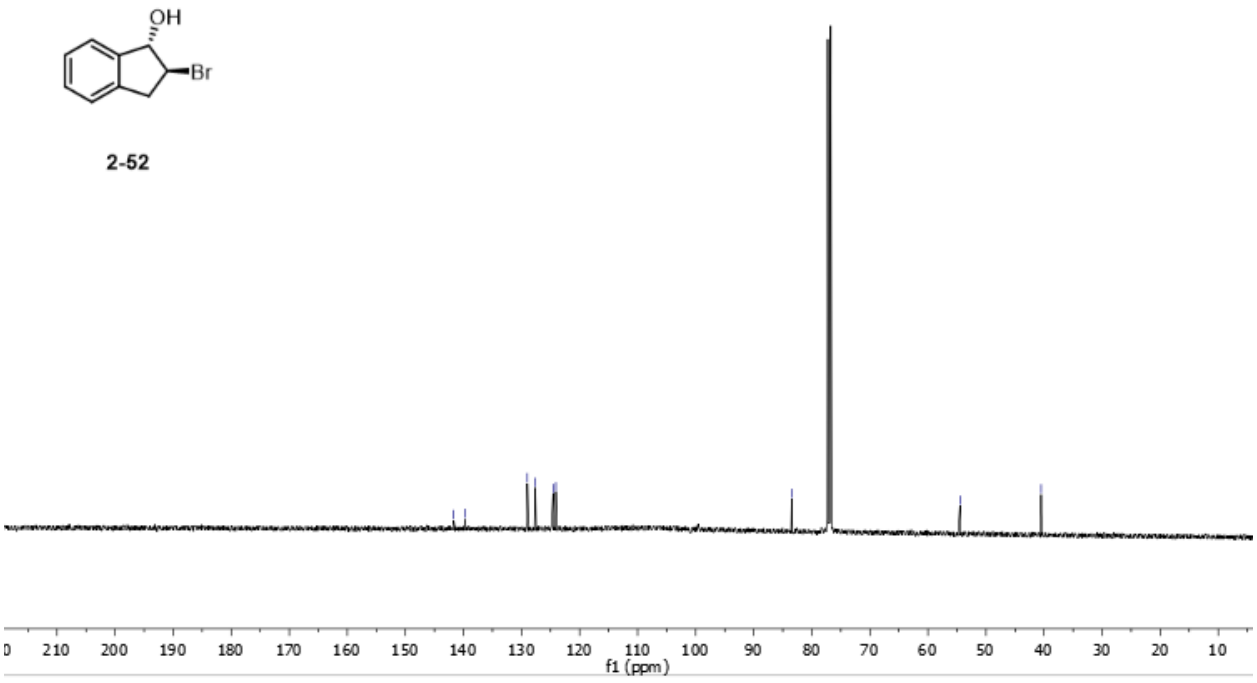
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

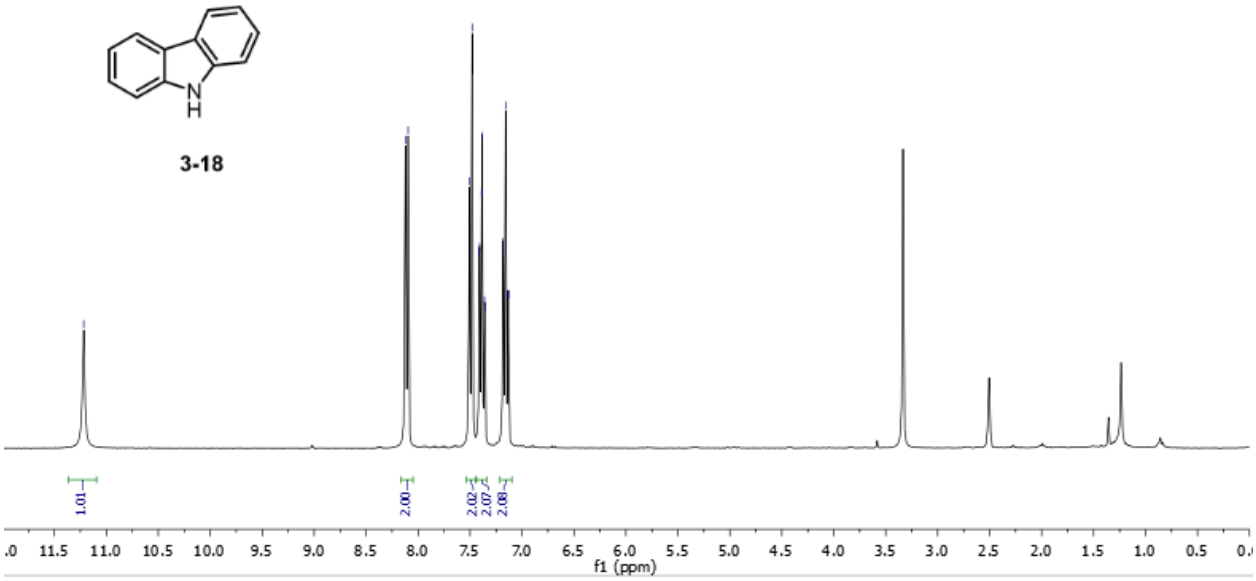


Appendix II

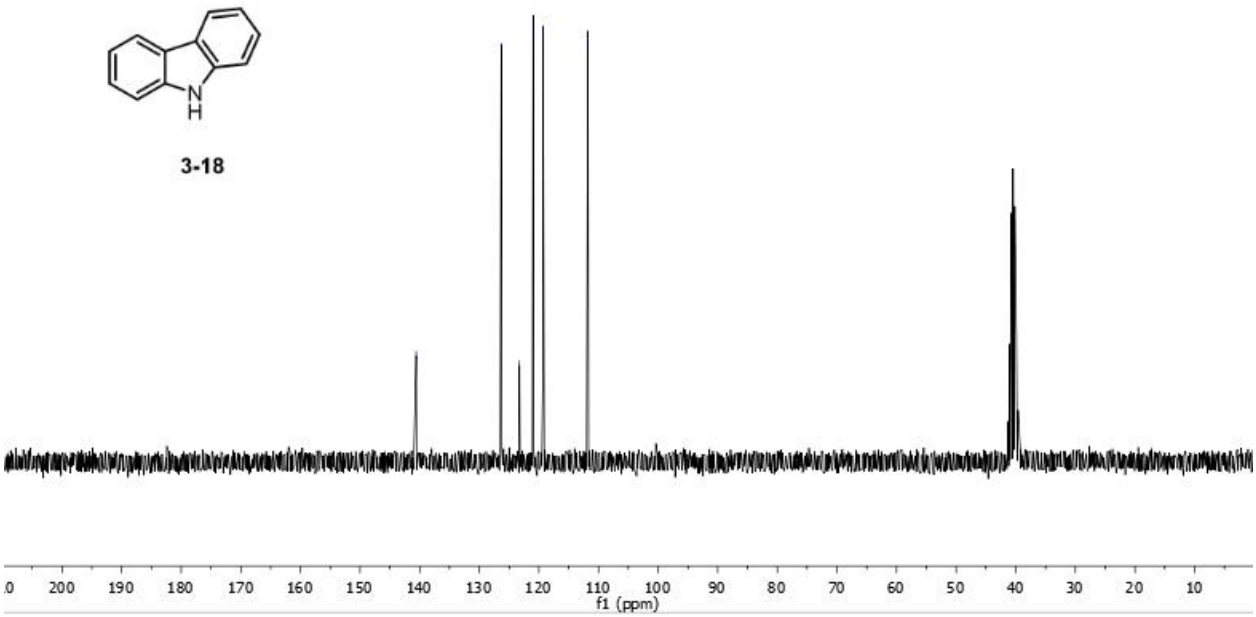
^{1}H and ^{13}C NMR spectra

Chapter 3

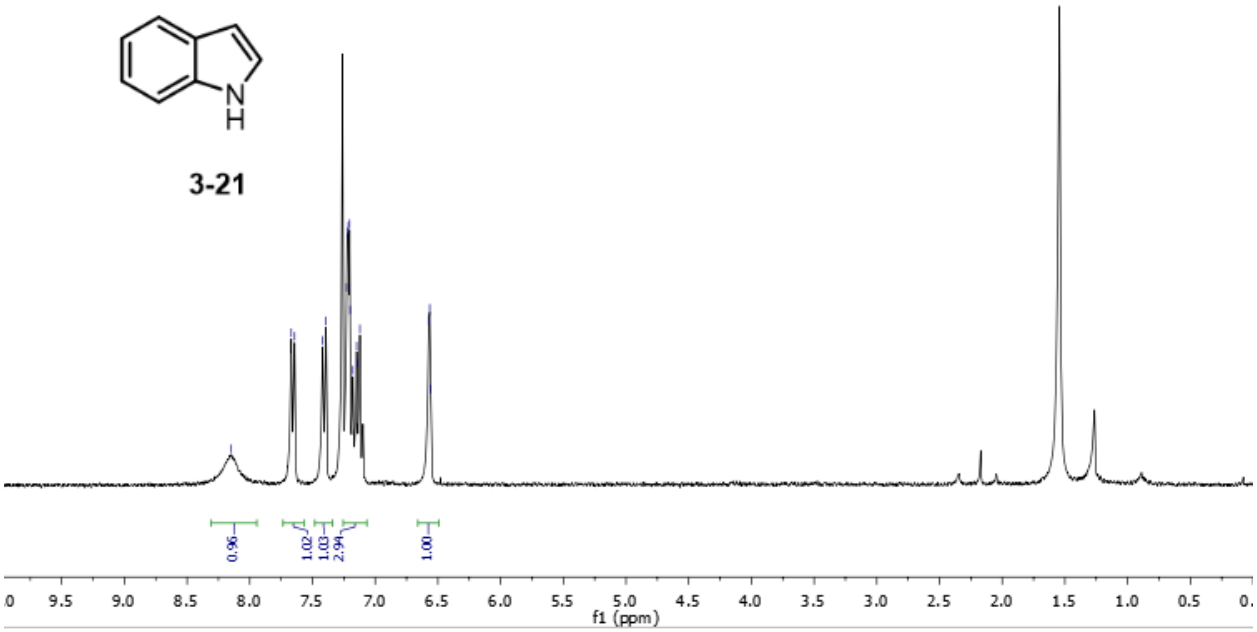
^{1}H NMR spectrum (DMSO-d_6, 300 MHz)



^{13}C NMR spectrum (DMSO-d_6, 75 MHz)



^{1}H NMR spectrum ($CDCl_3$, 300 MHz)



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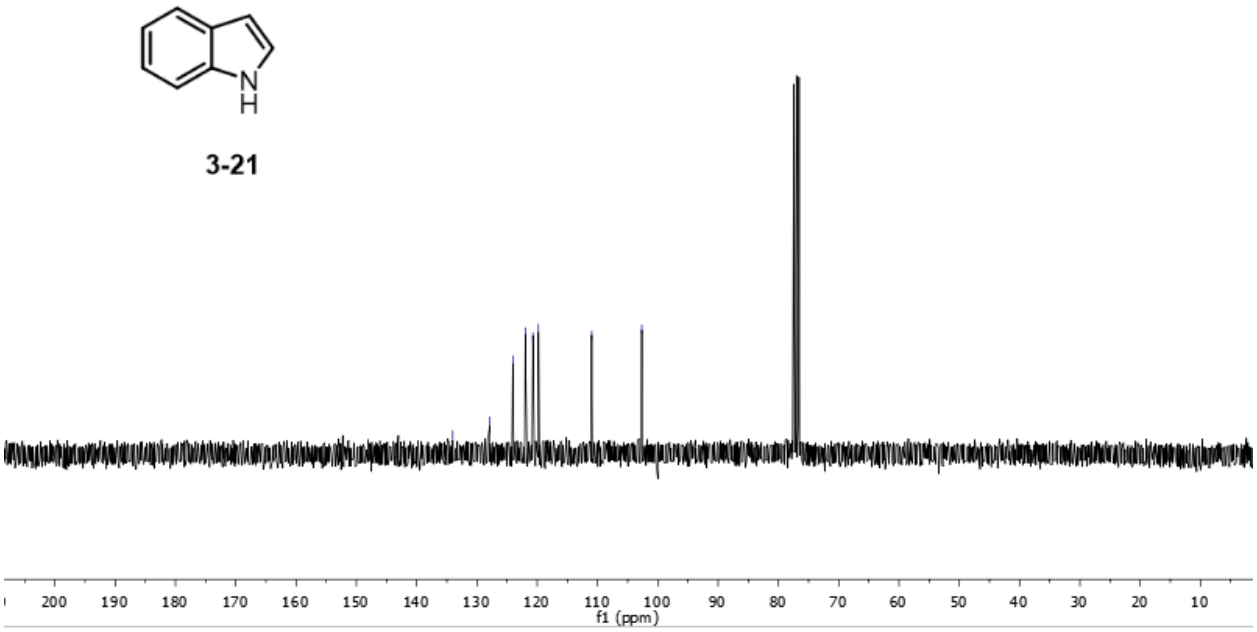
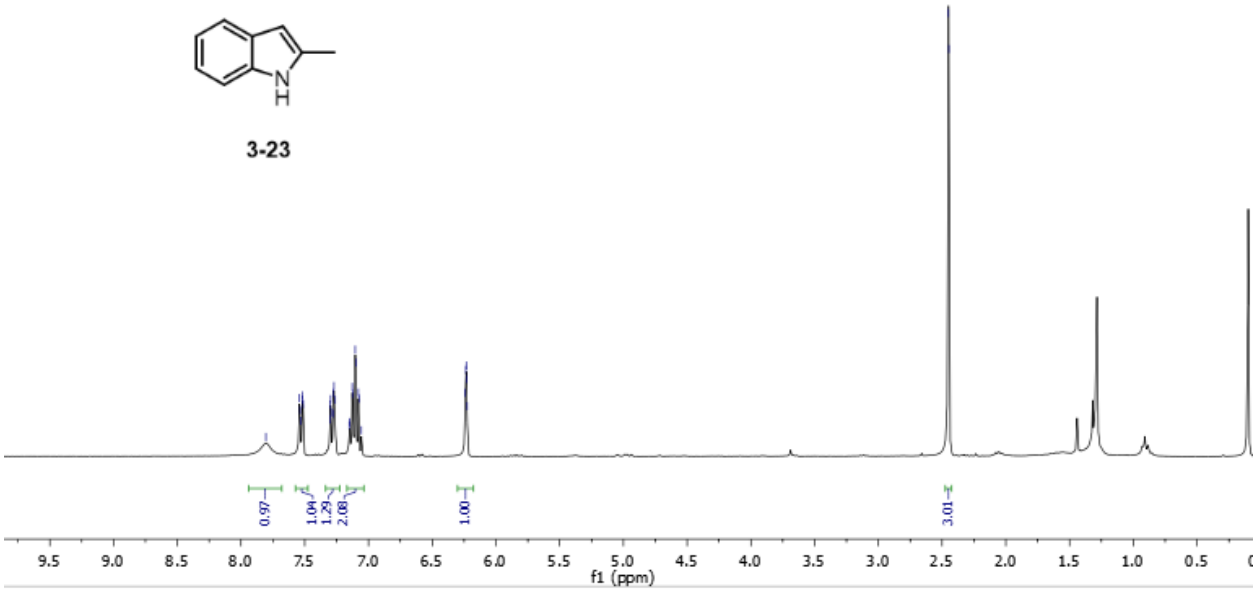
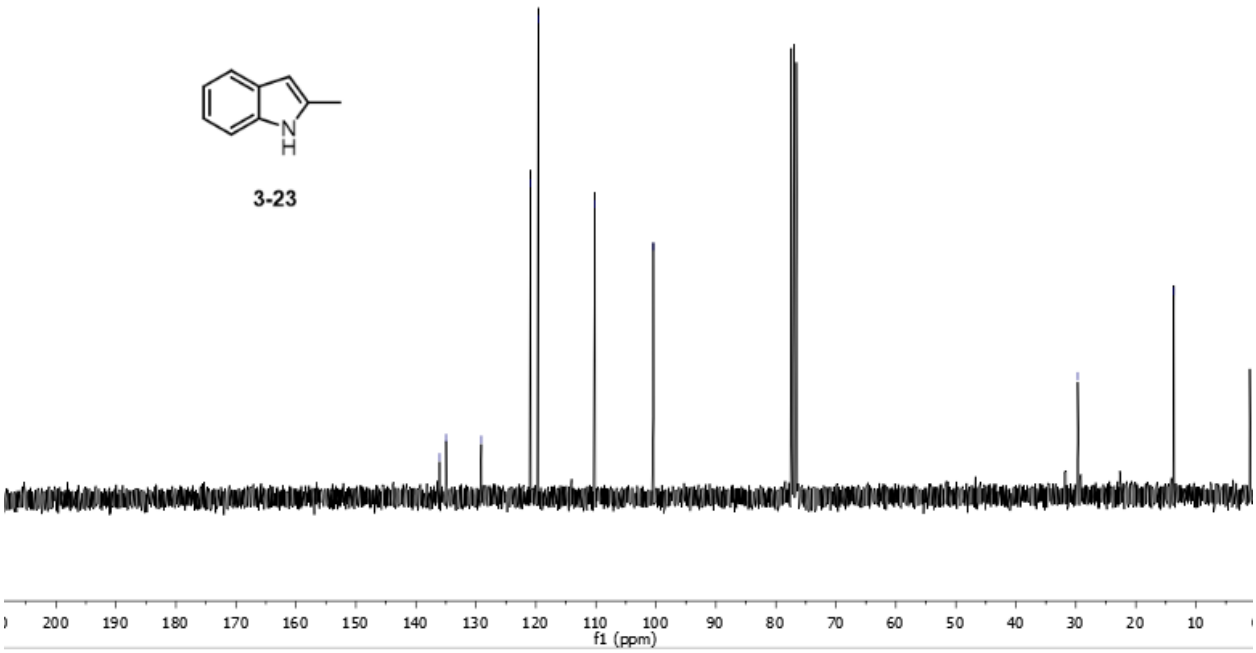


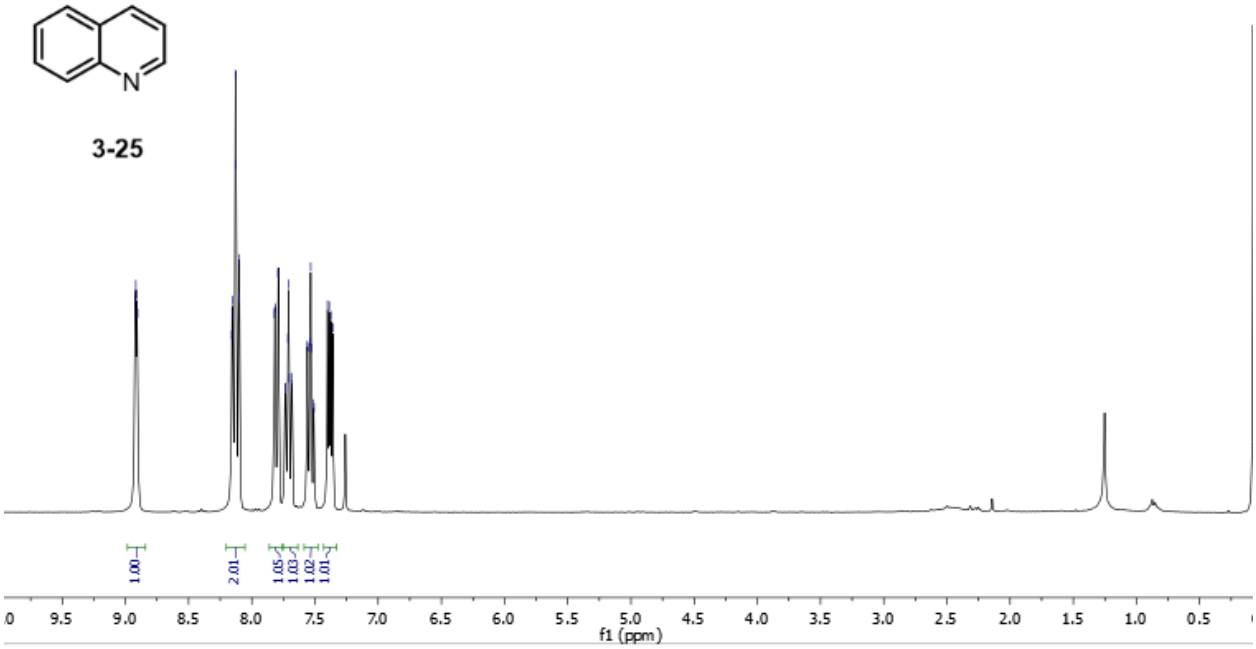
^{1}H NMR spectrum ($CDCl_3$, 300 MHz)



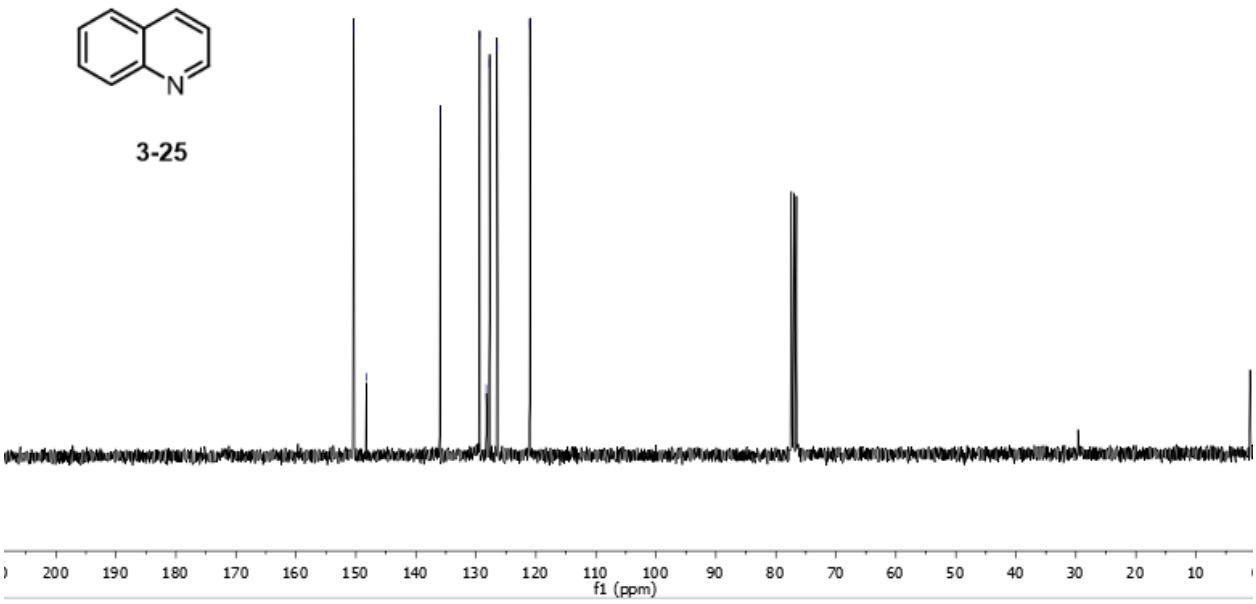
^{13}C NMR spectrum ($CDCl_3$, 75 MHz)



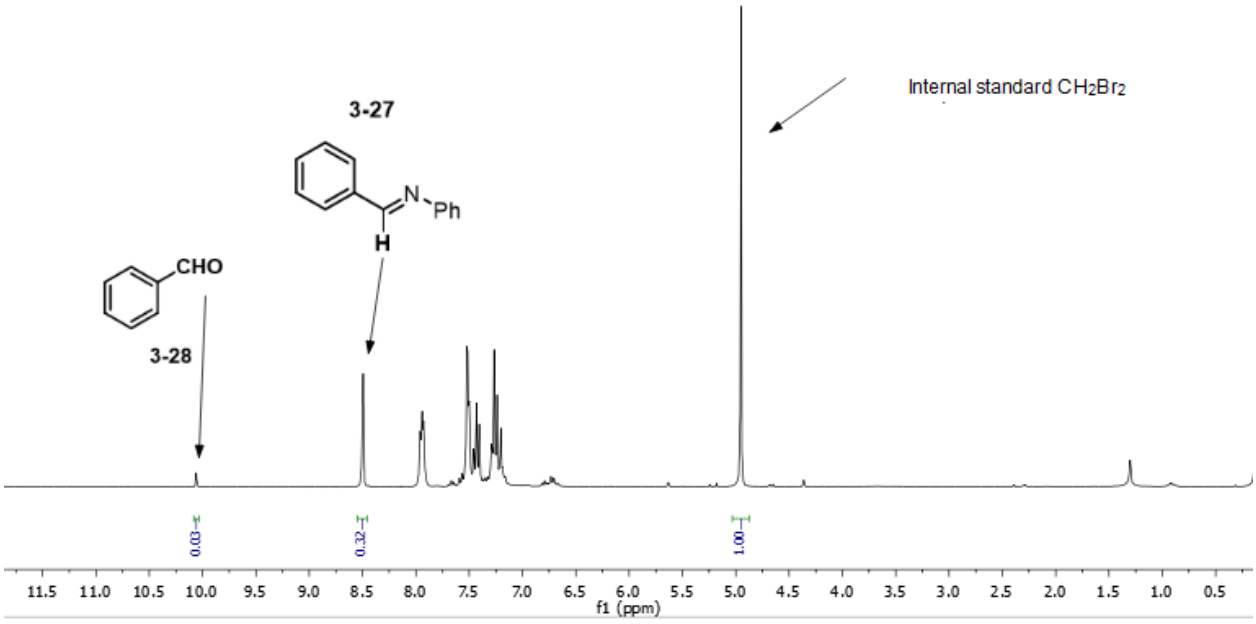
^{1}H NMR spectrum ($CDCl_3$, 300 MHz)



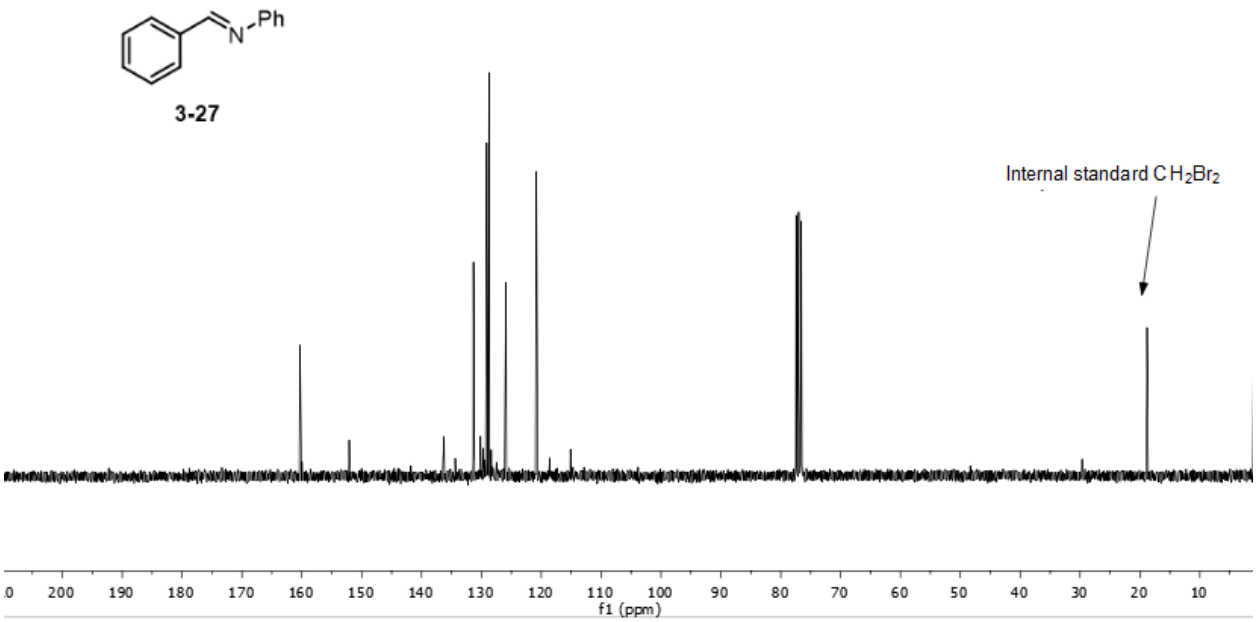
^{13}C NMR spectrum ($CDCl_3$, 75 MHz)



^{1}H NMR spectrum ($CDCl_3$, 300 MHz)



^{13}C NMR spectrum ($CDCl_3$, 75 MHz)



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June 23, 2015

Ms. Megha Karki
Dept of Chemistry
University of Idaho
875 Perimeter Dr, MS 2343
Moscow ID 83843-2343
United States

Email: kark9896@vandals.uidaho.edu

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