C(sp^3)–H Activation *via* Dehydrogenation of Cyclic and Heterocyclic Alkanes by Single-Site Iridium Pincer Ligated Complexes

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Dedicated To my Mom and Dad, my Husband Abdulaziz, and my son Talal

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possessed a special power that always made me feel better and ready to embark on the next step whenever I talked to him.

Beyond my scientific journey, Bob and Brian have also supported me personally, particularly when I became pregnant during my graduate research. I was overwhelmed by how supportive they were and how much they cared about me and my safety. I'm forever grateful for them because honestly, they truly made every impediment through the PhD journey easier to overcome.

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ABSTRACT

The direct dehydroaromatization of C(sp^3)–H alkanes may seem conceptually simple but in fact is a challenging transformation. Industrially practiced methods utilize energy-intensive processes operating at high pressures and temperatures due to the requirement of such conditions to overcome the endergonic and unreactive nature of alkanes. **Chapter 1** briefly discusses early and recent achievements in the field of alkanes dehydrogenation by Ir pincer ligated complexes. While there has been great advancement in the dehydrogenation transformation recently, the direct dehydroaromatization of heterocyclic substrates generating functionalized aromatics is significantly underdeveloped. In **Chapter 2**, we successfully extended the applicability of Ir-catalyzed dehydrogenation systems using pincer ligated complexes on a diverse collection of heterocyclic alkanes with functionalities known to be strongly coordinating and poorly compatible with (PCP)–Ir type catalysts. Carbo- and heteroarenes containing oxygen and nitrogen can be synthesized in moderate to excellent yields up to 99%, and the reaction tolerates functional groups such as bromides and fluorides. In **Chapter 3**, we demonstrate the efficient disproportionation of cycloalkenes to the corresponding arenes and cycloalkanes with up to 100% conversion, which has been a long-standing challenge in the field of pincer-ligated Ir-catalyzed dehydrogenation studies. For example, 1-cyclohexene was disproportionated to benzene and cyclohexane and 1-4-vinyl-1-cyclohexene was disproportionated to ethylbenzene and ethylcyclohexane. We also demonstrate that a key mechanistic feature of our system is a lack of catalyst inhibition by arenes. In addition, our method is advantageous to previous reports as no sacrificial olefin is used, thereby circumventing the requirement for exogeneous hydrogen acceptors. Our studies presented in **Chapter 2** and **Chapter 3** provides a novel

and a complementary pathway to access important aromatic building blocks and may help create alternative routes to complex molecules *via* late stage dehydrogenation without the need of stoichiometric oxidants.

PUBLISHED CONTENT AND CONTRIBUTIONS

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[†]ZAS led the project design, experimental work, data acquisition and analysis, and manuscript preparation and writing. This work is discussed in Chapter 2 and 3 and related appendices.

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LIST OF ABBREVIATIONS

°C	degrees Celsius
Å	Ångstrom
Ac	acetyl
AcOH	acetic acid
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
c	concentration for specific rotation measurements (g/100 mL)
ca.	about (Latin circa)
CAN	ceric ammonium nitrate
calc'd	calculated

cat.	catalyst
cm^{-1}	wavenumber(s)
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
D	deuterium
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
DFT	density functional theory
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DTBP	Di-$tert$-butyl peroxide
e.g.,	for example (Latin exempli gratia)
EI+	electron impact
EPR	electron paramagnetic resonance
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
Exs	excess
EWG	electron withdrawing group
FAB	fast atom bombardment
g	gram(s)

GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)
HEX	1-Hexene
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	hertz
i-Pr	isopropyl
i.e.,	that is (Latin id est)
IPA	isopropanol, 2-propanol
IR	infrared (spectroscopy)
J	coupling constant
K	Kelvin(s) (absolute temperature)
KC_8	potassium intercalated graphite
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
KIE	kinetic isotope effect
L	liter; ligand
LDA	lithium diisopropylamide
LG	leaving group

lit.	literature value
m	multiplet; milli
m	meta
M	metal; molar; molecular ion
m/z	mass-to-charge ratio
Me	methyl
mg	milligram(s)
MHz	megahertz
Min	minute(s)
MM	mixed method
Mol.	mole(s)
MOM	methoxymethyl acetal
Mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal
n-Bu	butyl
NBS	*N*-bromosuccinimide
NBE	Norbornene
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho

p	para
Pd/C	palladium on carbon
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
Pin	2,3-dimethylbutane-2,3-diol (pinacol)
Piv	trimethylacetyl, pivaloyl
*p*Ka	*p*K for association of an acid
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Py	pyridine
q	quartet
R	generic for any atom or functional group
Ref.	reference
rt	retention time
*R*f	retention factor
s	singlet or strong or selectivity factor
sat.	saturated
t	triplet
t-Bu	*tert*-butyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl methyl ether

TBS   *tert*-butyldimethylsilyl

TBE   *tert*-butylethylene

TES   triethylsilyl

TFA   trifluoroacetic acid

THF   tetrahydrofuran

TIPS   triisopropylsilyl

TLC   thin-layer chromatography

TMS   trimethylsilyl

TOF   time-of-flight

Tol   tolyl

*t*R   retention time

Ts   *p*-toluenesulfonyl (tosyl)

UV   ultraviolet

v/v   volume to volume

w   weak

w/v   weight to volume

X   anionic ligand or halide

λ   wavelength

μ   micro

CHAPTER 1

ALKANE C(SP³)–H DEHYDROGENATION CATALYZED BY SINGLE-SITE IRIDIUM CATALYSIS

1.1   INTRODUCTION

Olefins and aromatics are common cores in organic chemistry and serve as building blocks for the synthesis of complex molecules in pharmaceuticals and polymers. In addition, benzene, toluene, and xylenes are among the six most important feedstock chemicals that are not naturally occurring (Figure 1.1a).[1] The current industrial production of these building blocks is through dehydrogenating aliphatic hydrocarbons from crude oil feedstock using heterogeneous catalysts, which is an energy-intensive process operating at high pressures up to 60 bar and temperatures up to 900 °C (Figure 1.1b).[2] Additionally, isomerization occurs at such high temperatures, which lowers product selectivity making such processes inefficient.

a. Six Most Important Building Blocks from Fossil Resources
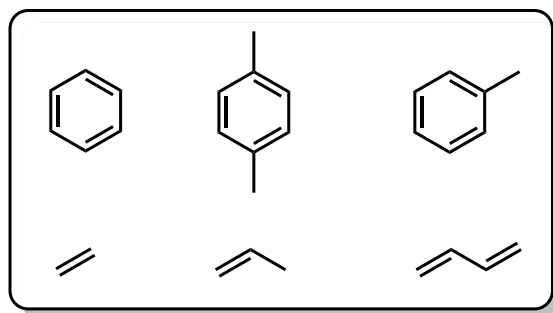
b. Industrial Process for Unsubstituted Aromatics Production

dehydrogenation, cracking, reforming

mixture of aliphatic hydrocarbons (petroleum feedstock)

Furnace
800 ˚C
2-3 bar
Chromium
Oxide/Al₂O₃

Me

+ olefins and other arenes
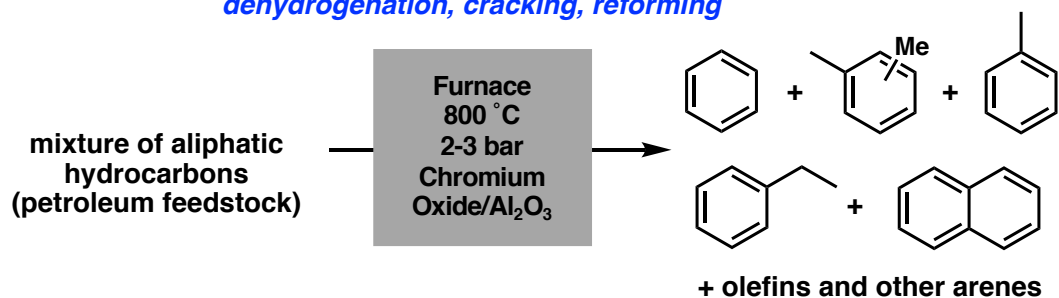
Figure 1.1 *Most Important Building Blocks and Current Industrial Production*

a. Aromatics in Drugs

Propranolol
top 41st in USA

Duloxetine
top 48th in USA

Chloroquine
SARS-CoV-2 potential
inhibitor "clinical trials"
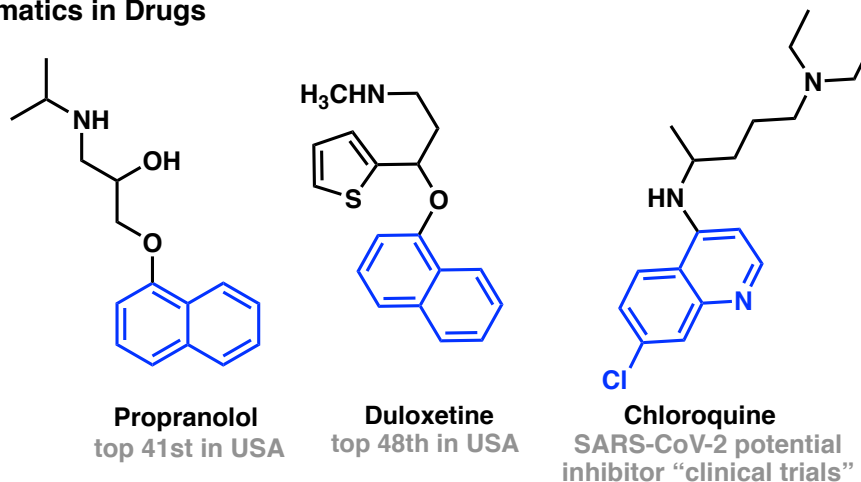
b. An Example of Industrial Methods for Substituted Aromatics Production

obtained from fossil
fuels processing
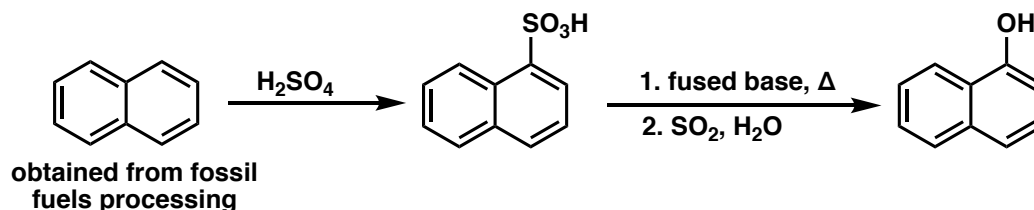
Figure 1.2 *Substituted Aromatics in Drugs and Industrial Synthesis*

In addition, functionalized aromatics are of great synthetic utility in a wide variety of organic reactions, complex molecules, and pharmaceuticals. Propranolol, duloxetine, and chloroquine are among various important drugs that contain substituted aromatics in their structure (Figure 1.2a).[3-8] However, synthesis of substituted aromatics and fused arenes can be cumbersome due to requiring harsh conditions such as strong acidic environments or highly toxic chemicals with large amounts of waste.[9] For example, 1-naphthol compounds are synthesized industrially from either sulfonated naphthalene or nitrated naphthalene, which requires using concentrated sulfuric acid or toxic nitration conditions at high pressures in addition to requiring multiple-step reactions (Figure 1.2b).[10-12]

Hence, there is a great interest in developing and identifying methods for the synthesis of substituted and unsubstituted aromatics with milder conditions. Ideally, such a method would occur under acid-free and redox-neutral conditions, and would tolerate a much broader range of functional groups, making itself attractive for fine chemical manipulation. Dehydrogenating C(sp³)–H alkanes using homogenous transition metal catalysis could ideally be used to generate functionalized aromatic systems such as quinolines and naphthalenes from aliphatic precursors, which is the focus of our work in the subsequent chapters (Figure 1.3).
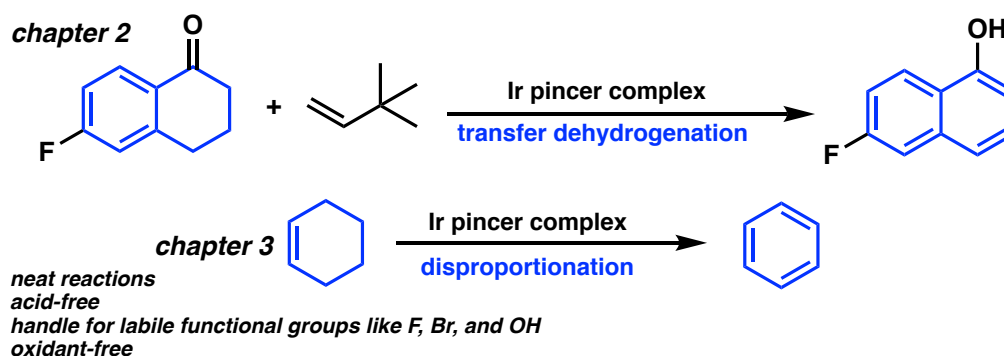
Figure 1.3 *Examples of Presented Work in Chapters 2 and 3*

1.2   CHALLENGES OF C(SP³)−H ALKANES DEHYDROGENATION

While alkanes dehydrogenation seems a conceptually simple process, C(sp³)−H activation is very challenging due to the chemical inertness of alkanes. Olefins and alkynes are good nucleophiles because they have the ability to donate or accept π-electrons, which can lead to metal-ligand π-backbonding (Figure 1.4). To the contrary, alkanes have strong,

localized C−C and C−H sigma bonds and coordinate weakly to metals with bond enthalpies of < 15 kcal/mol. making them poor nucleophiles and difficult to activate.[13-15]

Generally, C−H bonds in alkanes have high bond dissociation energies (BDE), in the range of 90-100 kcal/mol.[9] Activating terminal C−H bonds in alkanes are preferred, but differing BDE between secondary and primary alkanes can affect the selectivity of the reaction, which imposes an additional challenge. Generally, terminal C−H positions have higher BDEs than internal positions (Scheme 1.1).[1, 16] However, terminal C−H bond activation using transition-metal complexes is generally kinetically and thermodynamically favorable over secondary and tertiary C−H bonds.[10-12] One explanation for this observation is the bulky ligands around the metal center make C−H metal coordination more facile on the terminal position. In less sterically encumbered complexes, this effect may not be as strong and must be monitored.
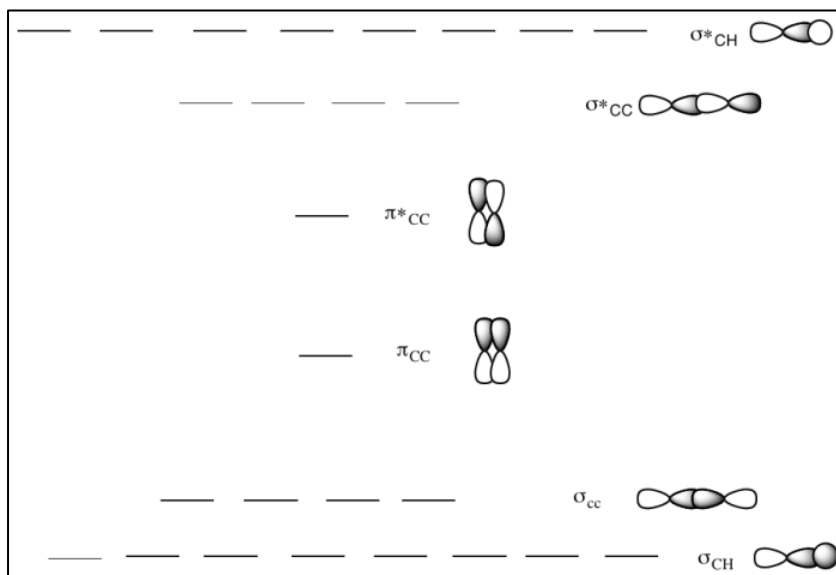
Figure 1.4 σ-Bonds vs. π-Bonds Molecular Orbitals

Scheme 1.1 *Representative Bond Dissociation Energies of Alkanes*
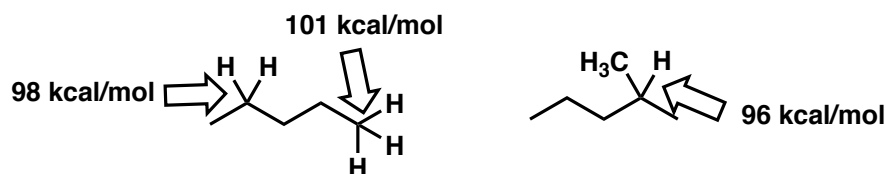
In addition, specific to $C(sp^3)-H$ dehydrogenation process, the chemical inertness increases as the hydrocarbon chain length decreases due to thermodynamic equilibrium, making it even more challenging to convert small chain alkanes to alkenes (Figure 1.5).[17-19] Hence, high temperatures are necessary in dehydrogenation because one needs to amplify the entropic term to offset the strong endergonic nature of dehydrogenation.

Furthermore, strong binding of the α-olefin or arene products to homogeneous catalysis can generate either a π-complex or a vinyl hydride with the catalyst, and thus dehydrogenation products may inhibit their catalytic activity.[24]
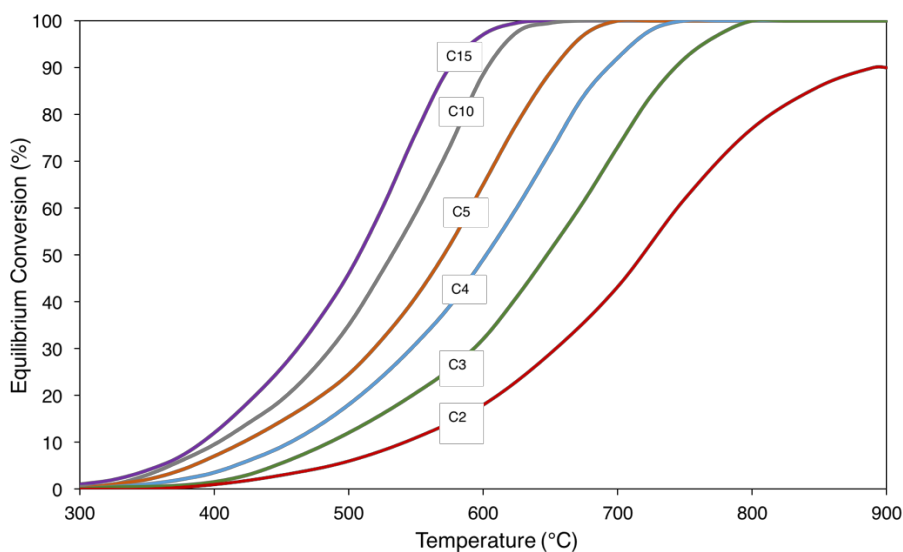
Figure 1.5 *Thermodynamic Equilibrium Conversion of n-Alkane Dehydrogenation[17]*

1.3   EARLY EXAMPLES OF C(SP³)−H DEHYDROGENATION USING IRIDIUM HOMOGENEOUS CATALYSTS

Alkane dehydrogenation has received increased attention over the last decade due to the synthetic versatility of olefins and aromatics. However, this conceptually simple process is difficult to implement in practice due to the requirement of activation of strong C−H bonds. Hence, most of the reported systems require a sacrificial olefin that serves as a hydrogen acceptor to render the overall reaction exothermic.[20] Crabtree and co-workers reported the first example of stoichiometric alkane dehydrogenation using the cationic Ir(III) complex $[(acetone)_2(PPh_3)_2−IrH_2]^+$ **c1** with cyclohexane yielding a 1,3-cyclohexadiene−Ir complex (Scheme 1.2a). More significantly, two important findings of the Crabtree studies were that cyclopentane and cyclooctane (**COA**) were dehydrogenated to cyclopentadienyl hydride and 1,5-cyclooctadiene complexes, respectively, in the presence of 3,3-dimethyl-1-butene commercially known as *t*-butylethylene (**TBE**) (Scheme 1.2b/1.2c).[19, 21-22]

Concurrently but independently, Felkin and co-workers reported the dehydrogenation of cycloalkanes using Re and Ir metal complexes. Felkin reported the transfer dehydrogenation of the **COA/TBE** system by complex $(^{i-Pr3}P)_2−IrH_5$ **c2** with turnover numbers (TONs) up to 70 when increasing reaction temperature to 150 °C (Scheme 1.3).[23-24]

Scheme 1.2 *First Reported Stoichiometric Alkane Dehydrogenation Examples by Crabtree*
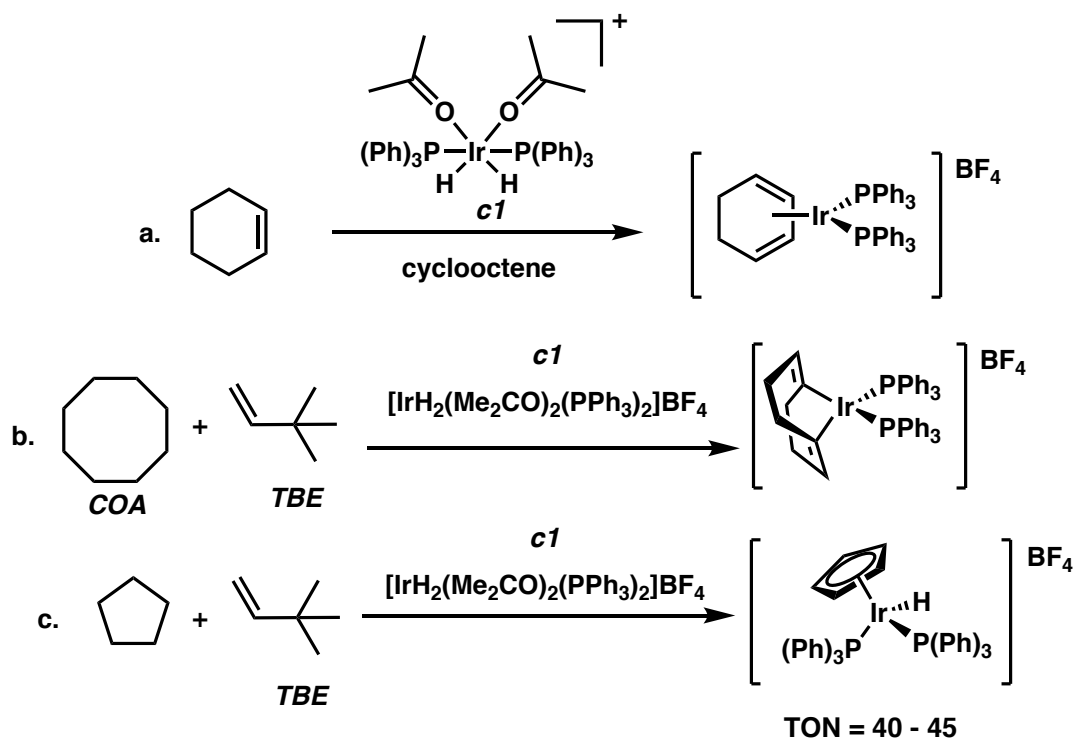
Scheme 1.3 Example of **COA/TBE** Dehydrogenation by Felkin
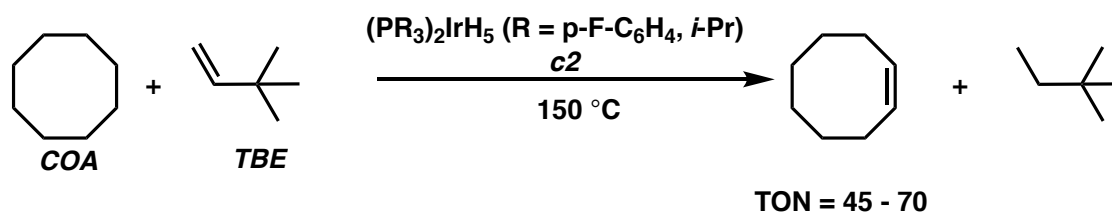
In addition, it has been shown that **TBE** is an effective hydrogen acceptor compared to ethylene or styrene because it offers great steric bulk that prevents strong coordination to the metal center and inhibiting catalysis. **TBE** also lacks allylic hydrogens so no allylic complex can irreversibly form and no isomers can be generated at the required temperatures for dehydrogenation *via* hydrogen migrations.

The transfer dehydrogenation reaction of **TBE/COA** has a substantial negative enthalpy (ca. -7 kcal/mol) due to the low dehydrogenation enthalpy of **COA** (+22.4 kcal/mol) relative to other alkanes (ca. 30 kcal/mol).[20] Hence, the **TBE/COA** system soon became the benchmark reaction for screening conditions and catalysis at play in transfer dehydrogenation studies.

1.4 RECENT EXAMPLES OF C(SP³)−H DEHYDROGENATION USING IRIDIUM PINCER LIGATED COMPLEXES

Most of the early examples of studied complexes showed poor thermal stability at the temperatures needed to achieve reasonable reaction rates. Pincer ligated complexes, however, were found to be thermally stable at these elevated temperatures, making them useful for this transformation.[25] These complexes are stable due to the tridentate coordination of ligands with the metal center. In 1996, Jensen and co-workers reported the first thermally stable pincer ligated complex used as dehydrogenation catalysts, ($^{t\text{-}Bu4}$PCP)–Ir **c3**.[26-27] Complex **c3** proved to be robust and reactive when employed on the **COA/TBE** system, yielding a maximum of 230 TONs.[26, 28-29] Since then, variations of complex **c3** have been reported with different aryl backbones, various linkers, and ligating groups (Figure 1.6).[30-52] That being said, it was found that varying the electronics around the metal center is not as effective as varying the geometry around the metal center in improving catalytic activity.[42] The complexes that showed high catalytic activity in most reactions were ($^{t\text{-}Bu4}$POCOP)–Ir **c13**, ($^{i\text{-}Pr4}$PSCOP)–Ir **c22**, and ($^{i\text{-}Pr4}$anthraphos)–Ir **c24**.

While most of the previous studies focused on investigating these Ir pincer ligated complexes as dehydrogenation catalysts on the **COA/TBE** system, there were several studies that investigated other substrates. In 2012, Brookhart and co-workers reported the disproportionation of 1-hexene to 2,4-hexadiene and *n*-hexane using different Ir pincer ligated complexes. It was found that the ($^{i\text{-}Pr4}$anthraphos)–Ir complex **c24** had the highest catalytic activity generating 777 TONs (Scheme 1.4a).[53] In a subsequent study, Brookhart and co-workers reported the synthesis of piperylene from *n*-pentane. Complex **c24** resulted in the highest activity generating 19.5 TONs even with employing **TBE** as the H_2 acceptor. One possible explanation for the lower catalytic activity of complex **c24** is that binding affinity of the product increases as the hydrocarbon chain length becomes smaller (Scheme 1.4b).[54] These examples demonstrate how catalytic activity vary significantly depending on the substrate investigated for dehydrogenation, even if it is only a change in carbon chain length.

c3 X = H, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c4 X = H, R₁ = R₂ = R₃ = R₄ = *i*-Pr
c5 X = H, R₁ = R₂ = R₃ = R₄ = Ad
c6 X = H, R₁ = R₂ = R₃ = R₄ = Me
c7 X = H, R₁ = R₂ = R₃ = R₄ = Me
c8 X = OMe, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c9 X = OMe, R₁ = R₂ = R₃ = R₄ = *i*-Pr
c10 X = NMe₂, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c11 X = CO₂Me, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c12 X = H, R₁ = R₂ = R₃ = R₄ = CF₃
Kaska, Jensen, Goldman, Roddick

c13 X = H, Y = Z = O, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c14 X = H, Y = Z = O, R₁ = R₂ = R₃ = R₄ = *i*-Pr
c15 X = OK, Y = Z = O, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c16 X = OMe, Y = Z = O, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c17 X = F, Y = Z = O, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c18 X = C₆F₅, Y = Z = O, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c19 X = H, Y = CH₂, Z = O, R₁ = R₂ = R₃ = R₄ = *t*-Bu
c20 X = H, Y = CH₂, Z = O, R₁ = R₂ = *t*-Bu, R₃=R₄= *i*-Pr
c21 X = H, Y = CH₂, Z = O, R₁ = R₂ = R₃ = R₄ = *i*-Pr
c22 X = H, Y = S, Z = O, R₁ = R₂ = R₃ = R₄ = *i*-Pr
Brookhart, Jensen, Goldman, Huang

c23 R₁ = R₂ = R₃ = R₄ = *t*-Bu
c24 R₁ = R₂ = R₃ = R₄ = *i*-Pr
Kaska, Brookhart

c25 R = H
c26 R = *t*-Bu
c27 R = Me
Huang

c28 R = *i*-Pr
c29 R = Cy
c30 R = Cp
Brookhart, Bezier, Gelman, Goldman

Figure 1.6 *Recent Developments in Iridium Pincer Ligated Complexes*

Scheme 1.4 *Selected Recent Examples of n-Alkanes Dehydrogenation*

a.

($^{i-Pr4}$Anthraphos)Ir c24
180 °C

TON = 777

+ + isomers

b.

TBE

($^{i-Pr4}$Anthraphos)Ir c24
180 °C

piperylene
TON = 19.5
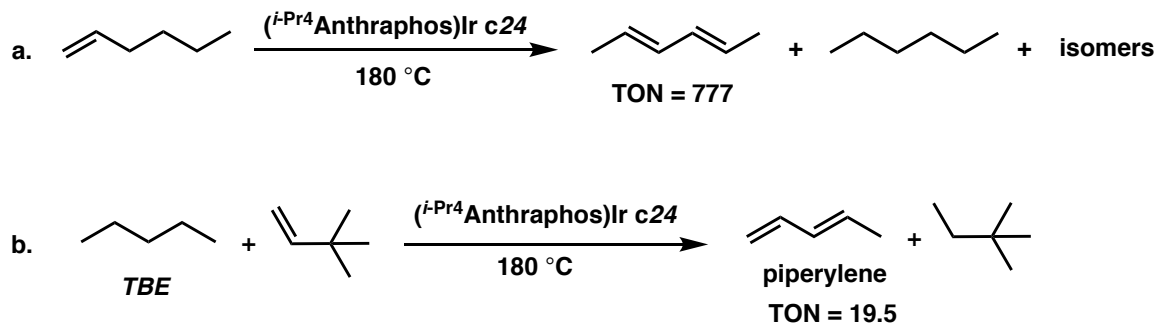
1.5   PINCER-LIGATED IRIDIUM-CATALYZED C(SP³)−H DEHYDROGENATION MECHANISM

The widely accepted mechanism for the ($^{t\text{-Bu}4}$PCP)–Ir **c3** catalytic dehydrogenation of the **COA/TBE** system occurs *via* an Ir(III)/Ir(I) catalytic cycle (Scheme 1.5).[55-57] The first step of the catalytic cycle starts with the insertion of **TBE** followed by a reductive elimination to generate the catalytically active 14-electron three-coordinate Ir(I) species **B**. Then an oxidative addition of **COA** followed by a β-hydride elimination furnishes the dehydrogenated product to close the catalytic cycle (Scheme 1.5). The resting state for ($^{t\text{-Bu}4}$PCP)–Ir **c3** at low concentrations of **TBE** is believed to be the Ir(III) hydrido-vinyl complex **D**.

Scheme 1.5 *Mechanism for (ᵗ⁻ᴮᵘ⁴PCP)–Ir-Catalyzed Dehydrogenation of **COA***
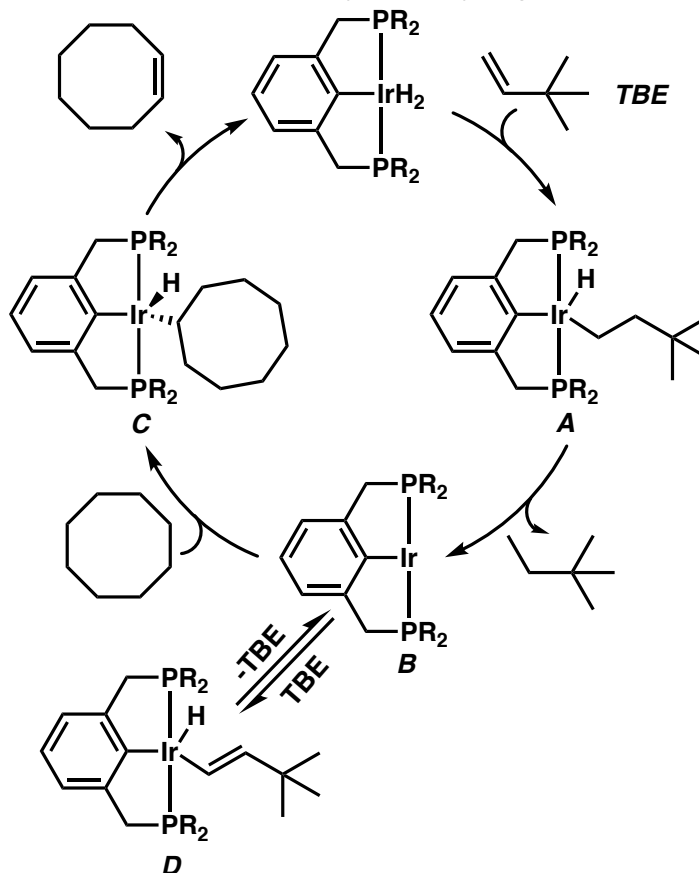
In the case of *n*-alkane dehydrogenation systems, it is envisioned to have a similar mechanistic pathway as the **COA/TBE** dehydrogenation system (Scheme 1.6). However, there is an additional inhibition pathway by the α-olefin product because it strongly binds to the active complex **B**. While the dehydrogenation cycle is similar for the various catalysts, the resting states are believed to vary for complexes other than (ᵗ⁻ᴮᵘ⁴PCP)–Ir **c3**, which require less sterically demanding olefin acceptor. For example, the (ᵗ⁻ᴮᵘ⁴POCOP)–Ir **c13** resting state is believed to be the alkene complex **H** and **I** and the rate determining step would be the release of the alkene.[55]

Scheme 1.6 *Mechanism for Pincer-Ligated Iridium-Catalyzed Dehydrogenation of n-Alkanes*
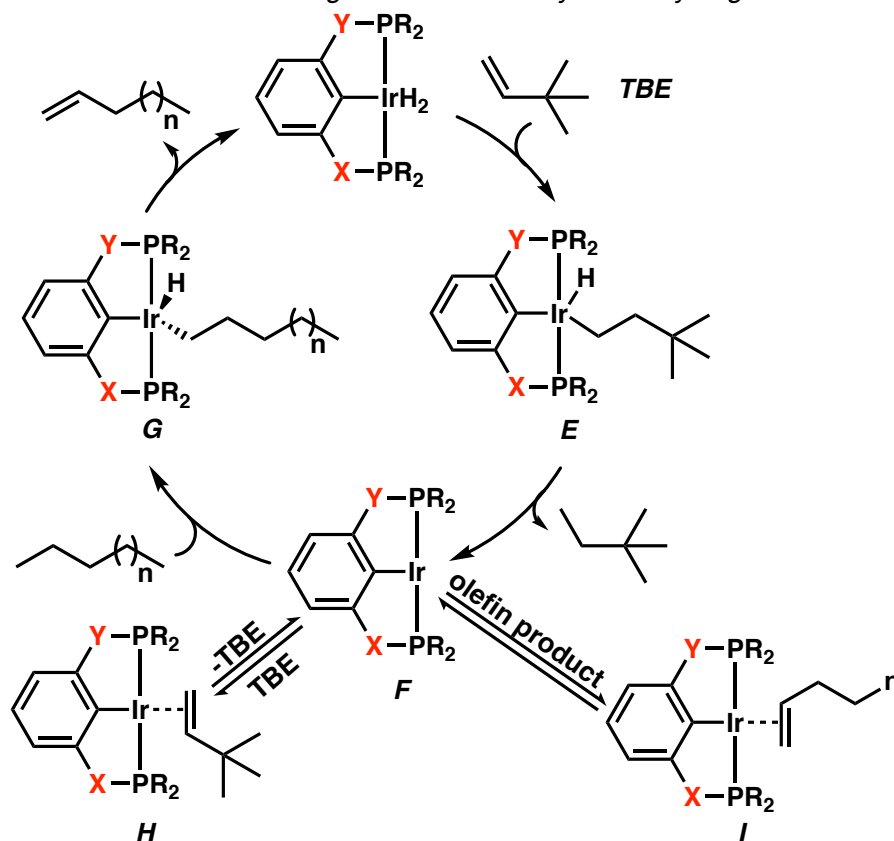
1.6   CONCLUSIONS

Substantial progress has been achieved in the field of homogeneous catalytic alkane dehydrogenation using Ir pincer ligated complexes. Kaska, Jensen, Goldman, Brookhart, Huang, and others reported a variety of pincer ligated complexes including ($^{t\text{-}Bu4}$PCP)–Ir **c3**, ($^{t\text{-}Bu4}$POCOP)–Ir **c13**, ($^{i\text{-}Pr4}$PSCOP)–Ir **c22**, and ($^{i\text{-}Pr4}$anthraphos)–Ir **c24** that were shown to be highly effective transfer dehydrogenation catalysts. However, most of the reported examples focus on dehydrogenating the **COA/TBE** system or dehydrogenating unfunctionalized

normal and cyclic alkanes to olefins. The field of dehydrogenating functionalized substrates that could lead to important building blocks is lacking and remains significantly underdeveloped due to the strong coordination of many functionalities to metal centers leading to catalysis inhibition. Hence, our work in the subsequent chapters focuses on investigating dehydrogenating a diverse collection of substrates by Ir pincer ligated complexes with an emphasis on a variety of functional groups that are known to be strongly coordinating and poorly compatible with (PCP)–Ir type catalysts.

1.7   NOTES AND REFERENCES

1.   Gunnoe, B. T. In *Alkane C-H Activation Activation By Single-Site Metal Catalysis*, 1 ed.; Perez, P. J., Ed. Springer Netherlands: Dordrecht, 2012; pp 1-15.

2.   Chenier, P. J., *Survey of Industrial Chemistry*. 3 ed.; Springer US: New York, 2002; p XV, 515.

3.   Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G., *Cell Res.* **2020,** 30 (3), 269-271.

4.   Holshue, M. L.; DeBolt, C.; Lindquist, S.; Lofy, K. H.; Wiesman, J.; Bruce, H.; Spitters, C.; Ericson, K.; Wilkerson, S.; Tural, A.; Diaz, G.; Cohn, A.; Fox, L.; Patel, A.; Gerber, S. I.; Kim, L.; Tong, S.; Lu, X.; Lindstrom, S.; Pallansch, M. A.; Weldon, W. C.; Biggs, H. M.; Uyeki, T. M.; Pillai, S. K., *N. Engl. J. Med.* **2020,** 382 (10), 929-936.

5.   Cortegiani, A.; Ingoglia, G.; Ippolito, M.; Giarratano, A.; Einav, S., *J. Crit. Care* **2020**.

6.   Bymaster, F. P.; Beedle, E. E.; Findlay, J.; Gallagher, P. T.; Krushinski, J. H.; Mitchell, S.; Robertson, D. W.; Thompson, D. C.; Wallace, L.; Wong, D. T., *Bioorg. Med. Chem. Lett.* **2003,** 13 (24), 4477-4480.

7.   Wong, D. T.; Robertson, D. W.; Bymaster, F. P.; Krushinski, J. K.; Reid, L. R., *Life Sci.* **1988,** 43 (24), 2049-2057.

8.   Black, J. W.; Crowther, A. F.; Shanks, R. G.; Smith, L. H.; Dornhorst, A. C., *The Lancet* **1964,** 283 (7342), 1080-1081.

9.   He, X.; Zheng, Y.-W.; Lei, T.; Liu, W.-Q.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z., *Catalysis Science & Technology* **2019,** 9 (13), 3337-3341.

10.   Stevens Donna, G. H. H., Marshall B. Pearlman Phenols From Aromatic Sulfonic, Sulfamic, and Sulfone Compounds. April 22, 1958.

11.   E.W. Schoeffel, D. M. B. Naphthalene. August 28, 1956.

12.   Franzen, H.; Kempf, H., *Berichte der deutschen chemischen Gesellschaft* **1917,** 50 (1), 101-104.

13.   Sun, X.-Z.; Grills, D. C.; Nikiforov, S. M.; Poliakoff, M.; George, M. W., *Journal of the American Chemical Society* **1997,** 119 (32), 7521-7525.

14.   Hall, C.; Perutz, R. N., *Chemical Reviews* **1996,** 96 (8), 3125-3146.

15.   Brown, C. E.; Ishikawa, Y.; Hackett, P. A.; Rayner, D. M., *Journal of the American Chemical Society* **1990,** 112 (7), 2530-2536.

16.   Luo, Y.-R., Handbook of Bond Dissociation Energies in Organic Compounds. CRC Press: Boca Raton, 2003.

17.   Treccani, Refining and Petrochemicals. In *Encyclopedia of Hydrocarbons*, Amadei, C., Ed. 2009; Vol. 2, p 668.

18.   Crabtree, R. H., *Chemical Reviews* **2010,** 110 (2), 575-575.

19.   Crabtree, R. H.; Mihelcic, J. M.; Quirk, J. M., *Journal of the American Chemical Society* **1979,** 101 (26), 7738-7740.

20.   Michael Findlater, J. C., Alan S. Goldman, Maurice Brookhart. In *Alkane C-H Activation Activation By Single-Site Metal Catalysis*, 1 ed.; Perez, P. J., Ed. Springer Netherlands: Dordrecht, 2012; pp 113-141.

21. Crabtree, R. H.; Mellea, M. F.; Mihelcic, J. M.; Quirk, J. M., *Journal of the American Chemical Society* **1982,** 104 (1), 107-113.

22. Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Parnell, C. A.; Quirk, J. M.; Morris, G. E., *Journal of the American Chemical Society* **1982,** 104 (25), 6994-7001.

23. Baudry, D.; Ephritikhine, M.; Felkin, H.; Holmes-Smith, R., *J. Chem. Soc., Chem. Commun.* **1983,** (14), 788-789.

24. Baudry, D.; Ephritikhine, M.; Felkin, H., *J. Chem. Soc., Chem. Commun.* **1980,** (24), 1243-1244.

25. M. Jensen, C., *Chem. Commun.* **1999,** (24), 2443-2449.

26. Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M., *Journal of the American Chemical Society* **1997,** 119 (4), 840-841.

27. Gupta, M.; C. Kaska, W.; M. Jensen, C., *Chem. Commun.* **1997,** (5), 461-462.

28. Gupta, M.; Hagen, C.; Flesher, R. J.; Kaska, W. C.; Jensen, C. M., *Chem. Commun.* **1996,** (17), 2083-2084.

29. Kumar, A.; Bhatti, T. M.; Goldman, A. S., *Chemical Reviews* **2017,** 117 (19), 12357-12384.

30. Yao, W.; Zhang, Y.; Jia, X.; Huang, Z., *Angewandte Chemie International Edition* **2014,** 53 (5), 1390-1394.

31. Jia, X.; Zhang, L.; Qin, C.; Leng, X.; Huang, Z., *Chem. Commun.* **2014,** 50 (75), 11056-11059.

32. Brayton, D. F.; Beaumont, P. R.; Fukushima, E. Y.; Sartain, H. T.; Morales-Morales, D.; Jensen, C. M., *Organometallics* **2014,** 33 (19), 5198-5202.

33. Bézier, D.; Brookhart, M., *ACS Catalysis* **2014,** 4 (10), 3411-3420.

34. Shi, Y.; Suguri, T.; Dohi, C.; Yamada, H.; Kojima, S.; Yamamoto, Y., *Chemistry – A European Journal* **2013,** 19 (32), 10672-10689.

35. Nawara-Hultzsch, A. J.; Hackenberg, J. D.; Punji, B.; Supplee, C.; Emge, T. J.; Bailey, B. C.; Schrock, R. R.; Brookhart, M.; Goldman, A. S., *ACS Catalysis* **2013,** 3 (11), 2505-2514.

36. Musa, S.; Ackermann, L.; Gelman, D., *Adv. Synth. Catal.* **2013,** 355 (14-15), 3077-3080.

37. Romm, D. G. a. R. In *Organometallic Pincer Chemistry*, Gerard Van Koten, D. M., Ed. Springer-Verlag Berlin Heidelberg: Heidelberg, 2013; pp 289-317.

38. Dobereiner, G. E.; Yuan, J.; Schrock, R. R.; Goldman, A. S.; Hackenberg, J. D., *Journal of the American Chemical Society* **2013,** 135 (34), 12572-12575.

39. Punji, B.; Emge, T. J.; Goldman, A. S., *Organometallics* **2010,** 29 (12), 2702-2709.

40. Huang, Z.; Rolfe, E.; Carson, E. C.; Brookhart, M.; Goldman, A. S.; El-Khalafy, S. H.; MacArthur, A. H. R., *Adv. Synth. Catal.* **2010,** 352 (1), 125-135.

41. Ahuja, R.; Punji, B.; Findlater, M.; Supplee, C.; Schinski, W.; Brookhart, M.; Goldman, A. S., *Nat. Chem.* **2010,** 3, 167.

42.   Kundu, S.; Choliy, Y.; Zhuo, G.; Ahuja, R.; Emge, T. J.; Warmuth, R.; Brookhart, M.; Krogh-Jespersen, K.; Goldman, A. S., *Organometallics* **2009,** 28 (18), 5432-5444.

43.   Huang, Z.; Brookhart, M.; Goldman, A. S.; Kundu, S.; Ray, A.; Scott, S. L.; Vicente, B. C., *Adv. Synth. Catal.* **2009,** 351 (1-2), 188-206.

44.   Azerraf, C.; Gelman, D., *Organometallics* **2009,** 28 (22), 6578-6584.

45.   Kuklin, S. A.; Sheloumov, A. M.; Dolgushin, F. M.; Ezernitskaya, M. G.; Peregudov, A. S.; Petrovskii, P. V.; Koridze, A. A., *Organometallics* **2006,** 25 (22), 5466-5476.

46.   Zhu, K.; Achord, P. D.; Zhang, X.; Krogh-Jespersen, K.; Goldman, A. S., *Journal of the American Chemical Society* **2004,** 126 (40), 13044-13053.

47.   Morales-Morales, D.; Redón, R. o.; Yung, C.; Jensen, C. M., *Inorg. Chim. Acta* **2004,** 357 (10), 2953-2956.

48.   Göttker-Schnetmann, I.; White, P. S.; Brookhart, M., *Organometallics* **2004,** 23 (8), 1766-1776.

49.   Göttker-Schnetmann, I.; White, P.; Brookhart, M., *Journal of the American Chemical Society* **2004,** 126 (6), 1804-1811.

50.   Göttker-Schnetmann, I.; Brookhart, M., *Journal of the American Chemical Society* **2004,** 126 (30), 9330-9338.

51.   Haenel, M. W.; Oevers, S.; Angermund, K.; Kaska, W. C.; Fan, H.-J.; Hall, M. B., *Angewandte Chemie International Edition* **2001,** 40 (19), 3596-3600.

52.   Liu, F.; S. Goldman, A., *Chem. Commun.* **1999,** (7), 655-656.

53.   Lyons, T. W.; Guironnet, D.; Findlater, M.; Brookhart, M., *Journal of the American Chemical Society* **2012,** 134 (38), 15708-15711.

54.   Kundu, S.; Lyons, T. W.; Brookhart, M., *ACS Catalysis* **2013,** 3 (8), 1768-1773.

55.   Akshai Kumar, A. S. G. In *The Privileged Pincer-Metal Platform: Coordination Chemistry & Applications*, Gerard Van Koten, R. A. G., Ed. Springer, Cham: Cham, 2015; Vol. 54, pp 307-334.

56.   Renkema, K. B.; Kissin, Y. V.; Goldman, A. S., *Journal of the American Chemical Society* **2003,** 125 (26), 7770-7771.

CHAPTER 2

C(SP³)–H DEHYDROAROMATIZATION OF CYCLIC AND
HETEROCYCLIC ALKANES CATALYZED BY IRIDIUM PINCER
LIGATED COMPLEXES

2.1   INTRODUCTION

Functionalized aromatic skeletons constitute a large variety of important organic compounds' substructures and serve as building blocks for the synthesis of complex molecules in pharmaceuticals and monomers for the production of polymers. As noted in Chapter 1, the synthesis of substituted aromatics and fused arenes can be cumbersome, often requiring harsh conditions such as strongly acidic environments or highly toxic chemicals that generate large amounts of waste. Hence, there is a great interest in developing and identifying methods for the synthesis of substituted and unsubstituted aromatics under milder conditions.

While the previous chapter discussed the substantial efforts in the past twenty years on C(sp^3)–H dehydrogenation by Ir pincer ligated complexes, only a few examples reported the direct dehydroaromatization of heteroatomic hydrocarbons precursors. Additionally, the scope of such reactions is fairly narrow due to the Lewis basic nature of the heteroatoms, particulary by binding of dehydrogenated functionalized species to (PCP)–Ir type catalysts.[1]

The purpose of the work presented in this chapter is to first expand the scope of dehydroaromatization beyond hydrocarbon substrates to generate heteroaromatics with an emphasis on a variety of functional groups that are known to be poorly compatible and strongly coordinating with (PCP)–Ir type catalysts, including halogens, ketones, arenes, and ethers. Second, we want to explore the effects of steric crowding on the ability of Ir pincer ligated complexes to accomplish these transformations.

2.2   RELATED LITERATURE

Since the first reports of Jensen and co-workers of the "parent catalyst" complex ($^{t\text{-Bu}4}$PCP)–Ir **c3** for transfer dehydrogenating the cyclooctane/3,3-dimethyl-1-butene (**COA/TBE)** system[2-3] many studies have utilized Ir pincer ligated complexes for dehydrogenating alkanes to alkenes.[2-8] Amongst the different variations of complex **c3** reported, complexes ($^{t\text{-Bu}4}$POCOP)–Ir **c13**, ($^{i\text{-Pr}4}$PSCOP)–Ir **c22**, and ($^{i\text{-Pr}4}$anthraphos)–Ir **c24** have been shown to exhibit high catalytic activity as dehydrogenation catalysts (Figure 2.1).
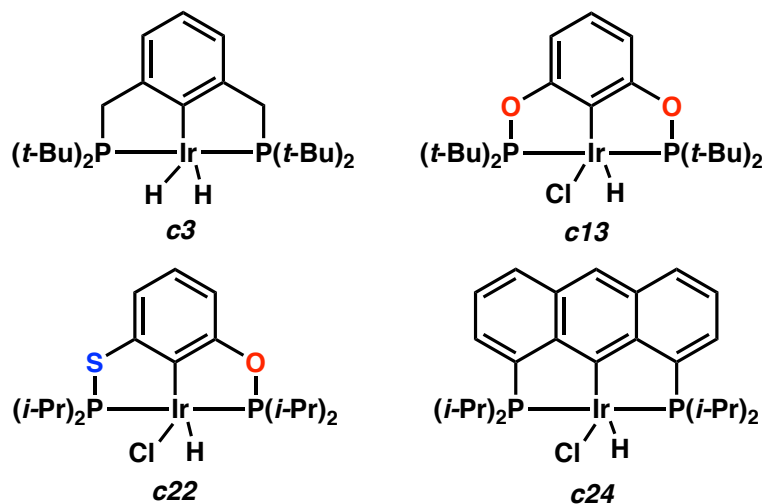
Figure 2.1 *Ir Pincer Ligated Complexes Utilized as Dehydrogenation Catalysts*

However, only a few studies have investigated the direct dehydroaromatization of heteroatom substituted alkanes by Ir pincer ligated complexes due to significant product inhibition by coordination to the Ir metal center. Early reports by Jensen and Kaska and co-workers in 1997 reported low activity of complex ($^{t-Bu4}$PCP)–Ir **c3** to catalyze the transfer dehydrogenation of tetrahydrofuran (**THF**) and using **TBE** as the H$_2$ acceptor (Scheme 2.1a).[1, 8]

Scheme 2.1 *Selected Examples of Cyclic Ethers Transfer Dehydrogenation Ir Complexes*

a.

THF   TBE

11.7 M   370 mM   86 mM   6 mM   53 mM   192 mM

Jensen and Kaska, 1997

b.   **c22**, 120 °C, *p*-xylene   57%

Huang, 2014   TBE

c.   **c24**, 120 °C, 15 h   90%

Brookhart, 2015   TBE

d.   **c3**, cyclodecane, 200 °C, 4.6% conversion   + side products + H_2

Nozaki, 2017
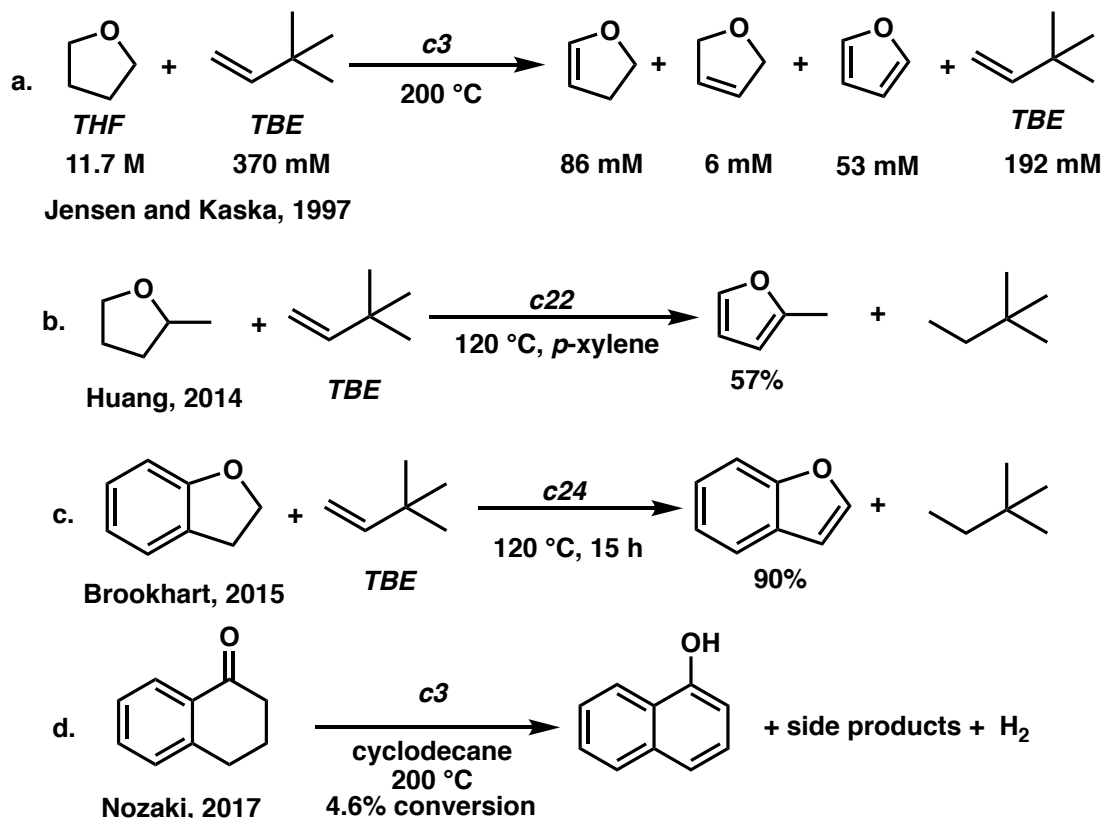
Even though this reaction is thermodynamically favorable, only partial hydrogenation of **TBE** occurred to yield 14% of furan, demonstrating the difficulty of such reactions. Further investigations using Ir pincer ligated complexes for dehydrogenating THF were not reported for over a decade afterward. Later in 2014, Huang and co-workers reported the transfer dehydrogenation of a broad scope of cyclic ethers including THF using (*i*-Pr4PSCOP)–Ir **c22** (Scheme 2.1b).[5] Later, Brookhart and Nozaki and co-workers reported dehydrogenation of linear and cyclic ethers using (*i*-Pr4anthraphos)–Ir **c24** and other variations of Ir pincer ligated complexes, and only limited examples exhibited the direct dehydroaromatization from its alkane precursor substrate (Scheme 2.1c/Scheme 2.1d).[9-10]

Goldman and co-workers attempted the transfer dehydrogenation of cyclohexanone using complex ($^{t\text{-Bu4}}$PCP)–Ir **c3** and found that catalysis was greatly inhibited by coordination of the phenol product (Scheme 2.2).[11]

Scheme 2.2 *Pincer-Ligated Ir Catalysis Inhibition by Coordination of Product*
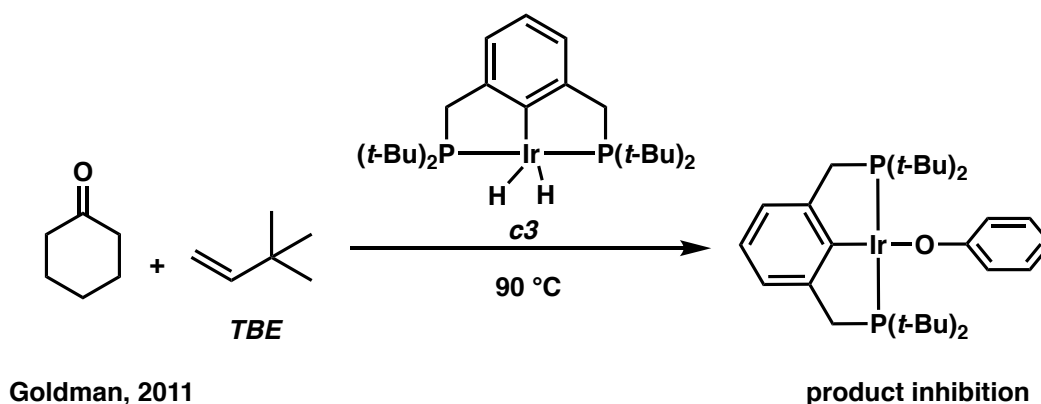
Other than oxygenated substrates, Goldman and Huang and co-workers also reported the dehydrogenation of amines using complexes ($^{t\text{-Bu4}}$PCP)–Ir **c3** and ($^{i\text{-Pr4}}$PSCOP)–Ir **c22** (Scheme 2.3).[5, 12-13] The only report for complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** as a dehydrogenation catalyst for functionalized substrates has been on indolic and carbazolic derivatives in the context of hydrogen storage by Brayton and co-workers in 2014 (Scheme 2.4).[14]

Scheme 2.3 *Selected Examples of Amines Transfer Dehydrogenation*
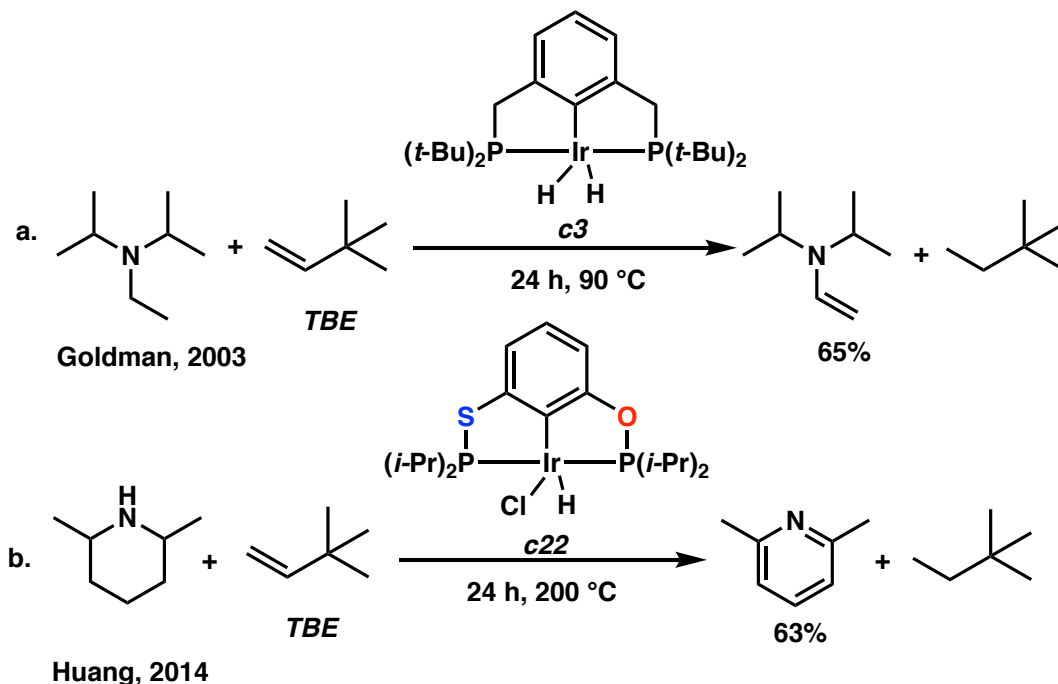
Scheme 2.4 *The Only Example of Dehydrogenating Heteroatomic Substrates by (t-Bu4POCOP)–*

*Ir **c13***
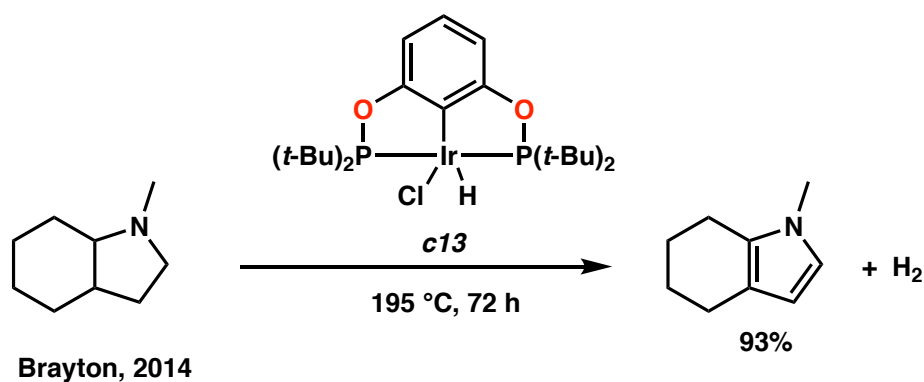
While these examples show significant achievements in the past twenty years, to date

the direct dehydroaromatization of substrates containing a diverse collection of functional

groups remains limited and significantly underdeveloped, mainly due to strong coordination

and product inhibition. Hence the purpose of this study is to investigate Ir pincer ligated

complexes as dehydrogenation catalysts to access substituted fused aromatics with an

emphasis on tolerating diverse functional groups (Scheme 2.5). This study presents novel

and complementary routes to complex molecules *via* late stage dehydrogenation without the

need of lengthy synthetic sequences, which would be useful for pharmaceuticals as well as

materials applications.

Scheme 2.5 *Transfer Dehydrogenation of Broad Range of Substrates with Functional Groups*

by Ir Pincer Ligated Complexes

X = F, Br, MeO
Y = ketone, amine

this work
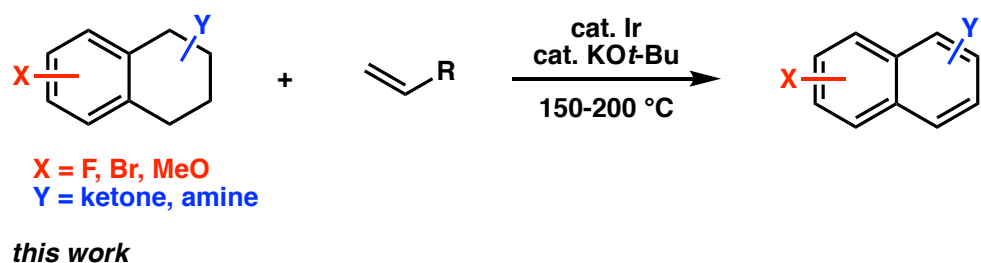
2.3 IRIDIUM PINCER LIGATED COMPLEXES SYNTHESIS AND APPLICATION ON COA/TBE SYSTEM

The synthetic routes toward four known complexes, ($^{t\text{-}Bu4}$PCP)–Ir **c3**, ($^{t\text{-}Bu4}$POCOP)–I **c13**, ($^{i\text{-}Pr4}$PSCOP)–Ir **c22**, and ($^{i\text{-}Pr4}$anthraphos)–Ir **c24**, are discussed in this section.

2.3.1 Synthesis of ($^{t\text{-}Bu4}$PCP)–Ir Complex c3
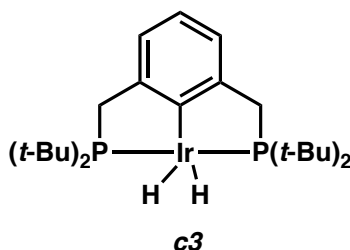
Jensen and co-workers first reported complex ($^{t\text{-}Bu4}$PCP)–Ir **c3**, which is referred to as the "parent catalyst."[3] Complex **c3** achieved a maximum turnover numbers (TONs) of 230 on the **COA/TBE** system and was found to exhibit a low catalytic activity when dehydrogenating *n*-alkanes.[15] Although other complexes such as ($^{i\text{-}Pr4}$PSCOP)–Ir **c22** performed better when applied on the **COA/TBE** system (maximum of 2,900 TONs)[5], complex **c3** was synthesized to replicate the transfer dehydrogenation results of the **COA/TBE** system as a control experiment before attempting to dehydrogenate alternative systems.

Scheme 2.6 *Synthesis of (t-Bu4PCP)–Ir Complex **c3***
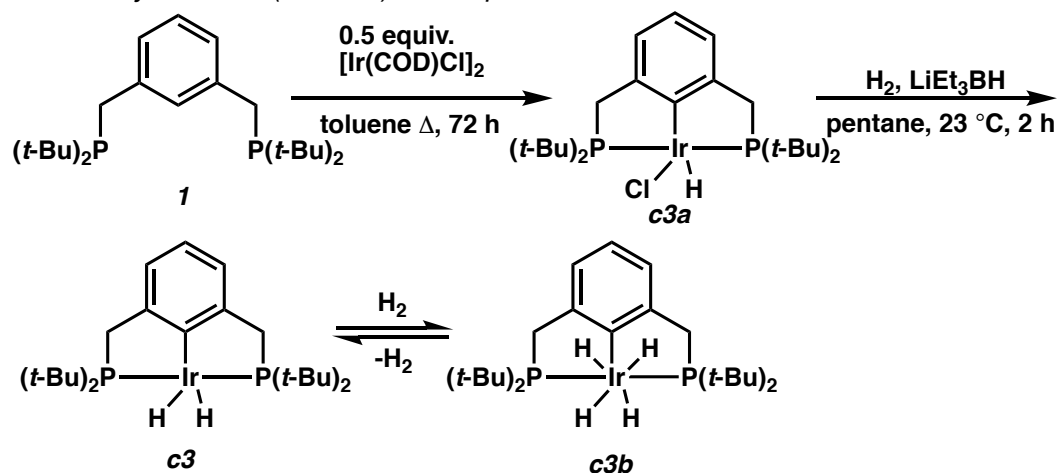
The hydrido chloride complex **c3a** was first synthesized from metalating the
commercially available 2,6-Bbis[(di-*t*-butylphosphino)methyl]phenyl ligand (**1**) in refluxing
toluene under an argon atmosphere (Scheme 2.6).[2-3, 16] The diagnostic NMR signals for
complex **c3a** are the hydride shift observed at -42.50 ppm in the ^{1}H NMR spectrum and the
phosphines signal observed at 67.09 ppm in the ^{31}P NMR spectrum. Then, complex **c3a** was
treated with LiBEt$_3$H under an H$_2$ atmosphere generating the dihydride ($^{t\text{-}Bu4}$PCP)–IrH$_2$
complex **c3**. It was found that the tetrahydride ($^{t\text{-}Bu4}$PCP)–IrH$_4$ complex **c3b** was in
equilibrium with complex **c3** and the diagnostic ^{1}H NMR shift for complex **c3b** was observed
at -9.11 ppm. The energy barrier for the interconversion between the tetrahydride and
dihydride species is almost negligible and the dehydrogenative catalytic activity for the
dihydride and tetrahydride complexes are believed to be similar.[12, 17] Hence, for consistency,
we will refer to the mixture of theses complexes as ($^{t\text{-}Bu4}$PCP)–Ir **c3**.

2.3.2 Synthesis of (*t*-Bu4POCOP)–Ir Complex c13/c13a
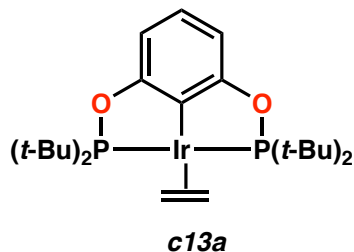
c13a

Complex (*t*-Bu4POCOP)–Ir **c13a** was first reported by Brookhart and co-workers.[18-21] Notably, complex **c13a** showed higher activity compared to the parent catalyst **c3** by achieving a maximum of turnover frequency (TOF) of 6,900 h⁻¹ when applied on the **COA/TBE** dehydrogenation system. This complex has been shown to exhibit higher activity when dehydrogenating cycloalkanes relative to *n*-alkanes. Since we are interested in developing a method to directly dehydroaromatize heterocyclic alkanes, it is of interest to synthesize the (*t*-Bu4POCOP)–Ir complex **c13a**.[1, 15]

The *t*-Bu4POCOP ligand **2** was synthesized from treating resorcinol (**1**) with (*t*-Bu)₂PCl, and DBU (Scheme 2.7). The diagnostic signal of the *t*-Bu4POCOP ligand **2** is the phosphinite shift at 153.22 ppm in ³¹P NMR spectrum. Ligand **2** was then cyclometalated with half an equivalent of [Ir(COD)Cl]₂ in refluxing toluene under an argon atmosphere to obtain the *t*-Bu4POCOP hydrido chloride complex **c13**. It is worth noting that unlike most pincer ligated-Ir complexes, **c13** is air stable. The diagnostic NMR signals of **c13** are the hydride shift at -40.69 ppm in the ¹H NMR spectrum and the phosphinite shift at 175.34 ppm in the ³¹P NMR spectrum. Lastly, the ethylene complex **c13a** was generated by treating **c13** with NaO*t*-Bu under an ethylene atmosphere overnight. The diagnostic ³¹P NMR shift for

the phosphinite was observed at 181.00 ppm. Both **c13** and **c13a** are active precatalysts and

believed to be similar in transfer dehydrogenation systems.

Scheme 2.7 *Synthesis of (t-Bu4POCOP)–Ir Complex **c13a***
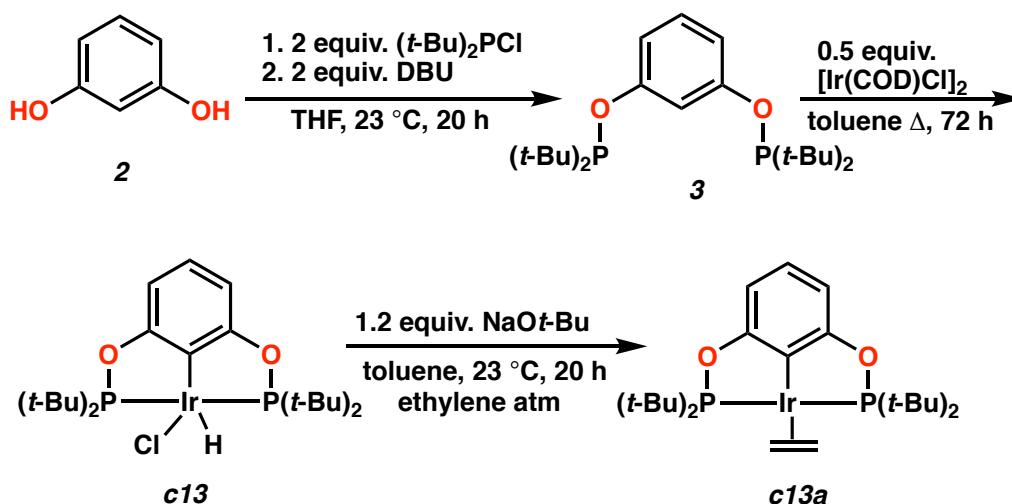
2.3.3 Synthesis of ($^{i\text{-}Pr4}$PSCOP)–Ir Complex c22
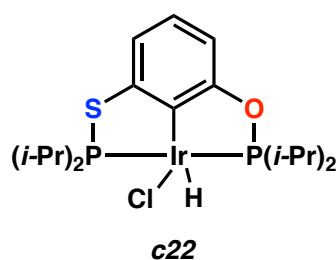
Complex ($^{i\text{-}Pr4}$PSCOP)–Ir **c22** was first reported by Huang and co-workers in 2014.[5]

Complex **c22** exhibited high catalytic activity on the **COA/TBE** system and generated a

maximum TONs of 5901 in 7.5 h. Given its high catalytic activity, we were interested to test

it and investigate it on underexplored systems for dehydrogenation. This complex was

synthesized by Dr. Michael Haibach in the Grubbs group following literature protocols

(Scheme 2.8).[5] Similar to the previous complexes, the PSCOP ligand **5** was first synthesized

from deprotonating meta-mercaptophenol (**4**) with NaH followed by diphosphorylation with

(*i*-Pr$_2$)$_2$PCl. The characteristic phosphinite shift is expected at 150.40 ppm and the phosphine

sulfide shift is expected at 68.70 ppm in the ^{31}P NMR spectrum. Then the obtained ligand **5**

was cyclometalated with half an equivalent of [Ir(COD)Cl]$_2$ in refluxing toluene affording

complex **c22**. The diagnostic NMR signal of **22** is the hydride shift and expected at -37.06

ppm in the ^{1}H NMR spectrum.

Scheme 2.8 *Synthesis of ($^{i-Pr4}$PSCOP)–Ir Complex **c22***
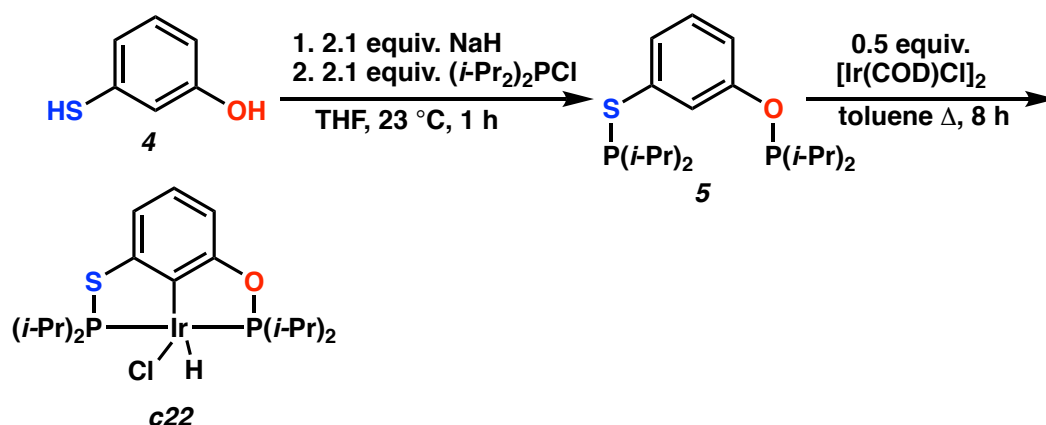
2.3.4 Synthesis of (*i-*Pr4Anthraphos)–Ir Complex c24

c24
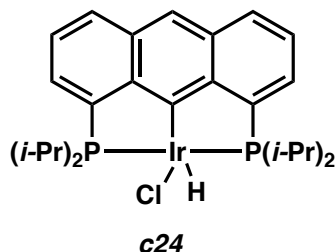
Complex (*i-*Pr4anthraphos)–Ir **c24** was first reported by Haenel *et al.* in 2001 for alkanes dehydrogenation.[22] Complex **c24** was found to have higher thermal stability (up to 250 °C) relative to other Ir pincer ligated complexes and exhibited high catalytic activity when used as a dehydrogenation catalyst on the **COA/TBE** system. This complex was synthesized by Dr. Michael Haibach following literature protocols (Scheme 2.9).[23-24] The anthraphos ligand **9** was first synthesized from commercially available 1,8-dichloroanthraquinone (**6**) followed by fluorination generating **7** and then reduction to 1,8-difluoroanthracene (**8**). Then **8** was treated with (*i-*Pr₂)₂PK affording the desired anthraphos ligand **9**. Finally, cyclometallation with half an equivalent of [Ir(COD)Cl]₂ in refluxing toluene generates the desired complex **c24**. The diagnostic NMR signals of **24** are the hydride shift expected at -35.90 ppm in the ¹H NMR spectrum and the phosphine shift expected at 61.00 ppm in the ³¹P NMR spectrum.[23]

Scheme 2.9 *Synthesis of (i-Pr4Anthraphos)–Ir Complex* **c24**
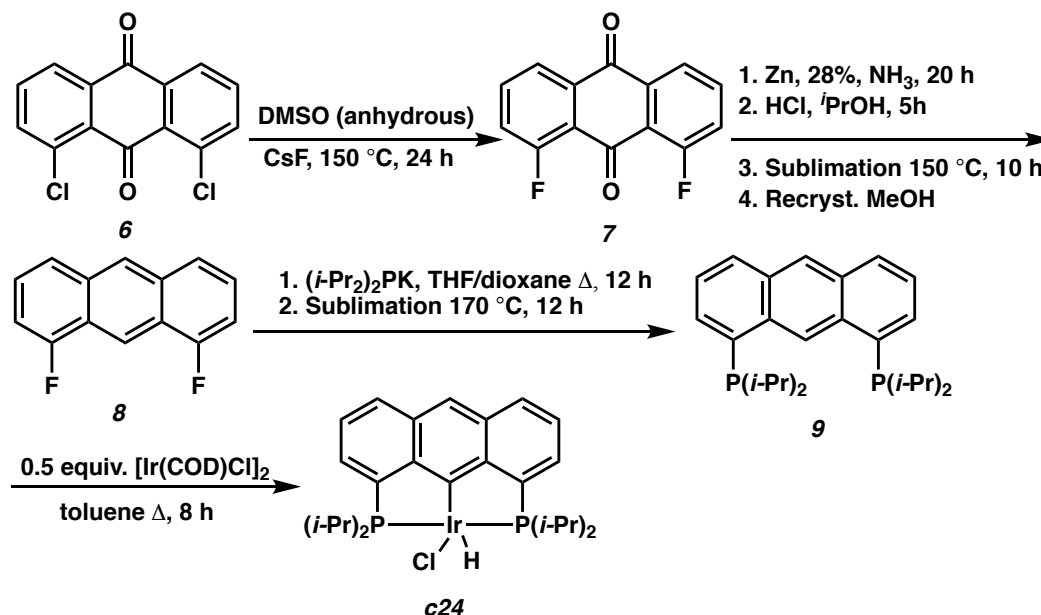
2.3.5 COA/TBE Transfer Dehydrogenation System and Reaction Set-Up Investigation

After synthesizing complexes ($^{t\text{-Bu4}}$PCP)–Ir **c3** and ($^{t\text{-Bu4}}$POCOP)–Ir **c13**, dehydrogenation reactions were performed on the **COA/TBE** system to validate the complexes activity as dehydrogenation catalysts.

Following the Jensen and Brookhart transfer dehydrogenation of **COA/TBE** system published procedures we tested the complexes in a degassed 0.4 mM stock solution under an argon atmosphere and the reaction mixture was prepared in a sealed vial inside the glovebox (setup a).[3, 19] The transfer dehydrogenation of **COA/TBE** system was first investigated with the parent complex ($^{t\text{-Bu4}}$PCP)–Ir **c3** using the hydrogenated version and precatalyst (Table 2.1 entry 1 and 2). Only 7.0 and 64.8 TONs were obtained and 16.2% to 17.6% of **TBE** was hydrogenated.

Table 2.1 COA/TBE *Transfer Dehydrogenation Reactions with Complexes (*$^{t\text{-}Bu4}$*PCP)–Ir* **c3** *and*

(*$^{t\text{-}Bu4}$POCOP)–Ir* **c13**
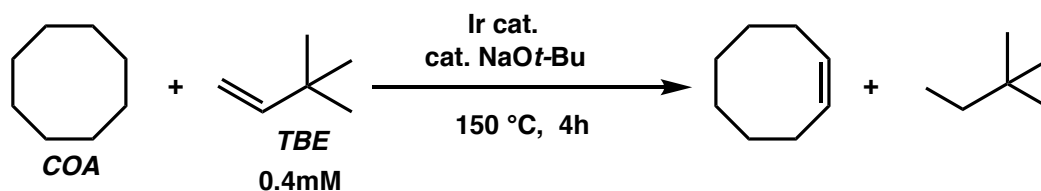
entry	cat.	loading (mol.%)	TON	TBE conv.	set up[a]
1	(c3)IrH$_2$	0.11	7.0	16.2%	a
2	(c3)IrHCl	0.08	64.8	17.6%	a
3	(c3)IrH$_2$	0.18	9.4	30.4%	b
4	(c3)IrH$_2$	0.14	12.5	25.7%	b
5	(c3)IrHCl	0.15	24.8	15.9%	b
6	(c3)IrHCl	0.11	20.9	27.2%	c
7	(c3)IrHCl	0.13	28.3	28.2%	d
8	(c13)Ir(C$_2$H$_2$)	0.09	13.2[b]	11.3%	a
9	(c13)Ir(C$_2$H$_2$)	0.22	23.5	35.4%	b
10	(c13)Ir(C$_2$H$_2$)	0.15	24.7	26.8%	b
11	(c13)Ir(C$_2$H$_2$)	0.14	11.4	22.5%	c
12	(c13)IrHCl	0.15	5.3	13.8%	c
13	(c13)IrHCl	0.34	11.4	28.3%	c

[a] set up conditions: a = sealed vial, b = sealed vial with new **COA**, c = sealed Schlenk pressure flask with new **COA** + **TBE**, d = J. Young Tube with new **COA** + **TBE**. [b] reaction was run overnight.

Then, we investigated complex (*$^{t\text{-}Bu4}$*POCOP)–Ir **c13** catalytic activity using the

ethylene species. Only 13.2 TONs were achieved and **TBE** was partially hydrogenated

(Table 2.1 entry 8). In contrast to the literature reports, these complexes exhibited low

catalytic activity and the results were not consistent with literature values. A new **COA/TBE**

stock solution was prepared and reaction mixtures were mixed in a sealed vial inside an argon

glovebox (setup b). The obtained TONs with setup b with complexes **c3** and **c13** were again

very low and exhibited low catalytic activity (Table 2.1 entries 3-5, and 9-10).

The dehydrogenation reactions of **COA/TBE** run at 150 °C, and there is a possibility

that the vial cap was not sealing properly due to the high vapor pressure from the reaction

mixture. Hence, a new reaction setup was investigated that replaced the sealed vial with a

sealed Schlenk pressure flask (setup c). The transfer dehydrogenation of **COA/TBE** system

was tested with setup c using complexes **c3** and **c13** (Table 2.1 entries 6, 11-13) and low

TONs were still observed.   We performed ^{31}P NMR spectroscopy of complex

($^{t\text{-Bu}4}$PCP)IrHCl **c3** to investigate the reasons behind the observed low catalytic activity. The

diagnostic phosphine shift of complex **c3** is 67.02 ppm in the ^{31}P NMR spectrum and we

found that the complex had become significantly oxidized while being exposed to the

glovebox atmosphere (Figure 2.2a). Hence, we investigated the transfer dehydrogenation of

COA/TBE system with the same complex in a J. Young NMR tube (set up d) (Table 2.1

entry 7). After heating the reaction mixture to the required temperature for dehydrogenation,

^{31}P NMR revealed that the all of the complex had oxidized product (Figure 2.2b).

It was concluded that rigorous air-free conditions were needed for the catalytic

activity for dehydrogenation type reactions and even low ppm oxygen levels from the

glovebox resulted in inhibition of catalytic activity. This conclusion is in agreement with

previous reports by Jensen and Yamashita that reported (PCP)–Ir type pincer catalysts can

be inhibited by small amounts of impurities.[25-26]
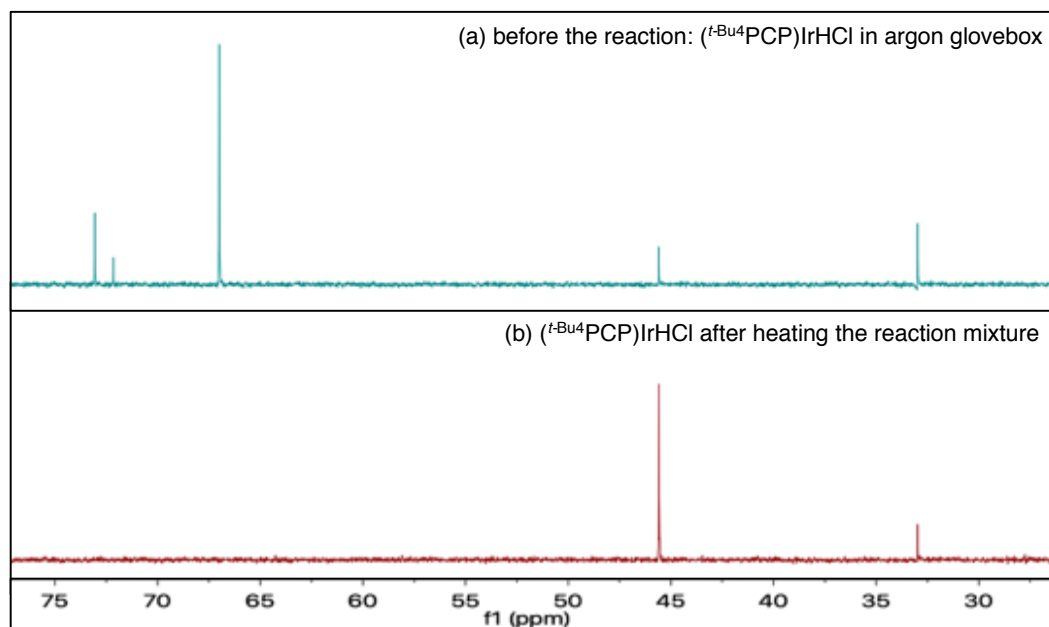
Figure 2.2 *(a)* [31]*P NMR of (*[t-Bu4]*PCP)IrHCl* **c3** *Before the Reaction (b)* [31]*P NMR of (*[t-Bu4]*PCP)IrHCl*

c3 *After Heating the Reaction Mixture in Table 2.1 Entry 7*

Hence, all dehydrogenation reactions must be performed in a flame-dried sealed

Schlenk pressure flask with rigorously distilled, degassed *via* performing freeze-pump-thaw

x5 cycles, and dried solvents with molecular sieves, NaH, or Na-K alloy. We have observed

improved catalytic activity of the Ir pincer ligated complexes when these preparations were

made.

2.4   TRANSFER DEHYDROGENATION OF HETEROCYCLIC ALKANES CATALYZED BY IRIDIUM PINCER LIGATED COMPLEXES

2.4.1 6-Methoxy-1,2,3,4-Tetrahydronaphthalane Transfer Dehydrogenation

A. Introduction

Substituted naphthalene derivatives are important building blocks in pharmaceuticals and in many biologically active compounds that possess antibiotic and anticancer activities.[27-31] In addition, substituted naphthalene derivatives have found applications due to their desired optical and electronic characteristics.[32-34] There have been great efforts in developing new methods for the synthesis of naphthalene skeletons in the recent years. However, the synthesis of substituted naphthalenes can be cumbersome and is difficult *via* conventional electrophilic aromatic substitution owing to the poor regioselectivity.[35] Hence, it is of interest to develop new facile regioselective methods towards the synthesis of such molecules without lengthy synthetic sequences. For example, constructing substituted naphthalenes from corresponding cyclohexanes *via* $C(sp^3)$–H dehydrogenation by Ir pincer ligated complexes can be an attractive method to access such compounds.

Once we had established a successful rigorous air-free reaction set up and conditions for dehydrogenation systems by Ir pincer ligated complexes, the next part of our study focused on investigating the catalytic activity of synthesized Ir pincer ligated complexes towards transfer dehydrogenative aromatization by using

6-methoxy-1,2,3,4-tetrahydronaphthalaene (**10**) to 2-methoxynaphthalene (**11**) as a model

substrate (Scheme 2.10).

Scheme 2.10 *Transfer Dehydrogenation of 6-Methoxy-1,2,3,4-Tetrahydronaphthalene*

Catalyzed by Ir Pincer Ligated Complexes
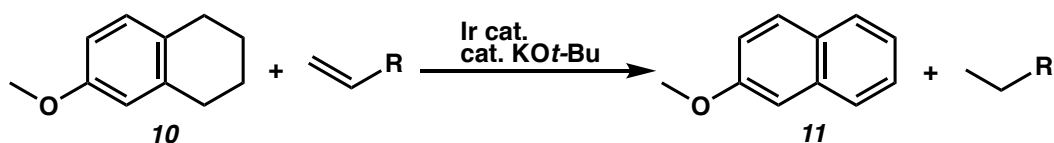
B. Catalyst Screening and Reaction Optimization

We began reaction optimization on 6-methoxy-1,2,3,4-tetrahydronaphthalaene (**10**)

using complexes ($^{t\text{-}Bu4}$POCOP)–Ir **c13**, ($^{i\text{-}Pr4}$PSCOP)–Ir **c22**, and ($^{i\text{-}Pr4}$anthraphos)–Ir **c24** and

3,3-dimethyl-1-butene (**TBE**) as an H$_2$ acceptor (Table 2.2). The reactions were carried

out neat under an argon atmosphere at 200 °C. We first conducted a control experiment

where only KOt-Bu was added without the Ir pincer ligated complex to ensure desired

product is not generated from this mild base alone (Table 2.2 entry 1); product was not

observed in the absence of Ir.

We found that complexes **c13** and **c24** were the most active in dehydrogenating **10**

and up to 52.5% of 2-methoxynaphthol (**11**) was generated and up to 96.5% of TBE was

hydrogenated (Table 2.2 entry 2 and 4), while complex **c22** showed modest activity even

when running the reaction for longer times (Table 2.2 entry 3).

Table 2.2 *Catalyst and Acceptor Screening of 6-Methoxy-1,2,3,4-Tetrahydronaphthalene*

Transfer Dehydrogenation
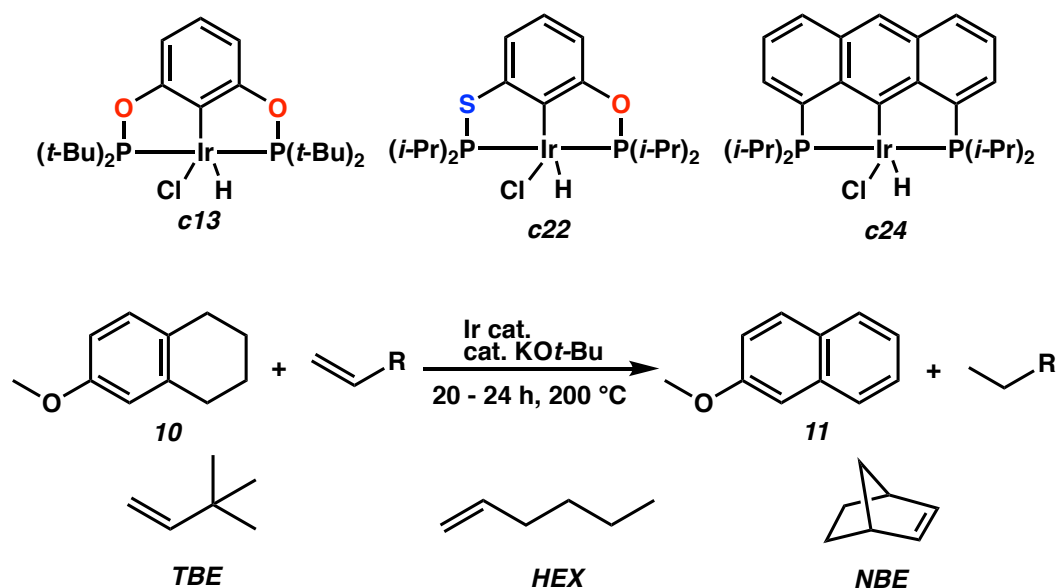
entry	cat.	loading (mol.%)	H₂ acceptor	equiv. of acceptor	acceptor conv.	11 yield[b]	TON[c]
1	-	-	TBE	1.0	-	0.2%	-
2	c13	0.13	TBE	1.0	96.5%	52.5%	404
3	c22	0.36	TBE	1.0	37.9%	33.2%[d]	92
4	c24	0.24	TBE	1.0	90.5%	49.8%	207
5	c13	0.12	NBE	1.0	98.3%	44.0%	293
6	c13	0.15	NBE	2.5	87.5%	63.9%	426
7	c13	0.25	HEX	1.0	82.9%	48.6%	194
8	c13	0.63	HEX	2.5	94.5%	67.1%	106

[a] Conditions: 3.2 mmol of **10**, Ir cat. with at least 1.2 equiv. KOt-Bu. [b] Conversion determined by GC. [c] TON per dehydrogenation. [d] reaction carried for 48 h.

In all cases, only the fully dehydroaromatized product 2-methoxynaphthalene (**11**) was observed and no olefinic product was observed corresponding to one dehydrogenation

cycle. Compared to the other complexes, ($^{t-Bu4}$POCOP)–Ir **c13** affords better access to the

metal site attributed to the more open geometry of P–Ir–P acute angle and the shorter C–O

and P–O bond lengths of the POCOP ligand.[36-37] For instance, ($^{t-Bu4}$POCOP)–Ir **c13** has

bite angle of 157.55(3)° and complex ($^{t-Bu4}$PCP)–Ir **c3** has bite angle of 164.510(8)°.

In addition, complex **c13** is air-stable which is advantageous relative to the other

complexes. Thus, we selected it to further optimize the reaction conditions for

dehydroaromatizing **10**.

We next examined 1-hexene (**HEX**) and norbornene (**NBE**) as alternative H_2

acceptors due to their economic advantage compared to **TBE**. However, **TBE** ultimately

proved to be the best H_2 acceptor as determined by yield of **11** under similar conditions for

10 (Table 2.2 entries 5-8). In addition, when higher catalyst loading and equivalence of

acceptor was used, only a modest increase of Ir catalytic activity was observed (Table 2.2

entry 6 and 8). Hence, we decided to further optimize the dehydrogenation of **10** using

TBE only as an acceptor (Table 2.3). While increasing either the equivalence of **TBE** or

the catalyst loading alone had minimal effect on increasing the yield (Table 2.3 entry 1 and

2), higher conversions were achieved when both parameters are increased simultaneously

(Table 2.3 entry 3 and 4). However, excessively high **TBE** to catalyst ratio deteriorated

the catalytic activity (Table 2.3 entry 5). A likely explanation is that the **TBE** inhibits the

catalyst by binding to it and favoring the resting state vinyl complex **H** shown in Scheme

1.6 in Chapter 1. Further optimization resulted in 99% yield of 2-methoxynaphthalene (**11**)

(Table 2.3 entry 6).

Next the effect of temperature on the catalytic activity of (^(*t*-Bu4)POCOP)–Ir **c13** was studied (Figure 2.3). The transfer dehydrogenation of **10** using **TBE** was run at 150 °C and 120 °C for longer times, while keeping all other conditions constant (Table 2.3 entries 7-9). It was observed that lowering the temperature decreased catalytic activity.

Table 2.3 *Reaction Optimization of 6-Methoxy-1,2,3,4-Tetrahydronaphthalene Transfer Dehydrogenation Using Complex (^(t-Bu4)POCOP)–Ir **c13***
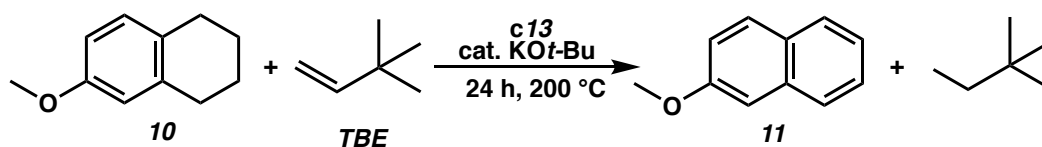
entry	cat. loading (mol.%)	equiv. of TBE	TBE conv.	11 yield[b]	TON[c]
1	0.15	1.5	73.0%	41.6%	277
2	0.15	2.0	51.1%	53.2%	341
3	0.26	2.0	51.4%	56.3%	198
4	0.40	2.0	97.9%	72.9%	182
5	0.41	3.0	44.9%	54.7%	133
6	0.59[d]	3.0	75.8%	99.0%	169
7*	0.16	1.0	78.6%	39.2%	245
8*	0.16	1.0	100.0%	38.2%	242
9**	0.16	1.0	60.5%	17.1%	107

[a] Conditions: 3.2 mmol of **10**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Conversion determined by GC ^{1}H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation. [d] **c13** (^(t-Bu4)POCOP)–Ir–C_2H_4 ethylene version was used. *entries 10 and 11 were run at 150 °C for 22 h and 48 h. ** entry 12 was run at 120 °C for 72 h.

When the reaction was run at 150 °C and reaction time was increased from 22 h to 48 h, the maximum TONs achieved was 245. Similarly, when the reaction was run at 120

°C for 72 h, complex **c13** exhibited low catalytic activity, achieving a maximum of 107

TONs. Hence, we conclude that carrying the reaction at 200 °C is necessary for achieving

optimal conversions. In all cases, only the fully dehydroaromatized product **11** was observed

and we do not observe an olefinic intermediate, hence we conclude that the direct

dehydroaromatization of 10 is selective to the desired product.
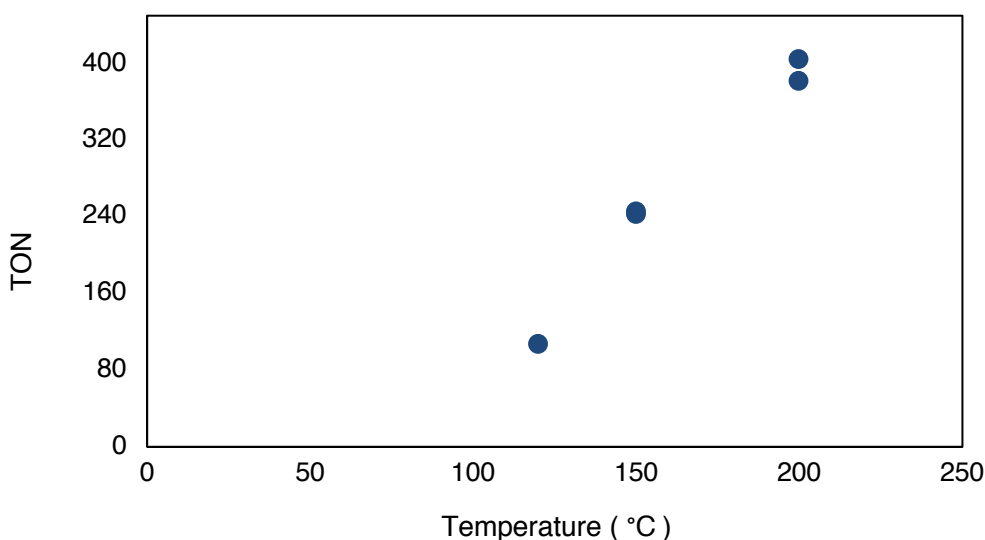
Figure 2.3 *Temperature Effect on (t-Bu4POCOP)–Ir* **c13** *Catalytic Activity as Dehydrogenation*
Catalyst of 6-Methoxy-1,2,3,4-Tetrahydronaphthalene **10**

2.4.2 Indane Transfer Dehydrogenation

A. Introduction

Many indene derivatives have interesting biological activity and have applications in

material science.[38-42] The traditional approaches of indene syntheses include intramolecular

electrophilic substitution reaction or cyclization induced by a nucleophilic attack to a suitable

functional group.[43-45] These synthetic methods require highly functionalized arenes, which can be cumbersome to prepare industrially. Here, we present an alternative and complementary approach to prepare indene *via* the direct dehydroaromatization of indane using complex ($^{t\text{-}Bu4}$POCOP)–Ir **c13** (Table 2.4).

B. Reaction Optimization

Having established optimized reaction conditions in the previous section 2.4.1, we used similar condition and carried out the reactions neat under an argon atmosphere after drying and distilling all reagents. The transfer dehydrogenation of indane (**12**) was investigated using **TBE** as the H_2 acceptor at 200 °C (Table 2.4 entry 1). The reaction successfully generated indene (**13**) with a yield of 42.3% and TONs of 184. Replications of the reactions with **TBE** or **HEX** as H_2 acceptors generated no product and formed black carbonaceous deposits in the flask (Table 2.4 entry 2 and 3). It is not fully understood why the results could not be replicated. One possibility is that both **12** and **13** are acidic, and at high temperatures other side reactions such as polymerization may occur.

Alternatively, the reaction was investigated at lower temperatures 180 °C and 150 °C, while carrying out the reactions for longer times (48 h) (Table 2.4 entries 4-7). In contrary to the transfer dehydrogenation of **10** to **11** results observed in the previous section 2.4.1, we found that complex ($^{t\text{-}Bu4}$POCOP)–Ir **c13** catalytic activity increased when decreasing the temperature. When the transfer dehydrogenation of indane (**12**) was investigated at 180 °C, the obtained yield of indene (**13**) was 47.5% (Table 2.4 entry 4).

Table 2.4 *Transfer Dehydrogenation of Indane to Indene by Complex (ᵗ⁻ᴮᵘ⁴POCOP)–Ir **c13***
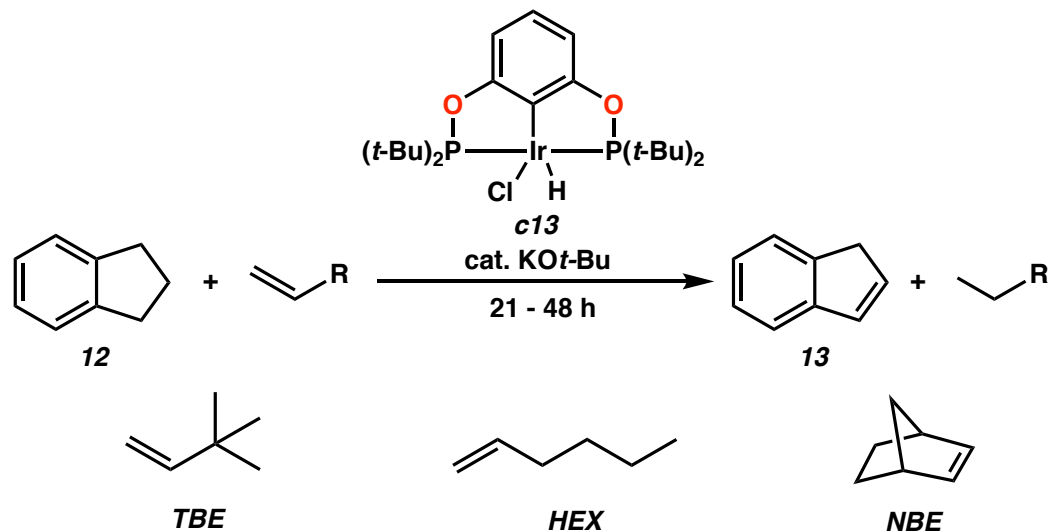
entry	cat. loading (mol.%)	H₂ acceptor	equiv. of acceptor	temperature (°C)	conv of acceptor	13 yield[b]	TON[c]
1	0.23	TBE	1	200	42.0%	42.3%	184
2	0.24	TBE	1	200	96.5%	-	-
3	0.23	HEX	1	200	24.6%	-	-
4	0.26	TBE	1	180	95.5%	47.5%	182
5	0.24	TBE	1	150	98.3%	60.8%	253
6	0.26	HEX	1	150	73.0%	27.1%	104
7	0.26	NBE	1	150	51.1%	58.1%	224
8	0.59	TBE	2.5	150	45.4%	95.8%	162

[a] Conditions: 3.2 mmol of **12**, precatalyst with at least 1.2 equiv. KOt-Bu. [b] Yield determined by GC and ¹H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation.

However, when the reaction was carried under similar conditions at 150 °C, 60.8% of indene (**13**) was generated (Table 2.4 entry 5). It is worth noting that using **HEX** as an H₂ acceptor was worse than **TBE** or **NBE** in this dehydrogenation system (Table 2.4 entry 6 and

7). After reaction optimization using complex **c13**, **13** was generated in excellent yields showing that this catalytic system is highly effective (Table 2.4 entry 8). In all cases, only indene (**13**) and the hydrogenated olefin was observed and no side products were generated.

Given that ($^{i\text{-Pr4}}$anthraphos)–Ir **c24** exhibited high catalytic activity when used as a catalyst for transfer dehydrogenating **10** to **11** in the previous section 2.4.1, we employed it to transfer dehydrogenate **12** to **13** with **TBE** as the H$_2$ acceptor (Scheme 2.11). As we expected, complex **c24** achieved excellent yields generating 97.3% of **13** and 335 TONs. In summary, both complexes **c13** and **c24** exhibited high catalytic activity when dehydrogenating **12** to **13** and in all cases, the catalytic systems was selective to indene (**13**).

Scheme 2.11 *Transfer Dehydrogenation of Indane Catalyzed by Complex ($^{i\text{-Pr4}}$Anthraphos)–Ir*

c24
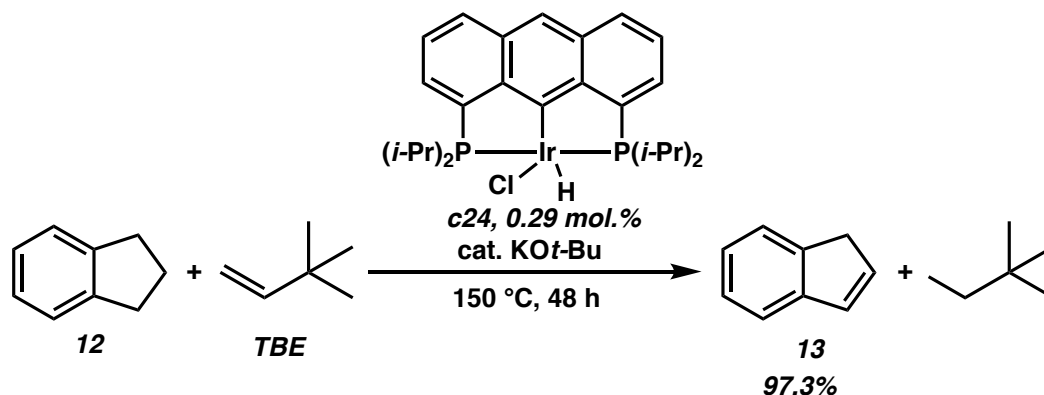
2.4.3 6-Methoxy-1,2,3,4-Tetrahydroquinoline Transfer Dehydrogenation

A. Introduction

Substituted quinoline scaffolds are important compounds that have been shown to possess a critical and a diverse range of biological activities such as antimalarial, antimicrobial, anti-inflammatory, and many other characteristics.[46-50] In addition, some of these scaffolds have found applications as functional materials for organic light-emitting diodes.[51-53]

Owing to their great synthetic utility and useful properties, there has been great interest in finding new methods for the synthesis of quinoline scaffolds in the recent years. However, most of the current methods that synthesize substituted quinolines suffer from harsh and toxic conditions, requiring an oxygen atmosphere, and complex raw reagents.[50] The direct dehydroaromatization from alkane precursors can be an alternative and a complementary method to the current approaches. Here we present the synthesis of 6-methoxyquinoline   and   *via*   C(sp³)–H   dehydrogenation   of   6-methoxy-1,2,3,4-tetrahydroquinoline by Ir pincer ligated complexes.

B. Catalyst Screening and Reaction Optimization

We commenced investigating the transfer dehydrogenation of 6-methoxy-1,2,3,4-tetrahydroquinoline (**14**) using complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** and **TBE** as the H_2 acceptor at 200 °C (Table 2.5, entry 1). The reactions were carried out neat under an argon am atmosphere after drying and distilling all reagents. Surprisingly, the complex

exhibited modest catalytic activity at the investigated initial conditions (cat. loading 1.38

mol.%) and reaction time (19 h) and only 29.9% of 6-methoxyquinoline (**15**) was generated.

Table 2.5. *Transfer Dehydrogenation of 6-Methoxy-1,2,3,4-Tetrahydroquinoline by Complex*

*($^{t\text{-}Bu4}$POCOP)–Ir **c13***
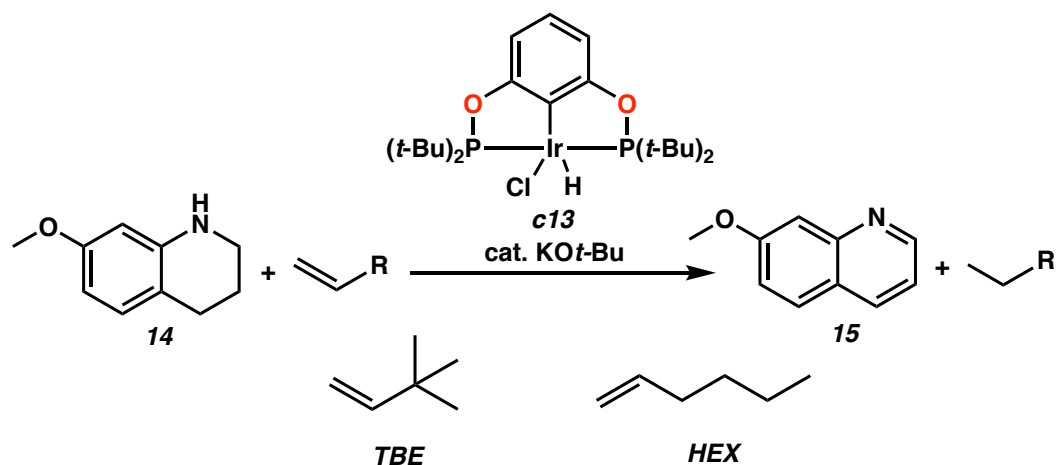
entry	cat. loading (mol.%)	H_2 acceptor	equiv. of acceptor	temperature (°C)	reaction time	15 yield[b]	TON[c]
1	1.38	TBE	3.0	200	19 h	29.9%	21
2	1.62	TBE	5.0	200	43 h	50.9%	31
3	1.98	TBE	5.0	150	48 h	16.7%	9
4	1.80	HEX	5.0	200	22 h	70.2%	39
5	4.09	HEX	6.0	200	22 h	93.5%	22
6	4.06	HEX	6.0	160	96 h	68.1%	17

[a] Conditions: 3.2 mmol of **14**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ¹H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation.

Hence, we carried out the reaction for longer time (43 h) and slightly increasing the

cat. loading to 1.62 mol.%, and we observed increased yield of **15** to 50.9% (Table 2.5 entry

2). It is evident that the transfer dehydrogenation of **14** with **TBE** as an H_2 acceptor is slower

compared to previously discussed substrates 6-methoxy-1,2,3,4-tetrahydronaphthalenea (**10**) (section 2.4.1) and indane (**12**) (section 2.4.2). Since we obtained better results when lowering the temperature for the transfer dehydrogenation of **12**, we also lowered the temperature to 150 °C when investigating the transfer dehydrogenation of **14** and increasing the catalyst loading to 1.98 mol.% (Table 2.5 entry 3). However, the yield of **15** was significantly deteriorated and only 16.7% was obtained.

Alternatively, the dehydrogenation reaction of **14** was investigated using **HEX** as the H_2 acceptor instead of **TBE**. We were delighted to find that the catalytic activity of **c13** was higher and 70% of **15** was generated when the reaction was carried out under similar conditions at 200 °C (Table 2.5 entry 4). Increasing the catalyst loading while maintaining all the other parameters similar generated optimized reaction conditions and excellent yields up to 93.5% of **15** (Table 2.5 entry 5). We then investigated lowering the temperature to 160 °C when using **HEX** as the H_2 acceptor but we found that the catalytic activity was poor even when carrying out the reaction for 96 h (Table 2.5 entry 6). It is not fully understood why using **HEX** was a better H_2 acceptor compared to **TBE** and generated better yields of **15**. This finding is contrary to literature reports where (PCP)–Ir pincer type complexes have been shown to have greater binding affinity to terminal and linear olefins relative to **TBE.** The greater steric hindrance of **TBE** is known to mitigate the binding of dehydrogenated products to the Ir metal center, thereby increasing (PCP)–Ir pincer complexes' catalytic activity.[1, 54]

Given that Huang and co-workers reported good catalytic activity of ($^{i\text{-}Pr4}$PSCOP)–Ir

c22 when dehydrogenating *N*-heterocyclic alkanes,[5] we investigated dehydrogenating **14** to

15 using complex **c22** (Scheme 2.12).   However, we observed lower catalytic activity

comparable to complex **c13** when the reaction was run under similar conditions with **TBE**

as the H$_2$ acceptor and only 28.3% of **15** was generated.   Hence, further optimization with

complex **c22** was not performed.   In all cases, the investigated transfer dehydrogenation

reactions of **14** generated the fully dehydroaromatized substrate **15** as the only product and

no side reactions were observed.

Scheme 2.12 *Transfer Dehydrogenation of 6-Methoxy-1,2,3,4-Tetrahydroquinoline d by*

*Complex ($^{i\text{-}Pr4}$PSCOP)–Ir **c22***
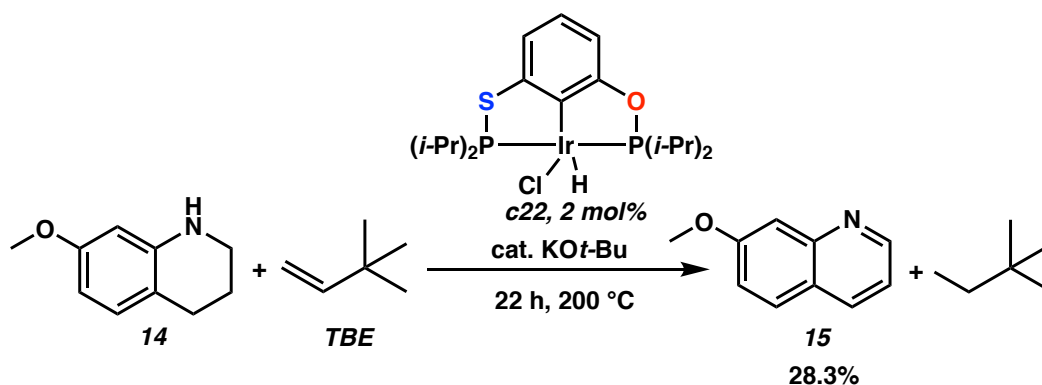
2.4.4 7-Bromo-1,2,3,4-Tetrahydroisoquinoline Transfer Dehydrogenation

A. Introduction

Isoquinoline skeletons constitute important structural framework in natural

products, pharmaceuticals, and functional materials.[55-59]   In addition, brominated

isoquinoline derivatives are extremely useful synthetic blocks that are used to synthesize

novel isoquinoline derivatives with fluorescence properties (Scheme 2.13).[60-63]   Hence,

there has been significant interest in constructing isoquinoline scaffolds. Classical methods

involve Bischler-Napieralski and Pictet-Spengler reactions which require harsh acidic

conditions limiting their practical usage.[64-65]   In addition, selective bromination of

quinolines is cumbersome and require lengthy reaction periods and difficult work up.[66-68]

Scheme 2.13 *Selected Examples of Brominated Isoquinoline Synthetic Utility*
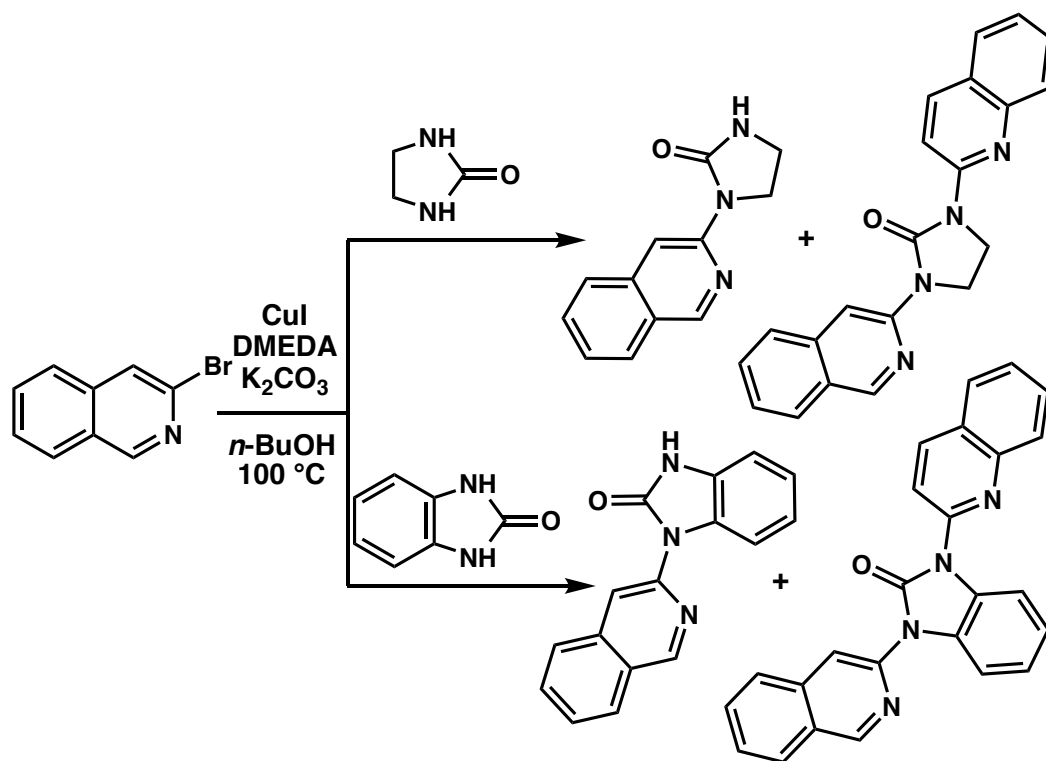
Herein, we present an alternative and complementary facile method of the synthesis

of   7-bromoisoquinoline   *via*   the   direct   C(sp³)–H   dehydrogenation   of

7-bromo-1,2,3,4-tetrahydroisoquinoline by Ir pincer ligated complexes.

B. Reaction Optimization

We began investigating the transfer dehydrogenation of 7-bromo-1,2,3,4-tetrahydroisoquinoline (**16**) using complex ($^{t\text{-Bu}4}$POCOP)–Ir **c13** and **TBE** as the H_2 acceptor at 200 °C (Table 2.6, entry 1). The reactions were carried out neat under an argon atmosphere after drying and distilling all reagents. The complex exhibited good catalytic activity at the investigated conditions and 66.7% of 7-bromoisoquinoline (**17**) was generated. In an attempt to optimize the product yield, we carried out the reaction with excess **TBE** and longer reaction times up to 144h, we only observed 50.1% and 49.1% of **17** however (Table 2.6 entry 2 and 3). Similar to what we observed in the previous section 2.4.3 when investigating the transfer dehydrogenation of **14**, we found that high concentrations of **TBE** limited the catalytic activity of complex **c13** due to the possibility of shifting the binding equilibrium at higher concentrations. Hence, alternatively we investigated the transfer dehydrogenation of **16** with **HEX** as the H_2 acceptor (Table 2.6 entry 4). We optimized reaction conditions with **HEX** and we achieved excellent yields up to 91.4% of **17** was generated. In all cases, only the fully dehydroaromatized product **17** was observed and no side reactions were detected, thus providing a new complementary and an alternative selective method toward the synthesis of brominated isoquinoline skeletons.

Table 2.6 *Transfer Dehydrogenation of 7-Bromo-1,2,3,4-Tetrahydrisoquinoline by Complex*

(t-Bu4POCOP)–Ir **c13**
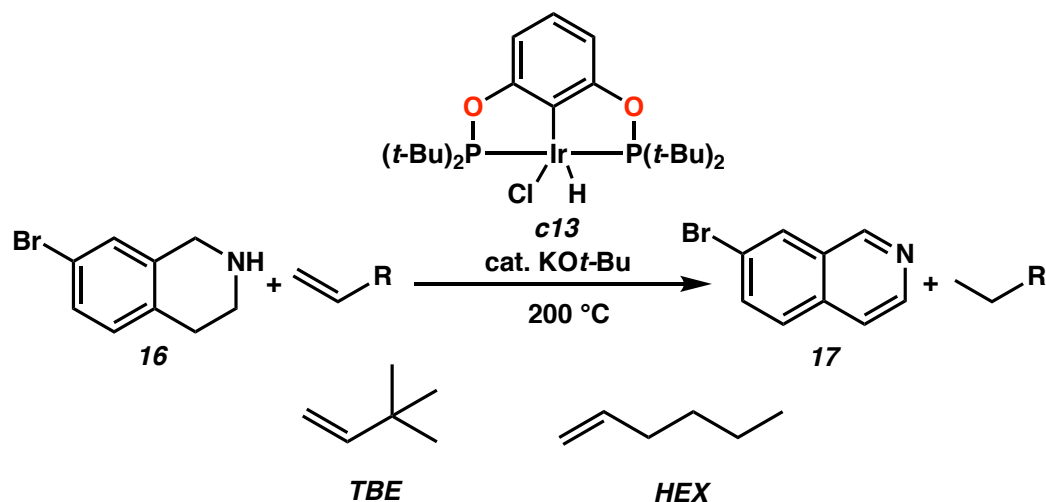
entry	cat. loading (mol.%)	H$_2$ acceptor	equiv. of acceptor	reaction time	17 yield[b]	TON[c]
1	3.42	TBE	1.0	24 h	66.7%	20
2	8.27	TBE	10.0	45 h	50.1%	6
3	8.75	TBE	exs	144 h	49.1%	6
4	6.24	HEX	exs	24 h	91.4%	15

[a] Conditions: 3.2 mmol of **16**, precatalyst with at least 1.2 equiv. KOt-Bu. [b] Yield determined by GC and ¹H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation.

2.4.5 Tetralone Derivatives Transfer Dehydrogenation

A. Introduction

Naphthol derivatives serve as important building blocks in pharmaceuticals, agrochemicals, polymers, and natural products.[69-71] Classical industrial methods to make naphthol compounds rely on the alkali fusion of naphthalene sulfuric acid or

α-naphthylamine hydrolysis at elevated temperatures and high pressures (Scheme 2.14).[72]

Due to their synthetic utility, alternative approaches have been reported utilizing the direct

dehydrogenation of 1-tetralone to 1-naphthol *via* heterogeneous catalysis at high

temperatures or *via* photocatalytic continuous flow technology (Scheme 2.15).[73-76]

Scheme 2.14 *Industrial Methods for the Synthesis of α-Naphthol*
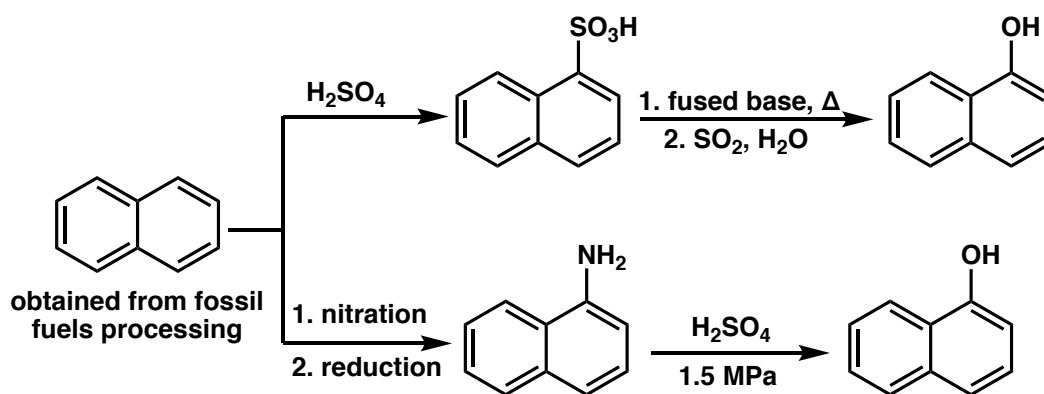
Scheme 2.15 *Selected Examples of 1-Tetralone Dehydrogenation*
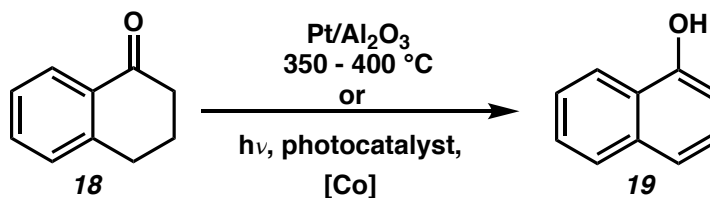
While these methods are promising, they suffer from the requirement of high

temperatures and aerobic conditions. In addition, the requirement of a photocatalyst system

lacks industrial practicality and would be difficult to translate to large scale. As shown in

the introduction, Goldman and Nozaki reported the dehydrogenation of oxygenated

heterocycles and ketones using Ir pincer ligated complexes, albeit with very limited

applicability. Here we present an alternative and complementary method of 1-tetralone (**18**) transfer dehydrogenation to 1-naphthol (**19**) using Ir pincer ligated complexes. In addition, fluorinated phenol skeletons are synthetically useful and often encountered in biologically active molecules and in pharmaceuticals.[77-80] Thus, we also present the transfer dehydrogenation of 7-fluoro-1-tetralone (**20**) to 7-fluoro-1-naphthalenol (**21**).

B. Reaction Optimization of 1-Tetralone Transfer Dehydrogenation

We began investigating the transfer dehydrogenation of 1-tetralone (**18**) using complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** and **TBE** as the H_2 acceptor at 200 °C (Table 2.7, entry 1 and 2). The reactions were carried out neat under an argon atmosphere after drying and distilling all reagents. The complex exhibited good catalytic activity at the investigated conditions and 47.6% of 1-naphthol (**19**) was generated. In an attempt to optimize the product yield, we carried out the reaction with higher equivalence of **TBE** and found that the yield of **19** was increased to 62.3% (Table 2.7 entry 4). We also investigated using **HEX** as an alternative acceptor under similar conditions to entry 2 and observed similar yields and up to 46.9% was generated (Table 2.7 entry 3). Overall, the catalytic activity of complex **c13** did not change when changing the H_2 acceptor in this system. That being said, we found that annulene and tetralin were generated as by-products in both cases.

Table 2.7 *Transfer Dehydrogenation of 1-Tetralone by Complex (t-Bu4POCOP)–Ir **c13***
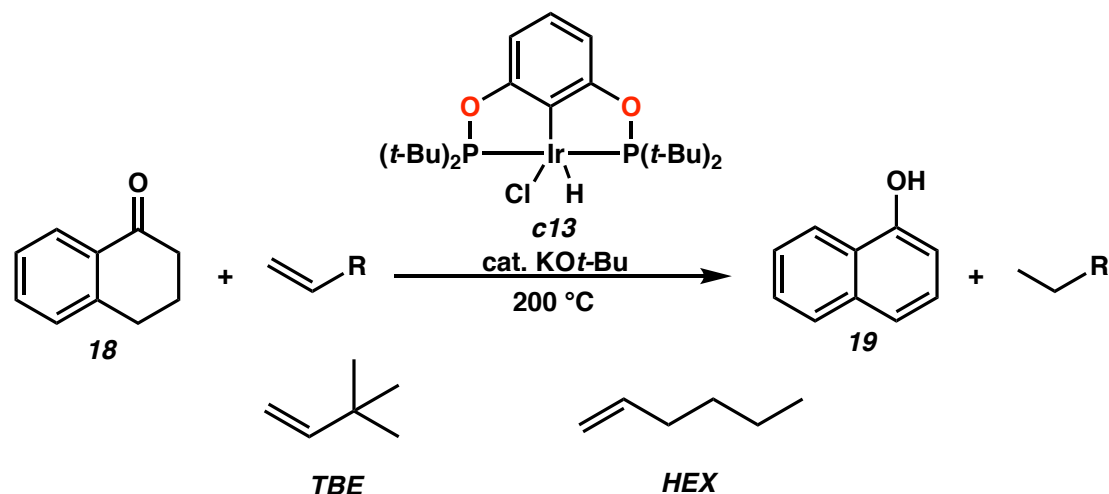
entry	cat. loading (mol.%)	H₂ acceptor	equiv. of acceptor	reaction time	19 yield[b]	TON[c]
1	-	TBE	1.4	24 h	-	-
2	1.59	TBE	1.8	24 h	47.6%	30
3	1.00	HEX	1.8	45 h	46.9%	47
4	1.60	TBE	3.1	24 h	62.3%	39

[a] Conditions: 3.2-4.0 mmol of **18**, precatalyst with at least 1.2 equiv. KOt-Bu. [b] Yield determined by GC and ¹H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation.

C. Reaction Optimization of 7-Fluoro-1-Tetralone Transfer Dehydrogenation

Similarly, we began investigating the transfer dehydrogenation of 7-fluoro-1-tetralone (**20**) using **TBE** as the H₂ and complex (t-Bu4POCOP)–Ir **c13** given its superior performance relative to the other investigated complexes shown in the previous sections. The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents (Table 2.8). We found that the complex exhibited low catalytic activity even when carrying the reaction for 48 h and up to 17.9 % of

7-fluoronaphthalen-1-ol (**21**) was generated (Table 2.8 entries 1-3). Increasing the catalyst loading 4.61 mol.% increased the yield of **21** up to 20.6% (Tables 2.8 entry 4 and 5). It is evident that complex **c13** exhibits very low TOF in this system and a substantial increase of catalyst loading and reaction time is required to generate reasonable yields of **21**.

Therefore, we then investigated **HEX** as the H_2 acceptor and found that **c13** catalytic activity was higher and up to 36.6% of **21** was generated (Tables 2.8 entry 6 and 7). We do not fully understand why the catalytic activity increased with **HEX**, and one possible explanation is that **HEX** binding affinity to the complex may be higher than the product itself, leading to releasing it faster from the metal complex.

Alternatively, we investigated the transfer dehydrogenation of **20** to **21** using complexes (*i*-Pr4PSCOP)–Ir **c22** and (*i*-Pr4anthraphos)–Ir **c24** given that reported studies with these complexes exhibited high catalytic activity when employed on dehydrogenating heteroatomic systems. Complex **c22** exhibited similar low catalytic activity to **c13** under the same conditions and only up to 12.2% of **21** was generated (Table 2.8 entry 8). In contrary, complex **c24** exhibited excellent catalytic activity and up to 80.6% of **21** was generated (Table 2.8 entry 9).

Table 2.8 *Transfer Dehydrogenation of 7-Fluoro-1-Tetralone Transfer Dehydrogenation by Ir*

Pincer Ligated Complexes
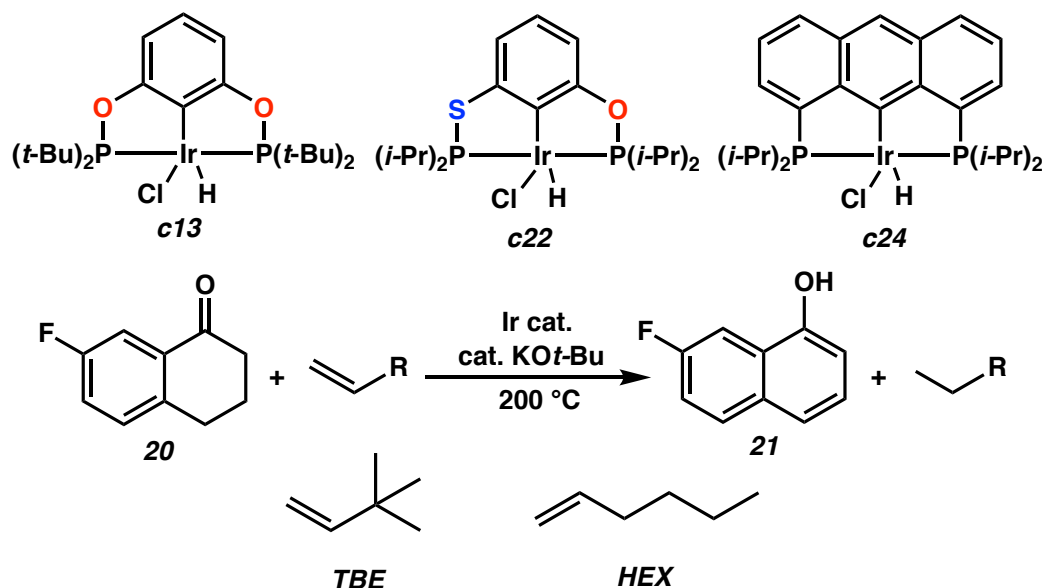
entry	cat. / loading (mol.%)	H₂ acceptor	equiv. of acceptor	reaction time	19 yield[b]	TON[c]
1	c13[d]/1.07	TBE	4.2	20 h	14.5%	13
2	c13/1.67	TBE	3.7	15 h	12.6%	7
3	c13/1.78	TBE	4.0	48 h	17.9%	10
4	c13/3.47	TBE	4.8	24 h	12.3%	3
5	c13[d]/4.61	TBE	4.0	24 h	20.6%	4
6	c13/1.99	HEX	5.1	24 h	23.4%	12
7	c13/4.04	HEX	6.8	24 h	36.6%	9
8	c22/1.33	TBE	3.6	24 h	12.2%	9
9	c24/1.14	TBE	4.9	24 h	80.6%	71

[a] Conditions: 3.2 mmol of **20**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ¹H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation. [d] **c13** (*t*-Bu4POCOP)–Ir–C₂H₄ ethylene version was used.

Despite the similarity of the tridentate pincer structure of complexes **c13**, **c22**, and **c24**, the transfer dehydrogenation of **20** to **21** epitomizes how these complexes offer unexpected reactivities in different systems. We suspect that **c13** may form a more stable adduct with the naphthol product than the more sterically hindered **c24** given the more open geometry of P–Ir–P and shorter C–O and P–O bond lengths. Similarly, we believe the geometry of **c22** may account for its low catalytic activity. In all cases, we observed unidentified aromatic and olefinic side products and some decomposed starting material in reactions subjected to **c22**.

2.4.6 Acenaphthene Transfer Dehydrogenation

A. Introduction

Polycyclic aromatic hydrocarbons (PAHs) generally exhibit attractive electron-donating properties or electron-accepting properties making them useful in various applications. Such applications include functional dyes, semiconductors, and fluorescent materials.[81-86] Specifically, acenaphthylene is considered a versatile building block for constructing PAHs owing to its highly reactive C–C double bond ascribed to the ring strain of the fused cyclopentane ring.[87]

Acenaphthylene is more expensive than acenaphthene and its derivatives are synthetically useful and serve as a versatile building block in organic reactions and materials applications owing to their capability to undergo ozonolysis or silylation reactions or to perform Diels-Alder reactions (Scheme 2.16).[87-93] Hence, there has been a great interest in

finding and developing methods for the preparation of acenaphthylene and its derivatives

(Scheme 2.17).

Scheme 2.16 *Selected Examples Manifesting Acenaphthylene Synthetic Utility*
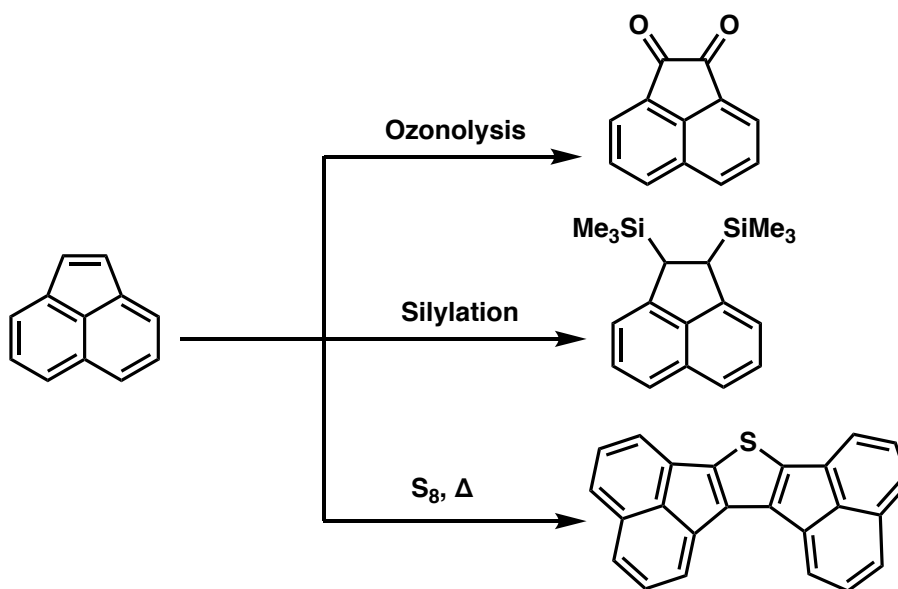
Industrially, the only method of producing acenaphthylene is from dehydrogenating

acenaphthene using heterogeneous catalysts at elevated temperatures up to 900 ºC (Scheme

2.17a).[94-95] Alternatively, there has been reports of synthetic approaches to acenaphthylene

via dibromination of acenaphthene using two equivalents of *N*-bromosuccinimide (**NBS**)

followed by debromination using zinc and an alcohol, or *via* vapor phase pyrolysis (Scheme

2.17b).[96] These approaches suffer from the use of stoichiometric toxic reagents or from

highly energy intensive pyrolysis at up to 500 °C.   We present the direct

dehydroaromatization of acenaphthene to acenaphthylene without the need of stoichiometric

reagents or oxidants, and with milder conditions relative to industry practice by using Ir

pincer ligated complexes.

Scheme 2.17 *Selected Methods of Acenaphthylene Synthesis*
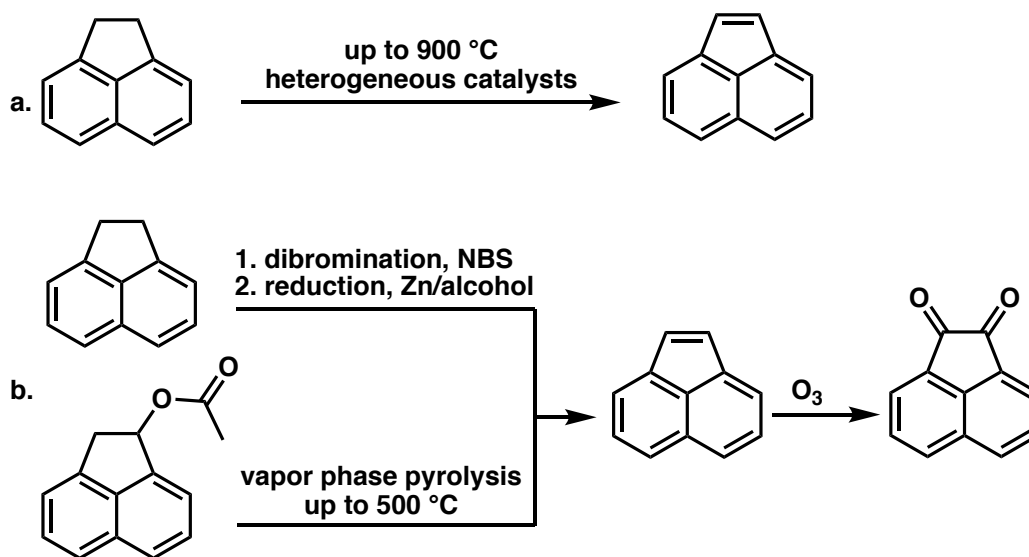
B. Reaction Optimization

We began investigating the transfer dehydrogenation of acenaphthene (**22**) using

complex (*$^{t\text{-Bu4}}$*POCOP)–Ir **c13** and **TBE** as the H_2 acceptor at 200 °C (Table 2.9, entry 1).

The reactions were carried out neat at 200 °C under an argon atmosphere after drying and

distilling all reagents. The complex exhibited low catalytic activity at the investigated

conditions and only 20.3% of acenaphthylene (**23**) was generated. Alternatively, we

performed the reaction using **HEX** as the H_2 acceptor and observed an increase in yield of

23 and up to 49.2% was generated (Table 2.9 entry 2 and 3). Steric hindrance of **22** is

suspected to be responsible for the moderate catalytic activity in this system. We then

investigated the catalytic activity of (*$^{i\text{-Pr4}}$*PSCOP)–Ir **c22** in transfer dehydrogenating **22** to

23 using **TBE** as the H_2 acceptor (Table 2.9 entry 4). We observed poor catalytic activity of

c22 and only trace amounts of product were observed. In all cases only the desired product

23 was observed along with remaining unreacted starting material.

Table 2.9 *Transfer Dehydrogenation of Acenaphthene using (t-Bu4POCOP)–Ir* **c13** *and*

(i-Pr4PSCOP)–Ir **c122**
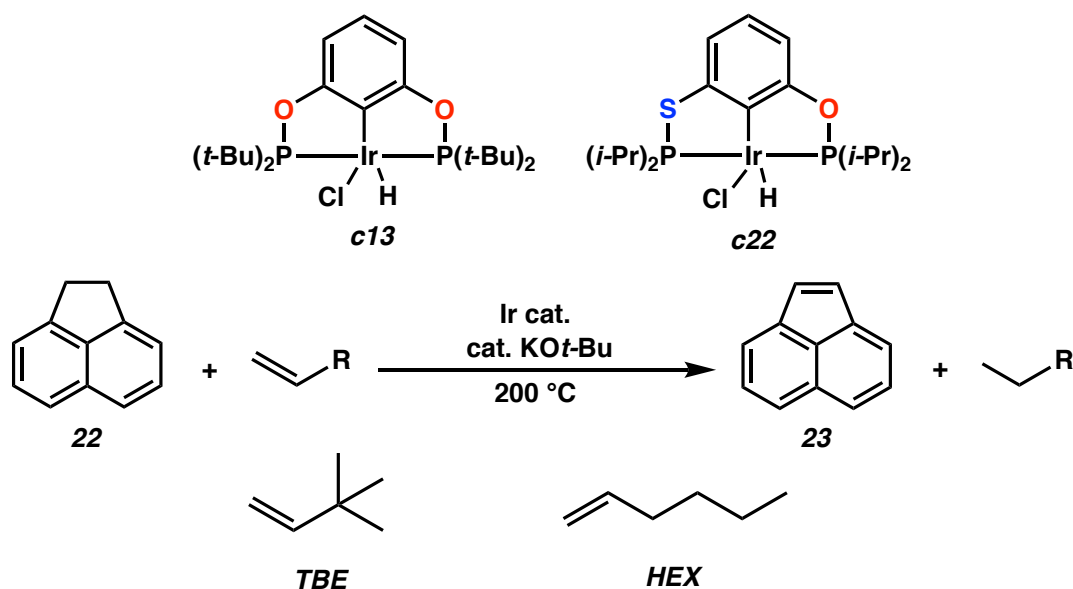
entry	cat./loading (mol.%)	H_2 acceptor	equiv. of acceptor	reaction time	19 yield[b]	TON[c]
1	c13/1.78	TBE	3.5	24 h	20.3%	11
2	c13/3.22	HEX	4.2	20 h	41.5%	13
3	c13/4.21	HEX	6.2	24 h	49.1%	13
4	c22/1.07	TBE	4.0	48 h	2.6%	2

[a] Conditions: 3.2 mmol **22**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ¹H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation.
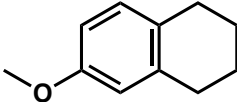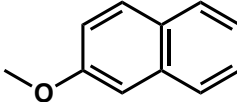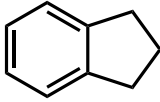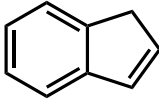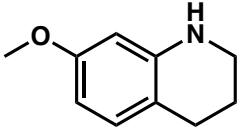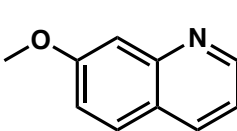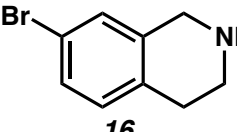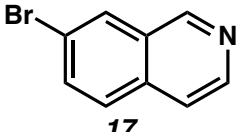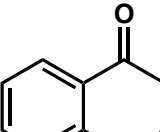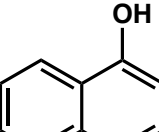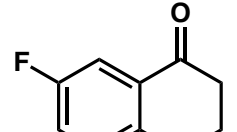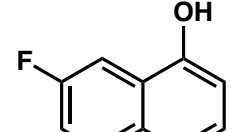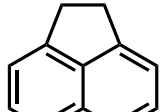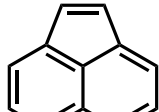
2.5   SUMMARY AND CONCLUSIONS

Aromatic frameworks are a core building block in organic chemistry and have been found in diverse applications such as pharmaceuticals and materials due to their synthetic utility. The direct dehydroaromatization of $C(sp^3)$–H alkanes may seem conceptually simple but in fact is a challenging trasnformation. Industrially practiced methods utilize energy-intensive processes operating at high pressures and temperatures to overcome the endergonic and unreactive nature of alkanes. While there has been great advancement in the dehydrogenation transformation recently, the direct dehydroaromatization of substituted substrates generating functionalized aromatics is significantly underdeveloped. Hence, there is a great interest in developing methods for the synthesis of functionalized aromatics under milder conditions.

We have successfully extended the applicability of Ir-catalyzed dehydrogenation systems using pincer ligated complexes on substituted heterocyclic alkanes with functionalities known to be strongly coordinating and poorly compatible with (PCP)–Ir type catalysts (Table 2.10). For example, synthetically useful compounds such as fluorinated naphthol and brominated hydroisoquinoline were obtained in excellent yields up to 91%. Functional groups tolerated by our conditions include ketones, ethers, and fused arenes. We found that in most cases, **c13** and **c24** had higher catalytic activity relative to **c22**. In addition, in some cases using **HEX** as the H_2 acceptor instead of **TBE** generated higher yields, which is considerably more economical.

In all cases except with **20**, the fully dehydroaromatized substrate was the only observed product. Hence, our method provides a new selective and complementary route to these important and synthetically useful building blocks.

Table 2.10 *Successfully Optimized Studied Dehydroaromatized Substrates by Ir Pincer Ligated*

Complexes

Substrate	Product	yield	cat./mol.%	H₂ acceptor	temp (C°)	TONᶜ
10	**11**	99.0%	c13ᵈ/0.59	TBE	200	169
12	**13**	95.8%	c13/0.59	TBE	150	162
14	**15**	93.5%	c13/4.09	HEX	200	22
16	**17**	91.4%	c13/6.24	HEX	200	15
18	**19**	62.3%	c13/1.60	TBE	200	39
20	**21**	80.6%	c24/4.09	TBE	200	71
22	**23**	49.1%	c13/4.21	HEX	200	13

[a] Conditions: 3.2 – 4.0 mmol, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ¹H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation. [d] ᵗBu4POCOP)Ir(C₂H₄) ethylene version of **c13**.

2.6　　　NOTES AND REFERENCES

1.　　Kumar, A.; Bhatti, T. M.; Goldman, A. S., *Chemical Reviews* **2017,** 117 (19), 12357-12384.

2.　　Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M., *Journal of the American Chemical Society* **1997,** 119 (4), 840-841.

3.　　Gupta, M.; Hagen, C.; Flesher, R. J.; Kaska, W. C.; Jensen, C. M., *Chem. Commun.* **1996,** (17), 2083-2084.

4.　　Yao, W.; Jia, X.; Leng, X.; Goldman, A. S.; Brookhart, M.; Huang, Z., *Polyhedron* **2016,** 116, 12-19.

5.　　Yao, W.; Zhang, Y.; Jia, X.; Huang, Z., *Angewandte Chemie International Edition* **2014,** 53 (5), 1390-1394.

6.　　Punji, B.; Emge, T. J.; Goldman, A. S., *Organometallics* **2010,** 29 (12), 2702-2709.

7.　　Huang, Z.; Brookhart, M.; Goldman, A. S.; Kundu, S.; Ray, A.; Scott, S. L.; Vicente, B. C., *Adv. Synth. Catal.* **2009,** 351 (1-2), 188-206.

8.　　Gupta, M.; C. Kaska, W.; M. Jensen, C., *Chem. Commun.* **1997,** (5), 461-462.

9.　　Lyons, T. W.; Bézier, D.; Brookhart, M., *Organometallics* **2015,** 34 (16), 4058-4062.

10.　Ando, H.; Kusumoto, S.; Wu, W.; Nozaki, K., *Organometallics* **2017,** 36 (12), 2317-2322.

11.　Zhang, X.; Wang, D. Y.; Emge, T. J.; Goldman, A. S., *Inorg. Chim. Acta* **2011,** 369 (1), 253-259.

12.   Renkema, K. B.; Kissin, Y. V.; Goldman, A. S., *Journal of the American Chemical Society* **2003,** 125 (26), 7770-7771.

13.   Zhang, X.; Fried, A.; Knapp, S.; Goldman, A. S., *Chem. Commun.* **2003,** (16), 2060-2061.

14.   Brayton, D. F.; Jensen, C. M., *Chem. Commun.* **2014,** 50 (45), 5987-5989.

15.   Akshai Kumar, A. S. G. In *The Privileged Pincer-Metal Platform: Coordination Chemistry & Applications*, Gerard Van Koten, R. A. G., Ed. Springer, Cham: Cham, 2015; Vol. 54, pp 307-334.

16.   Moulton, C. J.; Shaw, B. L., *J. Chem. Soc., Dalton Trans.* **1976,** (11), 1020-1024.

17.   Hebden, T. J.; Goldberg, K. I.; Heinekey, D. M.; Zhang, X.; Emge, T. J.; Goldman, A. S.; Krogh-Jespersen, K., *Inorg. Chem.* **2010,** 49 (4), 1733-1742.

18.   Göttker-Schnetmann, I.; White, P. S.; Brookhart, M., *Organometallics* **2004,** 23 (8), 1766-1776.

19.   Göttker-Schnetmann, I.; White, P.; Brookhart, M., *Journal of the American Chemical Society* **2004,** 126 (6), 1804-1811.

20.   Göttker-Schnetmann, I.; Brookhart, M., *Journal of the American Chemical Society* **2004,** 126 (30), 9330-9338.

21.   Bézier, D.; Brookhart, M., *ACS Catalysis* **2014,** 4 (10), 3411-3420.

22.   Haenel, M. W.; Oevers, S.; Angermund, K.; Kaska, W. C.; Fan, H.-J.; Hall, M. B., *Angewandte Chemie International Edition* **2001,** 40 (19), 3596-3600.

23.   Romero, P. E.; Whited, M. T.; Grubbs, R. H., *Organometallics* **2008,** 27 (14), 3422-3429.

24. Ozerov, O. V.; Guo, C.; Papkov, V. A.; Foxman, B. M., *Journal of the American Chemical Society* **2004,** 126 (15), 4792-4793.

25. Kwan, E. H.; Kawai, Y. J.; Kamakura, S.; Yamashita, M., *Dalton Trans.* **2016,** 45 (40), 15931-15941.

26. M. Jensen, C., *Chem. Commun.* **1999,** (24), 2443-2449.

27. Ponra, S.; Vitale, M.; Michelet, V.; Ratovelomanana-Vidal, V., *Arkivoc* **2015,** 2016.

28. Wang, Y.; Zhang, X.; Zhao, J.; Xie, S.; Wang, C., *J. Med. Chem.* **2012,** 55 (7), 3502-3512.

29. Humljan, J.; Kotnik, M.; Contreras-Martel, C.; Blanot, D.; Urleb, U.; Dessen, A.; Šolmajer, T.; Gobec, S., *J. Med. Chem.* **2008,** 51 (23), 7486-7494.

30. Krohn, K.; Kouam, S. F.; Cludius-Brandt, S.; Draeger, S.; Schulz, B., *Eur. J. Org. Chem.* **2008,** 2008 (21), 3615-3618.

31. Lowell, A. N.; Fennie, M. W.; Kozlowski, M. C., *The Journal of Organic Chemistry* **2008,** 73 (5), 1911-1918.

32. Pan, M.; Lin, X.-M.; Li, G.-B.; Su, C.-Y., *Coord. Chem. Rev.* **2011,** 255 (15), 1921-1936.

33. Anthony, J. E., *Angewandte Chemie International Edition* **2008,** 47 (3), 452-483.

34. Watson, M. D.; Fechtenkötter, A.; Müllen, K., *Chemical Reviews* **2001,** 101 (5), 1267-1300.

35. de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L., *Tetrahedron* **2003,** 59 (1), 7-36.

36.   Kuklin, S. A.; Sheloumov, A. M.; Dolgushin, F. M.; Ezernitskaya, M. G.; Peregudov, A. S.; Petrovskii, P. V.; Koridze, A. A., *Organometallics* **2006,** 25 (22), 5466-5476.

37.   Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S., *Chemical Reviews* **2011,** 111 (3), 1761-1779.

38.   Banothu, J.; Basavoju, S.; Bavantula, R., *J. Heterocycl. Chem.* **2015,** 52 (3), 853-860.

39.   El-Sheshtawy, H. S.; Abou Baker, A. M., *J. Mol. Struct.* **2014,** 1067, 225-232.

40.   Dang, J.-S.; Wang, W.-W.; Zhao, X.; Nagase, S., *Org. Lett.* **2014,** 16 (1), 170-173.

41.   Ouros, A.; Oberson de Souza, M.; Pastore, H., *Journal of the Brazilian Chemical Society* **2014,** 25.

42.   Matano, Y.; Saito, A.; Suzuki, Y.; Miyajima, T.; Akiyama, S.; Otsubo, S.; Nakamoto, E.; Aramaki, S.; Imahori, H., *Chemistry – An Asian Journal* **2012,** 7 (10), 2305-2312.

43.   Buechi, G.; Wuest, H., *The Journal of Organic Chemistry* **1971,** 36 (4), 609-610.

44.   Jana, A.; Misztal, K.; Żak, A.; Grela, K., *The Journal of Organic Chemistry* **2017,** 82 (8), 4226-4234.

45.   Jayaram, V.; Sridhar, T.; Sharma, G. V. M.; Berrée, F.; Carboni, B., *The Journal of Organic Chemistry* **2017,** 82 (3), 1803-1811.

46.   Foley, M.; Tilley, L., *Pharmacol. Ther.* **1998,** 79 (1), 55-87.

47.   Kaminsky, D.; Meltzer, R. I., *J. Med. Chem.* **1968,** 11 (1), 160-163.

48.   Rossiter, S.; Péron, J.-M.; Whitfield, P. J.; Jones, K., *Bioorg. Med. Chem. Lett.* **2005,** 15 (21), 4806-4808.

49.   Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R., *Journal of the American Chemical Society* **2001,** 123 (14), 3239-3242.

50. Mahato, S.; Mukherjee, A.; Santra, S.; Zyryanov, G. V.; Majee, A., *Org. Biomol. Chem.* **2019,** 17 (34), 7907-7917.

51. Bizzarri, C.; Spuling, E.; Knoll, D. M.; Volz, D.; Bräse, S., *Coord. Chem. Rev.* **2018,** 373, 49-82.

52. Kim, J. I.; Shin, I.-S.; Kim, H.; Lee, J.-K., *Journal of the American Chemical Society* **2005,** 127 (6), 1614-1615.

53. Bangcuyo, C. G.; Rampey-Vaughn, M. E.; Quan, L. T.; Angel, S. M.; Smith, M. D.; Bunz, U. H. F., *Macromolecules* **2002,** 35 (5), 1563-1568.

54. Biswas, S.; Huang, Z.; Choliy, Y.; Wang, D. Y.; Brookhart, M.; Krogh-Jespersen, K.; Goldman, A. S., *Journal of the American Chemical Society* **2012,** 134 (32), 13276-13295.

55. Costa, E. V.; Pinheiro, M. L. B.; Maia, B. H. L. N. S.; Marques, F. A.; Ruiz, A. L. T. G.; Marchetti, G. M.; Carvalho, J. E. d.; Soares, M. B. P.; Costa, C. O. S.; Galvão, A. F. C.; Lopes, N. P.; Koolen, H. H. F.; Bezerra, D. P.; Barison, A., *J. Nat. Prod.* **2016,** 79 (6), 1524-1531.

56. Zhang, Z.-H.; Zhang, H.-J.; Deng, A.-J.; Wang, B.; Li, Z.-H.; Liu, Y.; Wu, L.-Q.; Wang, W.-J.; Qin, H.-L., *J. Med. Chem.* **2015,** 58 (18), 7557-7571.

57. DeBono, A.; Capuano, B.; Scammells, P. J., *J. Med. Chem.* **2015,** 58 (15), 5699-5727.

58. Bentley, K. W., *Nat. Prod. Rep.* **2006,** 23 (3), 444-463.

59. Wen, L.-R.; Dou, Q.; Wang, Y.-C.; Zhang, J.-W.; Guo, W.-S.; Li, M., *The Journal of Organic Chemistry* **2017,** 82 (3), 1428-1436.

60. Stabile, P.; Lamonica, A.; Ribecai, A.; Castoldi, D.; Guercio, G.; Curcuruto, O., *Tetrahedron Letters* **2010,** 51 (24), 3232-3235.

61. Klapars, A.; Huang, X.; Buchwald, S. L., *Journal of the American Chemical Society* **2002,** 124 (25), 7421-7428.

62. Balewski, Ł.; Sączewski, F.; Gdaniec, M.; Kornicka, A.; Cicha, K.; Jalińska, A., *Molecules (Basel, Switzerland)* **2019,** 24 (22), 4070.

63. Shiraiwa, M.; Sakamoto, T.; Yamanaka, H., *Chem. Pharm. Bull. (Tokyo)* **1983,** 31 (7), 2275-2280.

64. Bischler, A.; Napieralski, B., *Berichte der deutschen chemischen Gesellschaft* **1893,** 26 (2), 1903-1908.

65. Pictet, A.; Spengler, T., *Berichte der deutschen chemischen Gesellschaft* **1911,** 44 (3), 2030-2036.

66. Zhang, H.-P.; Li, H.-Y.; Xiao, H.-F., *Journal of Chemical Research* **2013,** 37 (9), 556-558.

67. Eisch, J. J. In *Adv. Heterocycl. Chem.*, Katritzky, A. R., Boulton, A. J., Eds. Academic Press: 1967; Vol. 7, pp 1-37.

68. Kress, T. J.; Costantino, S. M., *J. Heterocycl. Chem.* **1973,** 10 (3), 409-410.

69. Tyman, J. H. P. In *Studies in Organic Chemistry*, Elsevier: New York, 1996; Vol. 52, pp 558-661.

70. Chien, R.-H.; Lai, C.-T.; Hong, J.-L., *The Journal of Physical Chemistry C* **2011,** 115 (13), 5958-5965.

71.   Deria, P.; Von Bargen, C. D.; Olivier, J.-H.; Kumbhar, A. S.; Saven, J. G.; Therien, M. J., *Journal of the American Chemical Society* **2013,** 135 (43), 16220-16234.

72.   For industrial naphtol synthesis: (a) E.W. Schoeffel, D. M. B. Naphthalene. August 28, **1956**. (b) Stevens, D., Harris, G.H., Pearlman, M.B. Phenols From Aromatic Sulfonic, Sulfamic, and Sulfone Compounds. December 2, **1955.**

73.   He, X.; Zheng, Y.-W.; Lei, T.; Liu, W.-Q.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z., *Catalysis Science & Technology* **2019,** 9 (13), 3337-3341.

74.   Izawa, Y.; Pun, D.; Stahl, S. S., *Science* **2011,** 333 (6039), 209.

75.   Girard, S. A.; Huang, H.; Zhou, F.; Deng, G.-J.; Li, C.-J., *Organic Chemistry Frontiers* **2015,** 2 (3), 279-287.

76.   Franzen, H.; Kempf, H., *Berichte der deutschen chemischen Gesellschaft* **1917,** 50 (1), 101-104.

77.   Chang, J.; Song, X.; Huang, W.; Zhu, D.; Wang, M., *Chem. Commun.* **2015,** 51 (84), 15362-15365.

78.   Fancelli, D.; Abate, A.; Amici, R.; Bernardi, P.; Ballarini, M.; Cappa, A.; Carenzi, G.; Colombo, A.; Contursi, C.; Di Lisa, F.; Dondio, G.; Gagliardi, S.; Milanesi, E.; Minucci, S.; Pain, G.; Pelicci, P. G.; Saccani, A.; Storto, M.; Thaler, F.; Varasi, M.; Villa, M.; Plyte, S., *J. Med. Chem.* **2014,** 57 (12), 5333-5347.

79.   Spadaro, A.; Frotscher, M.; Hartmann, R. W., *J. Med. Chem.* **2012,** 55 (5), 2469-2473.

80.   Liu, X.; Jiang, L.; Li, J.; Wang, L.; Yu, Y.; Zhou, Q.; Lv, X.; Gong, W.; Lu, Y.; Wang, J., *Journal of the American Chemical Society* **2014,** 136 (38), 13094-13097.

81.   Li, Y.; Clevenger, R. G.; Jin, L.; Kilway, K. V.; Peng, Z., *The Journal of Physical Chemistry C* **2016,** 120 (2), 841-852.

82.   Yuan, B.; Zhuang, J.; Kirmess, K. M.; Bridgmohan, C. N.; Whalley, A. C.; Wang, L.; Plunkett, K. N., *The Journal of Organic Chemistry* **2016,** 81 (18), 8312-8318.

83.   Pho, T. V.; Toma, F. M.; Chabinyc, M. L.; Wudl, F., *Angewandte Chemie International Edition* **2013,** 52 (5), 1446-1451.

84.   Nishida, J.-i.; Tsukaguchi, S.; Yamashita, Y., *Chemistry – A European Journal* **2012,** 18 (29), 8964-8970.

85.   Wood, J. D.; Jellison, J. L.; Finke, A. D.; Wang, L.; Plunkett, K. N., *Journal of the American Chemical Society* **2012,** 134 (38), 15783-15789.

86.   Brunetti, F. G.; Gong, X.; Tong, M.; Heeger, A. J.; Wudl, F., *Angewandte Chemie International Edition* **2010,** 49 (3), 532-536.

87.   Matsuura, K.; Nishida, J.-i.; Ito, T.; Yokota, R.; Kitamura, C.; Kawase, T., *Tetrahedron* **2019,** 75 (2), 278-285.

88.   Laguerre, M.; Felix, G.; Dunogues, J.; Calas, R., *The Journal of Organic Chemistry* **1979,** 44 (24), 4275-4278.

89.   Nakayama, J. In *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds. Pergamon: Oxford, 1996; pp 607-677.

90.   Ding, L.; Yang, C.; Su, Z.; Pei, J., *Science China Chemistry* **2015,** 58 (2), 364-369.

91.   Cantrell, T. S.; Shechter, H., *The Journal of Organic Chemistry* **1968,** 33 (1), 114-118.

92.   Abe, M.; Eto, M.; Yamaguchi, K.; Yamasaki, M.; Misaka, J.; Yoshitake, Y.; Otsuka, M.; Harano, K., *Tetrahedron* **2012,** 68 (18), 3566-3576.

93.   Yavari, I.; Khajeh-Khezri, A., *Synthesis* **2018,** 50 (20), 3947-3973.

94.   Schmidt, R.; Griesbaum, K.; Behr, A.; Biedenkapp, D.; Voges, H.-W.; Garbe, D.; Paetz, C.; Collin, G.; Mayer, D.; Höke, H., *Ullmann's Encyclopedia of Industrial Chemistry* **2014**, 1-74.

95.   Griesbaum, K.; Behr, A.; Biedenkapp, D.; Voges, H.-W.; Garbe, D.; Paetz, C.; Collin, G.; Mayer, D.; Höke, H., *Ullmann's Encyclopedia of Industrial Chemistry* **2000**.

96.   Anderson, A. G.; Anderson, R. G., *Journal of the American Chemical Society* **1955,** 77 (24), 6610-6611.

APPENDIX 1

EXPERIMENTAL SECTION AND SPECTRA RELEVANT TO CHAPTER 2

A1.1   MATERIALS AND METHODS

Unless noted in the specific procedure, reactions were performed in oven-dried glassware. All dehydrogenation reactions were degassed by freeze-pump-thaw x 5 cycles and were carried out under air-free conditions in an oven-dried glassware. All liquid reagents were purified by distillation and dried using molecular sieves, NaH, or Na-K alloy. For all the investigated dehydrogenation systems, the substrate was mixed with the H_2 acceptor in a 4 mL sealed Schlenk pressure flask under an argon atmosphere. Then synthesized Ir pincer complexes were added to the reaction mixture with at least 1.2 equivalents of the Ir pincer complexes of KOt-Bu when the Ir–HCl version of precatalyst is used.

^{1}H and ^{31}P NMR spectra were recorded on a Varian spectrometer 400 MHz with broadband auto-tune OneProbeor or on a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, and are

reported in terms of chemical shift relative to residual CHCl$_3$ (δ 7.26). ^{19}F NMR spectra were recorded on Varian 400 MHz spectrometer. Dehydrogenation conversions were determined using ^{1}H NMR with cis-1,4-diacetoxy-2-butene standard.

In addition, the conversions were determined using an Agilent 6850 GC-FID equipped with a Supelco column (SPB^{TM}-1, fused silica capillary column, 30 m x 0.25 μm film thickness) and using methods with temperature programs shown in Tables A1.1 and A1.2 and inlet program showed in Table A1.3. The obtained products were also confirmed by spiking the reaction with a commercial sample of the product.

Table A1.1 ZAS2 General Method Temperature Ramping Program for **10, 14, 16, 18, 20**, and **22** Transfer Dehydrogenation

Oven Ramp	°C/min	Next °C	Hold min
Initial	-	38	1.50
Ramp 1	10.00	150	0.00
Ramp 2	20.00	250	5.00

Table A1.2 ZAS_INDANE Method GC Temperature Ramping Program for Indane **12** to Indene **13** Transfer Dehydrogenation

Oven Ramp	°C/min	Next °C	Hold min
Initial	-	38	1.50
Ramp 1	5.00	50	5.00
Ramp 2	10.00	100	0.00
Ramp 3	5.00	170	5.00
Ramp 4	20.00	250	0.00

Table A1.3 *Inlet Parameters used in All Methods*

Inlet	Setting
Mode	Split
Gas	He
Heater	250 °C
Pressure	9.52 psi
Total Flow	82.2
Split Ratio	100:1
Split Flow	78.5 mL/min

A1.2 KNOWN IRIDIUM PINCER LIGATED COMPLEXES

GENERAL SYNTHESIS PROCEDURE

A1.2.1 Synthesis of (*t*-Bu4PCP)IrHCl c3 and (*t*-Bu4PCP)IrH4 c3b Complexes
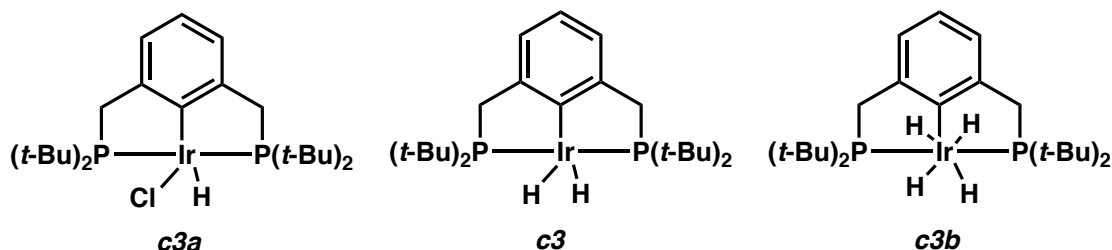
0.240 g of the commercially available *t*-Bu4PCP ligand **1** and 0.5 equivalent of [Ir(COD)Cl]$_2$, 0.224 g, were added in 10 mL toluene and heated to reflux for 72 h under argon atmosphere. After cooling the reaction mixture to room temperature, the mother liquor was evaporated under vacuum. Complex (*t*-Bu4PCP)IrHCl **c3a** was extracted with pentane (60 mL x 3) *via* a cannula and the combined pentane solutions were evaporated to obtain the red-orange crystalline product. Then complex **c3a** (0.150 g) was dissolved in pentane (100 mL), and a 1.0 M solution (in THF) of LiBEt$_3$H (0.29 mL) was added dropwise *via* syringe under H$_2$ atmosphere, causing the red solution to turn a pale orange brownish. The reaction mixture was stirred for 2 h and then dried over vacuum and then dissolved in pentane and filtered in a syringe obtaining the (*t*-Bu4PCP)IrH4 complex **c3b**. Complex **c3b** is air and nitrogen sensitive so it should only be kept in an argon glovebox.[1] (*t*-Bu4PCP)IrHCl **c3a**: ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.03 (d, 2H, Ar–H), 7.96 (m, 1H, Ar–H), 3.25 − 3.06 (m, 4H, CH$_2$), 1.36 (dt, J = 6.7 Hz, 36H, 2x P(*t*-Bu)$_2$), -42.50 (t, J = 12.6 Hz, 1H, Ir-H). ^{31}P NMR (162 MHz, Benzene-d_6) δ 67.09 (s). ^{13}C NMR (101 MHz, Benzene-d_6) δ 151.48 (t, Ar–C), 122.58, 121.07 (t, 4 Ar–C), 33.59 (m, 2 x CH$_2$), 29.65 (t, 4x *t*-Bu4), 28.06 (t, 4x CH$_3$). (*t*-Bu4PCP)IrH4 **c3b**: ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.09 (s,

3H, Ar–H), 3.26 (t, J = 3.9 Hz, 4H, 2x CH_2), 1.43 – 1.06 (m, 36H, t-Bu$_4$), -9.11 (t, J = 9.8 Hz, 2H). ^{31}P NMR (162 MHz, Benzene-d_6) δ 72.41 (s).

A1.2.2 Synthesis of ($^{t\text{-Bu4}}$POCOP)IrHCl c13 and ($^{t\text{-Bu4}}$POCOP)IrC$_2$H$_4$ c13a Complexes

c13   c13a

Synthesis of ($^{t\text{-Bu4}}$POCOP) Ligand 3.
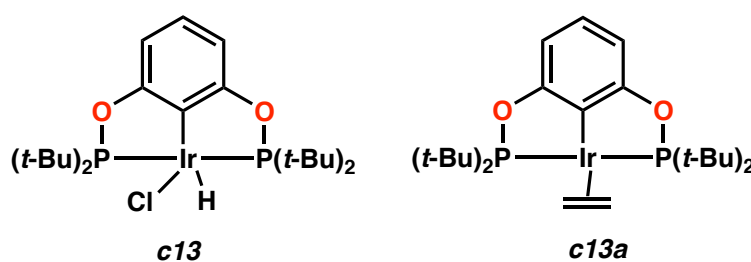
0.500 g of resorcinol **2** was dissolved in 45 mL THF. Then two equivalents of DBU and (t-Bu)$_2$PCl were added slowly. The reaction mixture was run at room temperature stirring overnight. After cooling the reaction mixture to room temperature, the mother liquor was evaporated under vacuum. The ligand ($^{t\text{-Bu4}}$POCOP) **3** was extracted with pentane *via* a cannula and filtered over a pad of Celite under vacuum. The pentane solution was dried over vacuum and the **3** was obtained.[2] ^{1}H NMR (400 MHz, Chloroform-d) δ 7.10 (td, J = 8.4, 2.8 Hz, 1H, Ar-H), 6.96 (p, J = 2.1 Hz, 1H, Ar-H), 6.77 (dp, J = 8.4, 2.1 Hz, 2H, Ar-H), 1.66 – 0.75 (m, 36H, 2x P(t-Bu)$_2$). ^{31}P NMR (162 MHz, Chloroform-d) δ 153.22. (s). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.23 (d, J = 9.7 Hz, 2C, Ar-C), 129.85, 111.61 (d, J = 10.9 Hz, 3C, Ar-C), 108.82 (t, J = 11.5 Hz, 1C, Ar-C), 35.39 (d, J = 26.7 Hz, 4C, P-C), 27.22 (d, J = 15.7 Hz, 12C, C-C)

Synthesis of ($^{t\text{-Bu4}}$POCOP)IrHCl *13* and ($^{t\text{-Bu4}}$POCOP)Ir(C$_2$H$_4$) *13a* Complexes

1.0143 g of the of the ($^{t\text{-Bu4}}$POCOP) ligand and 0.5 equivalents [Ir(COD)Cl]$_2$, 0.8505 g, were added in 30 mL toluene and heated to reflux for 72 h under argon atmosphere. After cooling the reaction mixture to room temperature, the mother liquor was evaporated under vacuum. The obtained crystalline powder was filtered in air and washed with pentane. ($^{t\text{-Bu4}}$POCOP)IrHCl 1*3a* is air stable and can be stored in vial on the shelf. Then for ($^{t\text{-Bu4}}$POCOP)IrH(C$_2$H$_4$) *13* synthesis, 0.260 g of *13a* and 1.2 equivalents of NaO*t*-Bu were dissolved in 40 mL degassed toluene. It's important to ensure that the solvent is nitrogen free as the complex is air and nitrogen sensitive. The resulting suspension was stirred for 10 min at room temperature. Ethylene was bubbled through the solution overnight. Then, solution was cannula-filtered through a pad of Celite, volatiles were evaporated under vacuum, and the resulting red solid was dried under vacuum and kept in argon glovebox.[2]). ($^{t\text{-Bu4}}$POCOP)IrHCl 1*3a*: ^{1}H NMR (400 MHz, Benzene-d_6) δ 6.81 – 6.68 (m, 3H, Ar-H), 1.24 (dt, J = 7.3 Hz, 36H, 2x P(*t*-Bu)$_2$), -40.69 (t, J = 13.1 Hz, 1H, Ir-H). ^{31}P NMR (162 MHz, Benzene-d_6) δ 175.34 (d, J = 6.0 Hz). ($^{t\text{-Bu4}}$POCOP)IrH(C$_2$H$_4$) *13*: ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.04 – 6.98 (m, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 6.89 (d, J = 0.9 Hz, 1H, Ar-H), 3.07 (t, J = 2.6 Hz, 4H, C$_2$H$_4$), 1.21 (m, 36H, 2x P(*t*-Bu)$_2$). ^{31}P NMR (162 MHz, Benzene-d_6) δ 181.13 (s).

A1.3   NOTES AND REFERENCES

1.   For complex *1* a) Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R.E.; Jensen, C. M. *Chem. Commun.* **1996**, 2083–2084. b) Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M. *J Am Chem So*c **1997**, *119*, 840–841. (c) Moulton, C. J.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1976**, *11*, 1020–1024.

2.   For complex *2* (a) Bézier, D.; Brookhart, M. *ACS Catalysis* **2014**, *4*, 3411–3420. (b) Göttker-Schnetmann, I.; Brookhart, M. *J. Am. Chem. Soc.* **2004**, *126,* 9330–9338. (c) Göttker-Schnetmann, I.; White, P. S.; (d) Brookhart, M. *J. Am. Chem. Soc.* **2004**, *126*, 1804–1811. (d) Göttker-Schnetmann, I.; White, P. S.; (e) Brookhart, M. *Organometallics* **2004**, *23*, 1766–1776. (f) Ahuja, R.; Punji, B.; Findlater, M.; Supplee, C.; Schinski, W.; Brookhart, M.; Goldman, A. S. *Nature Chemistry* **2010**, *3*, 167–171.

3.   For complex *3*: Haenel, M. W.; Oevers, S.; Angermund, K.; Kaska, W. C.; Fan, H.-J.; Hall, M. B. *Angew. Chem., Int. Ed.* **2001**, 40, 3596−3600.

4.   For complex *4*: Yao, W.; Zhang, Y.; Jia, X.; Huang, Z. *Angew. Chem., Int. Ed.* **2014**, 53, 1390−1394.

A1.4 RELEVANT SPECTRA
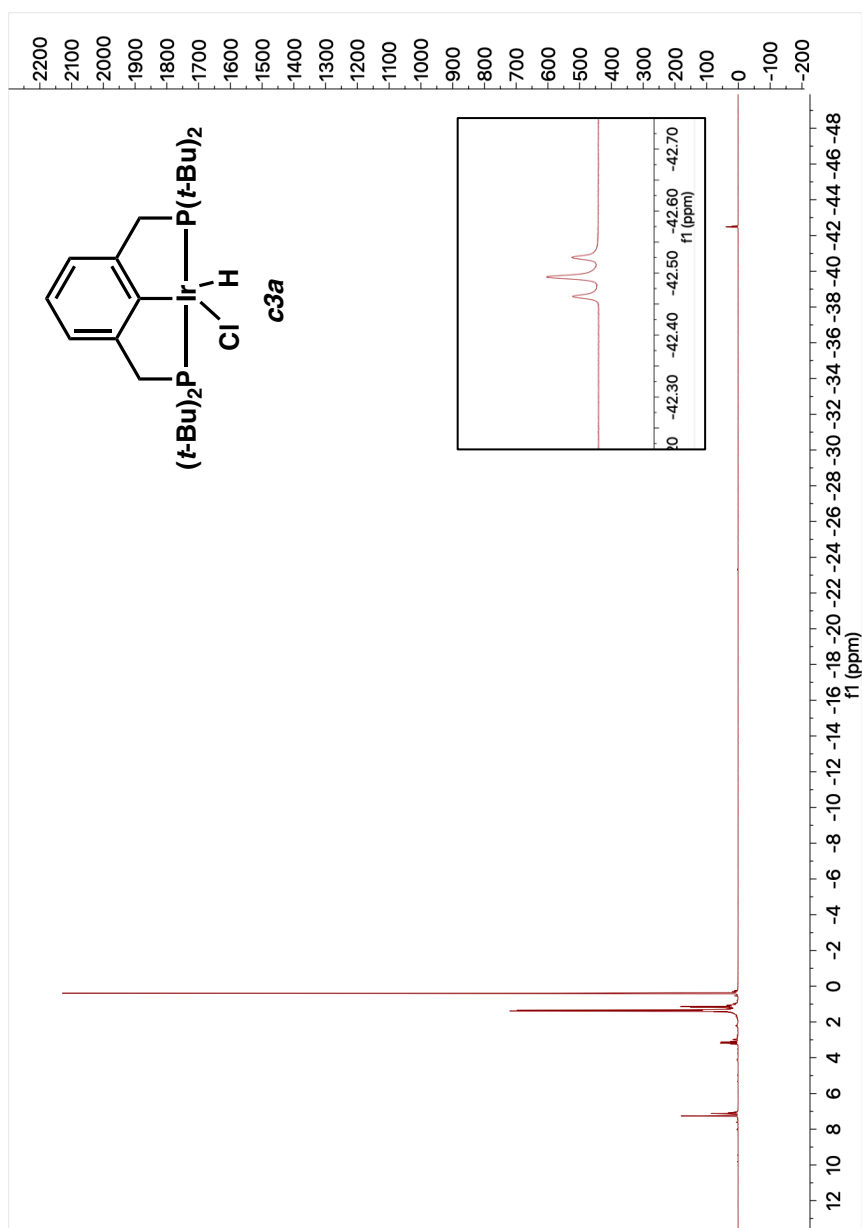
Figure A1.1 *^{1}H NMR (400 MHz, C6D6) of Complex **c3a***
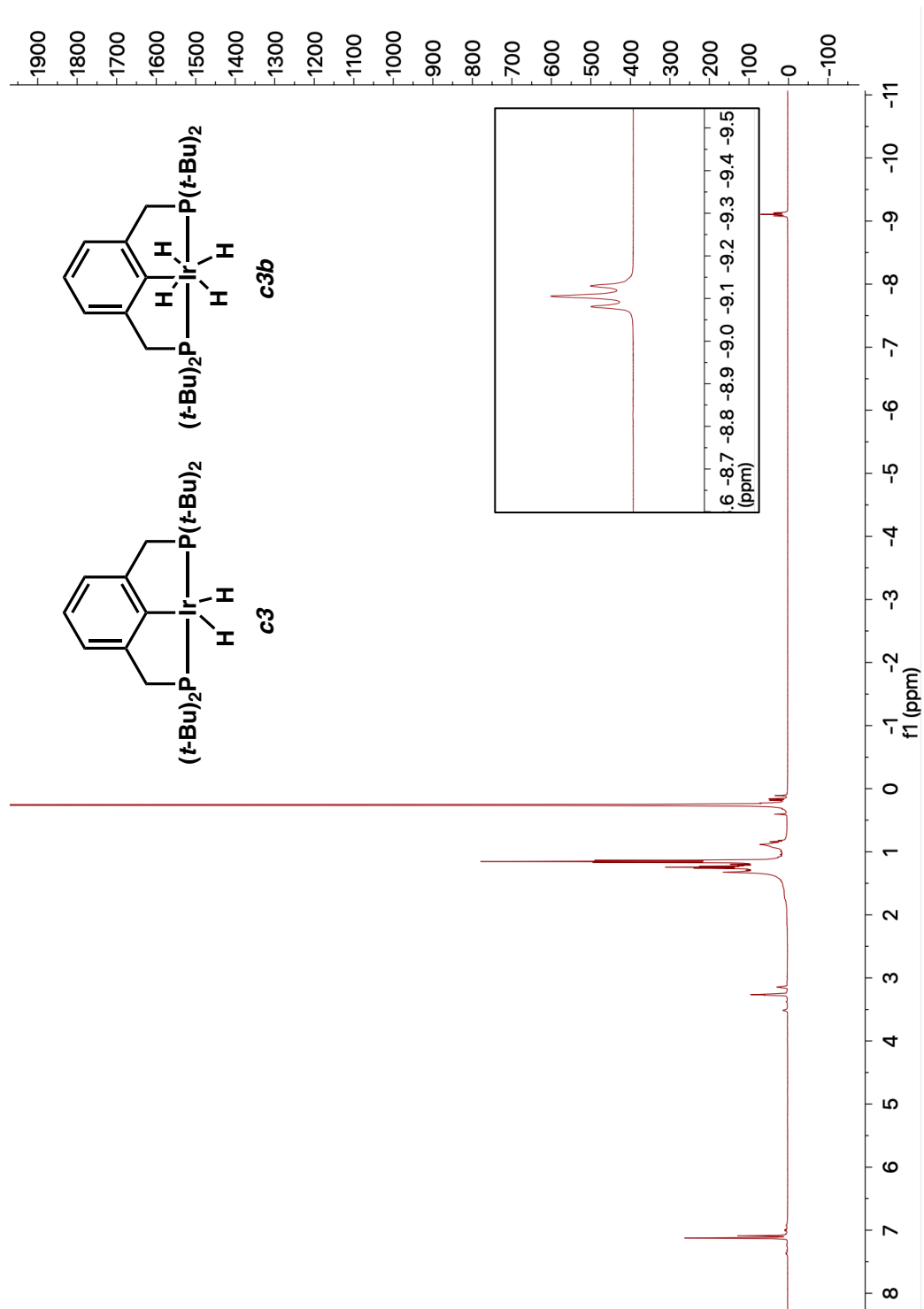
Figure A1.2 *^1H NMR (400 MHz, C6D6) of Complexes **c3/c3b***
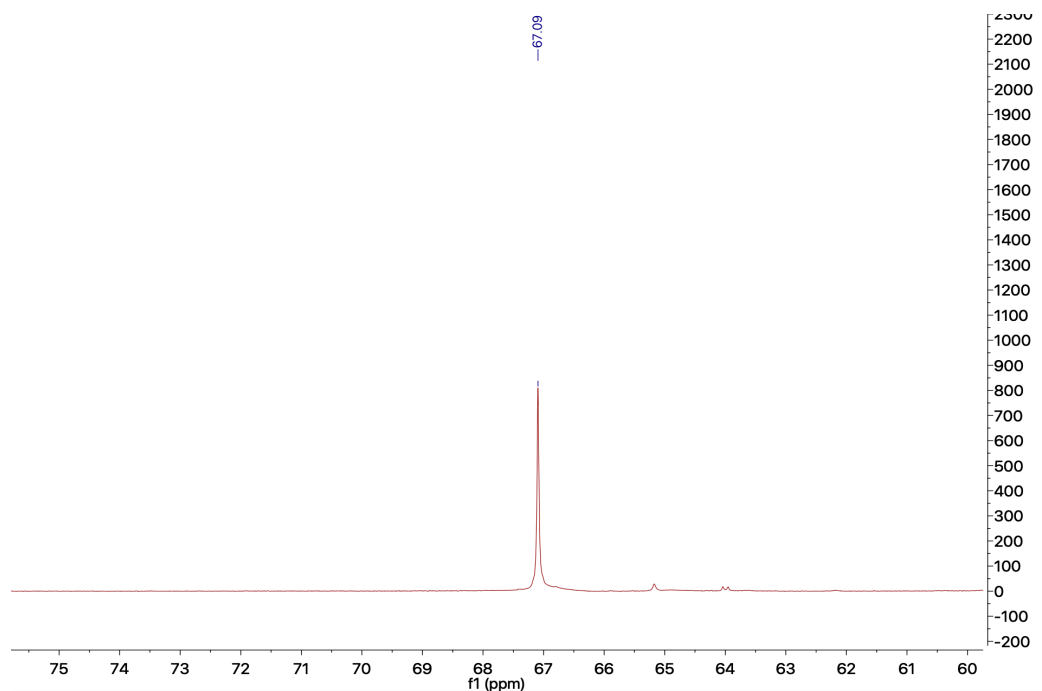
Figure A1.3 ^{31}P NMR (400 MHz, C6D6) of Complex **c3a**
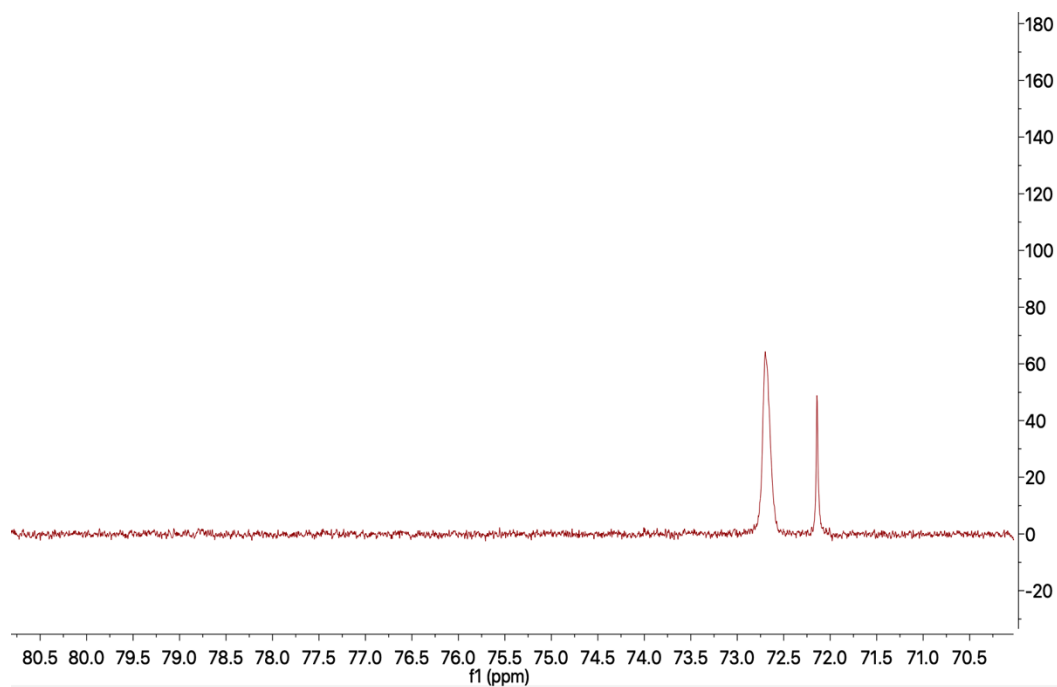
Figure A1.4 ^{31}P NMR (400 MHz, C6D6) of Mixture of Complexes **c3/c3b**
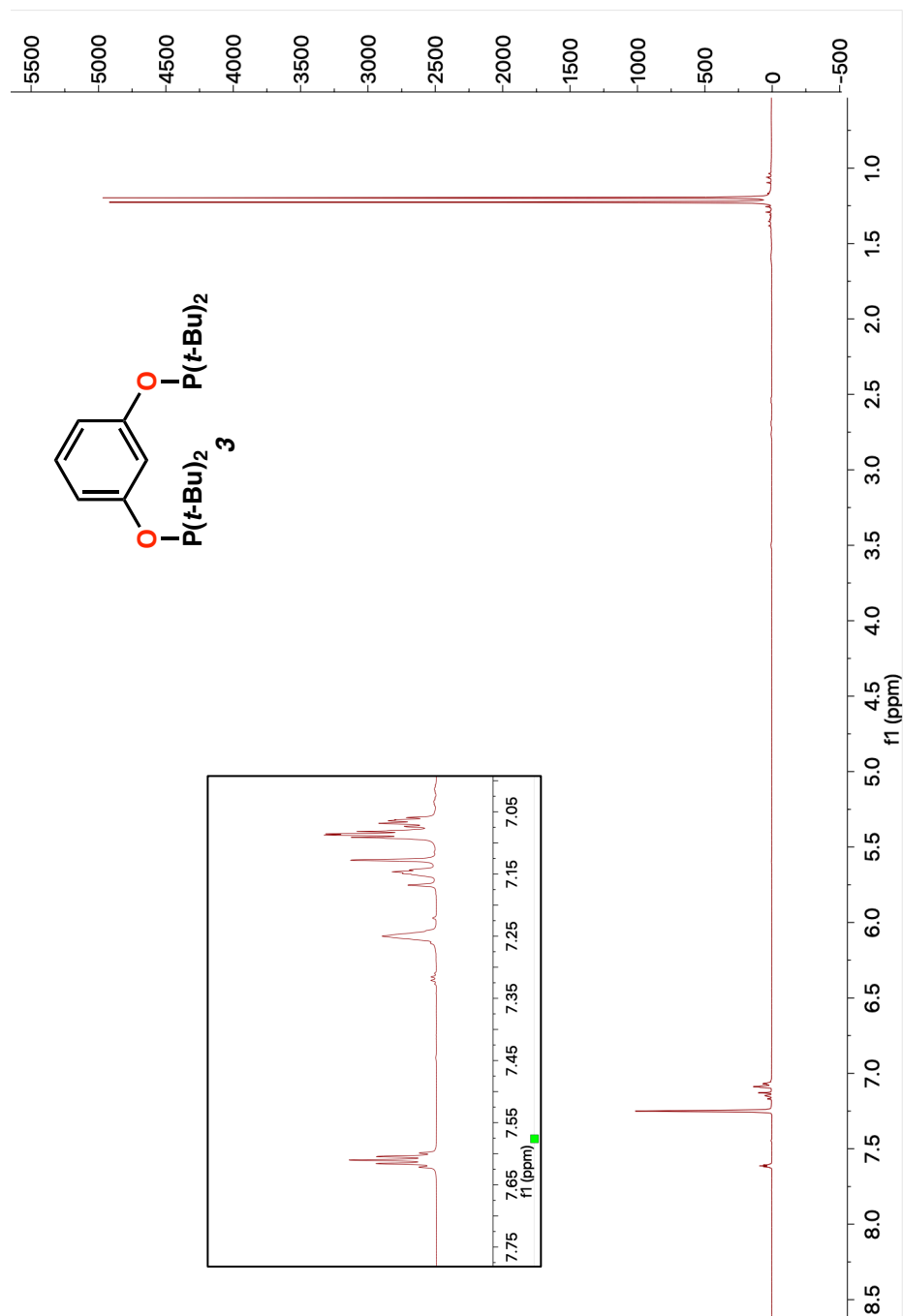
Figure A1.5 *^{1}H NMR (400 MHz, C6D6) of Ligand 3.*
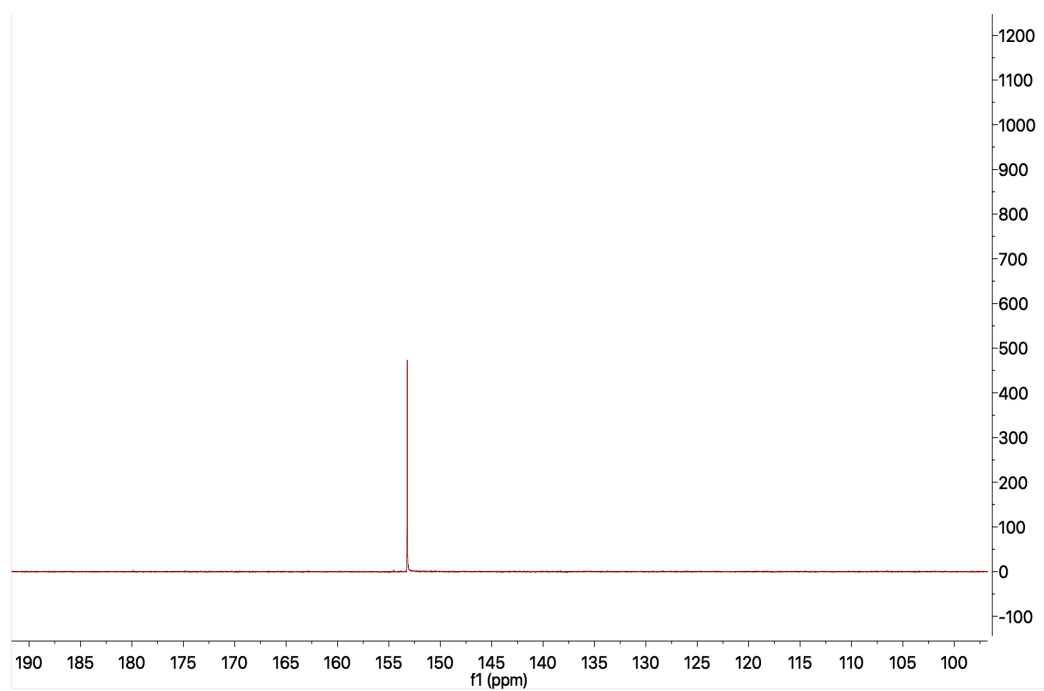
Figure A1.6 ^{31}P NMR (400 MHz, C6D6) of Ligand **3**
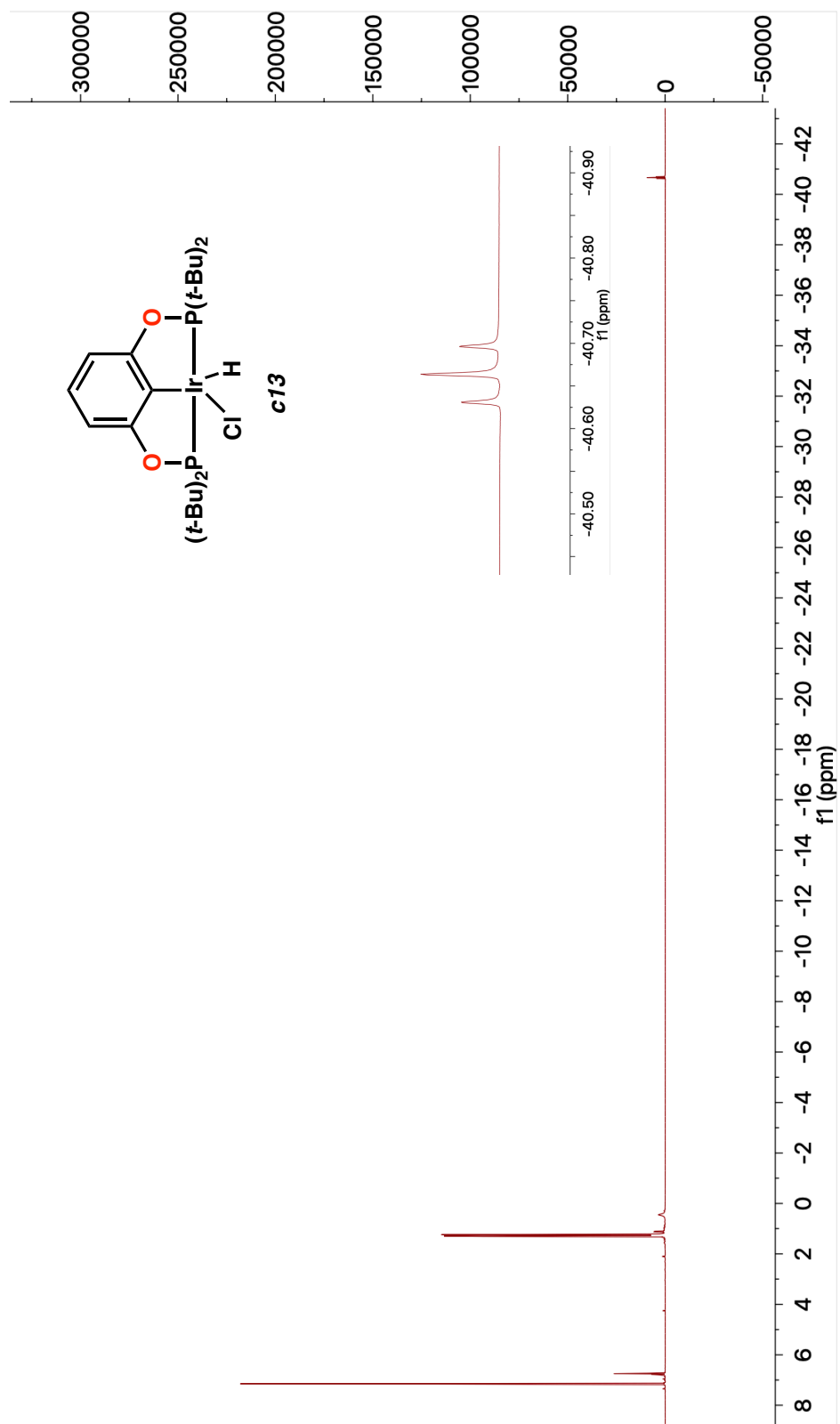
Figure A1.7 *¹H NMR (400 MHz, C6D6) of Ligand **c13***
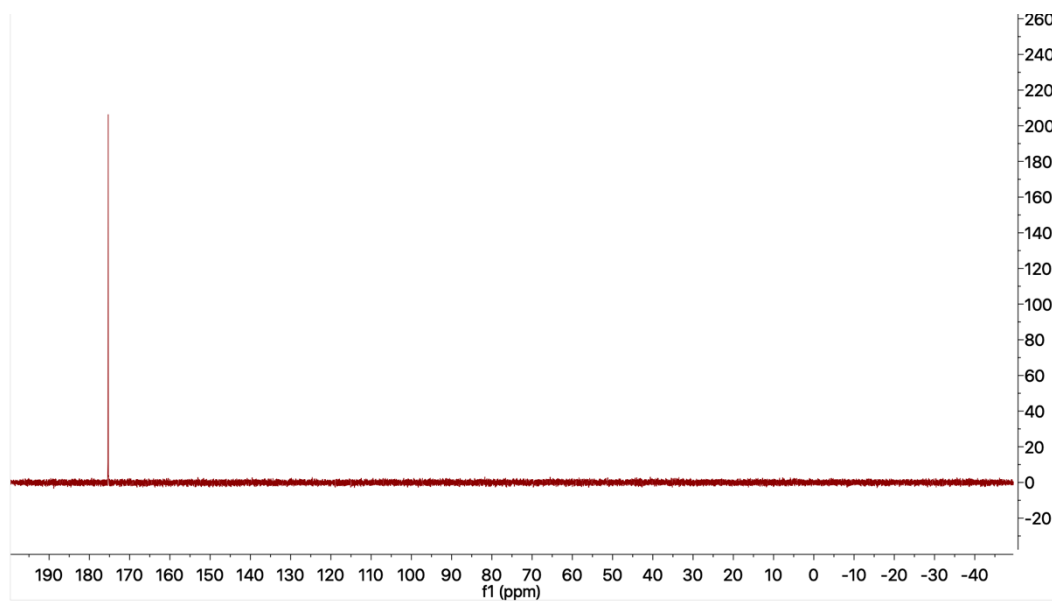
Figure A1.8 ^{31}P NMR (400 MHz, C6D6) of Complex **c13**
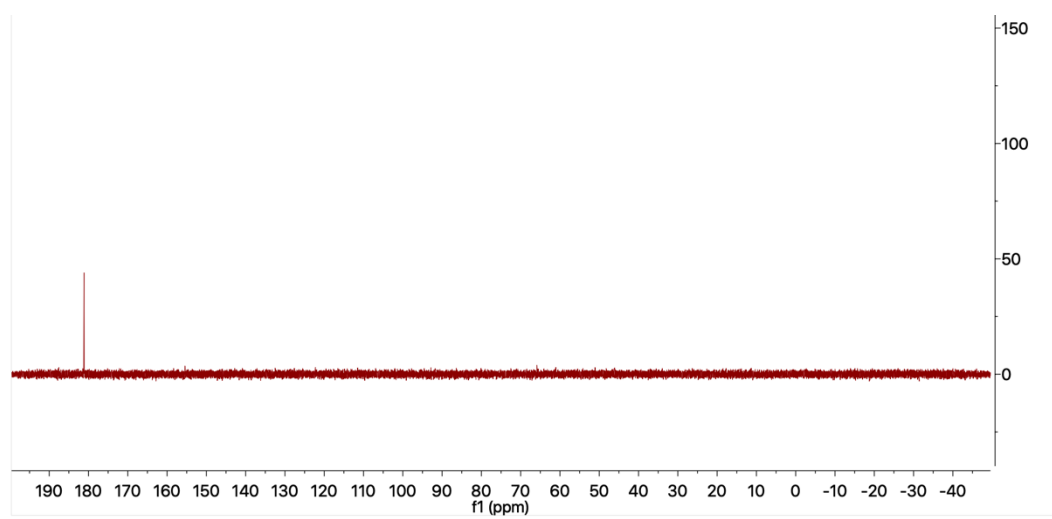
Figure A1.9 ^{31}P NMR (400 MHz, C6D6) of Complex **c13a**
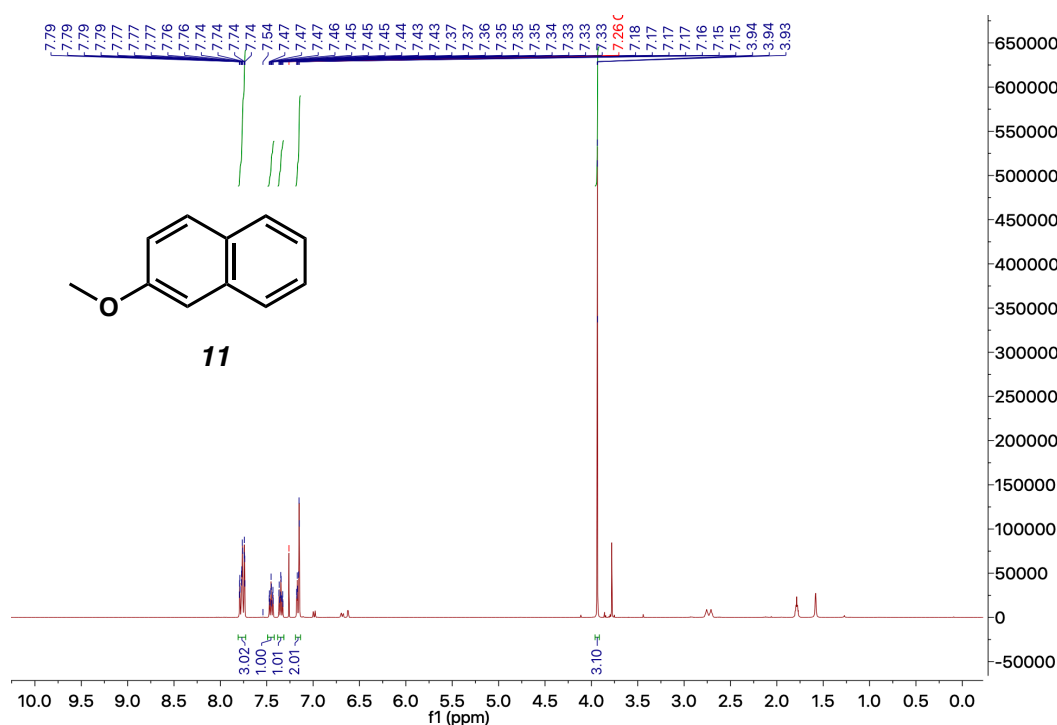
Figure A1.10 *Table 2.3 Entry 6* ^{1}H NMR (*400 MHz, Chloroform-d*) of **11** *(Isolated with* **10**), *Yield Calculated with Cis-1,4-Diacetoxy-2-Butene Standard*
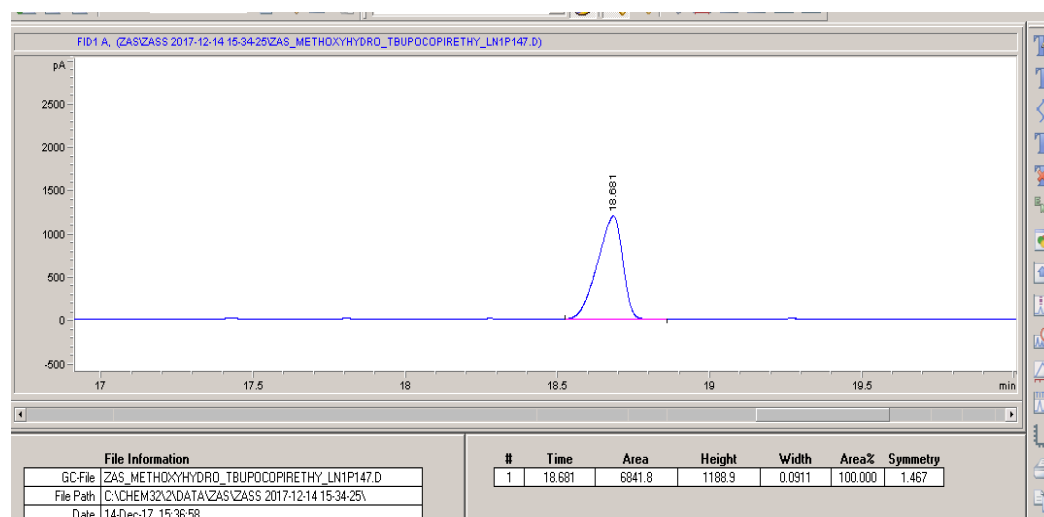
Figure A1.11 *GC Spectra of* **10** *Crude Reaction: Showing Full Conversion to* **11**@18.68 *Using ZAS2 Method in Table A1.1,* **10** *rt is Typically@18.25*
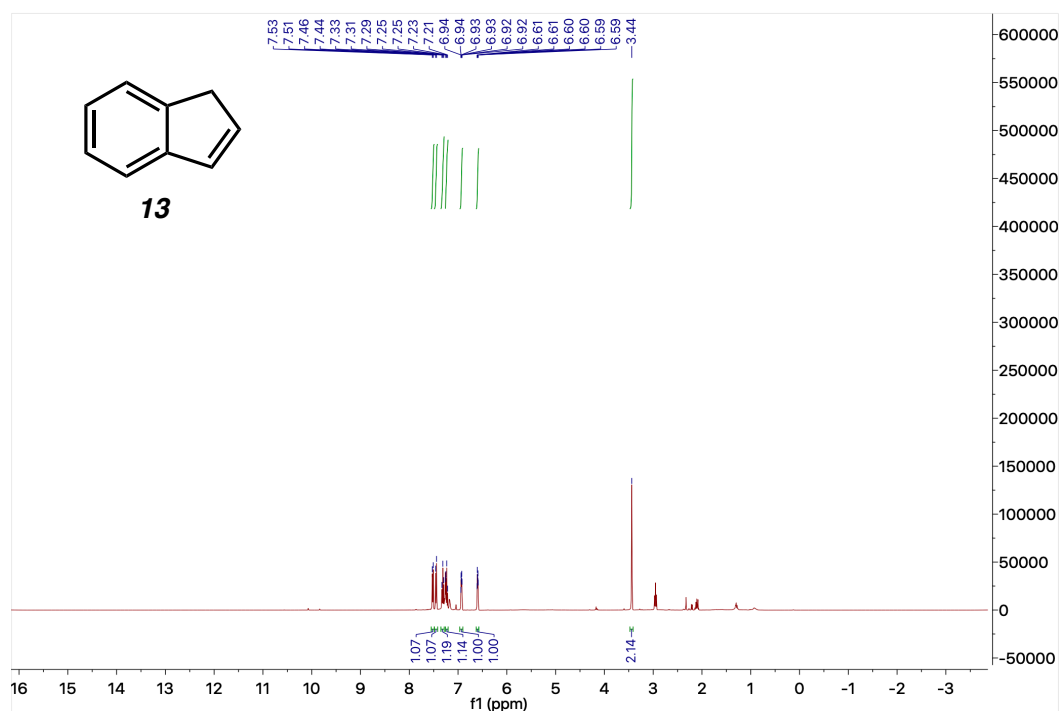
Figure A1.12 *Table 2.4 Entry 8 ¹H NMR (400 MHz, Chloroform-d) of Indene (13) (Isolated with Indane (12)), Yield Calculated with Cis-1,4-Diacetoxy-2-Butene Standard*
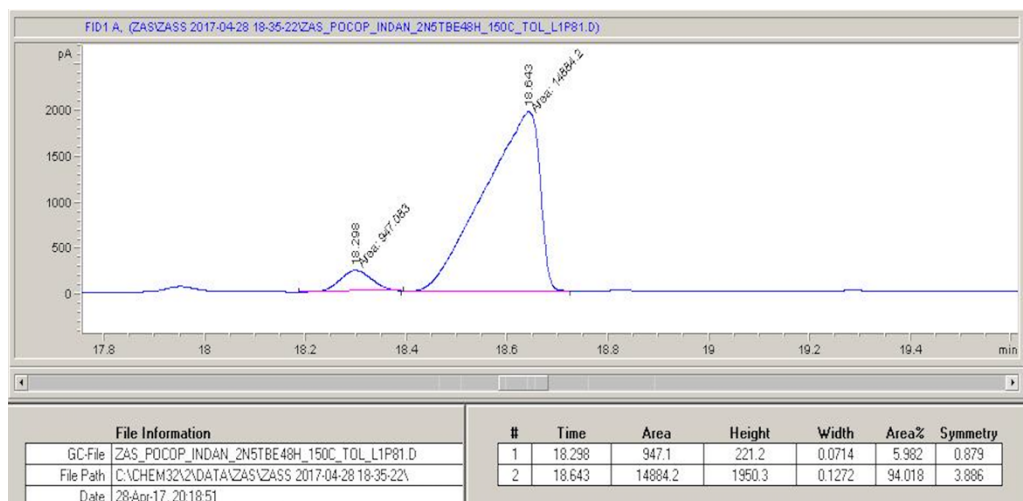
Figure A1.13 *GC Spectra of 12 Crude Reaction: 12@18.29 and 13@18.64 Using ZAS_Indane Method in Table A1.2*
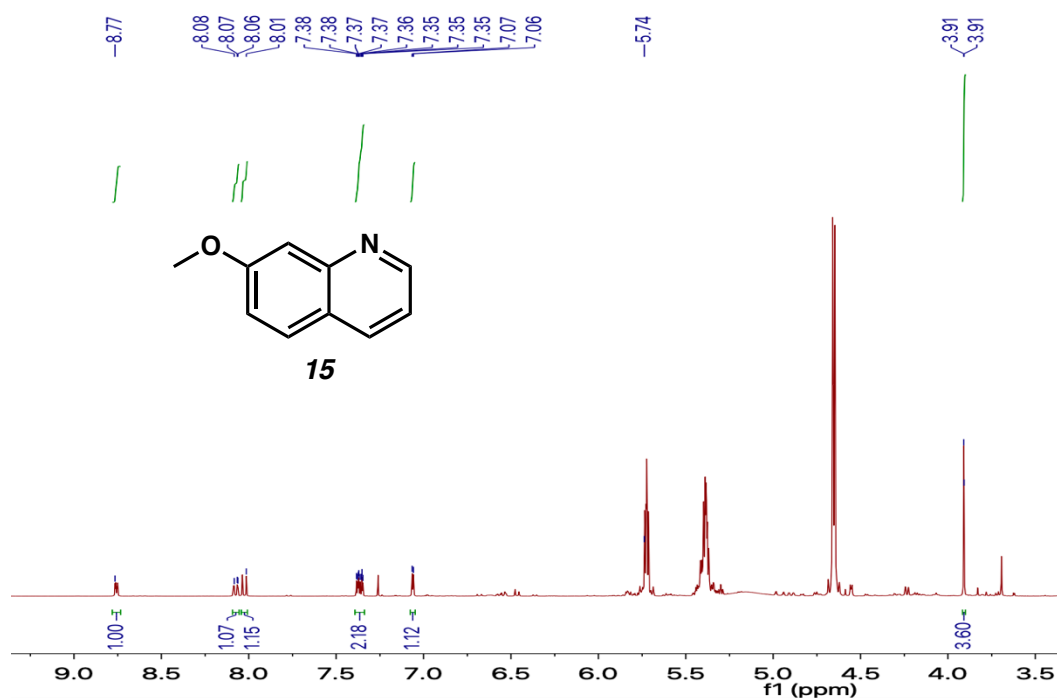
Figure A1.14 *Table 2.5 Entry 5 ¹H NMR (400 MHz, Chloroform-d) of Crude Reaction, Yield Calculated with Cis-1,4-Diacetoxy-2-Butene Standard*
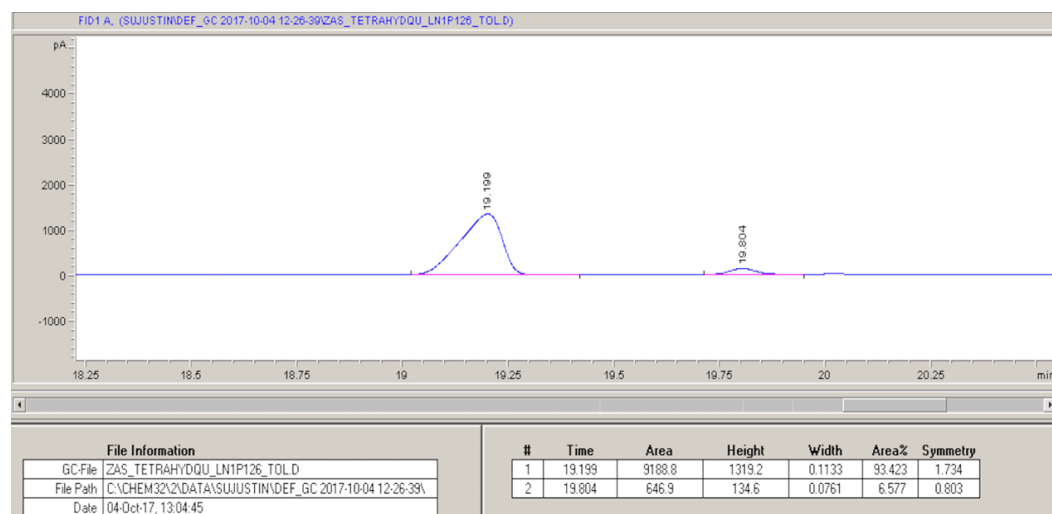
Figure A1.15 *GC Spectra of **14** Crude Reaction: **15**@19.80 and **14**@19.20 Using ZAS2 Method in Table A1.1*
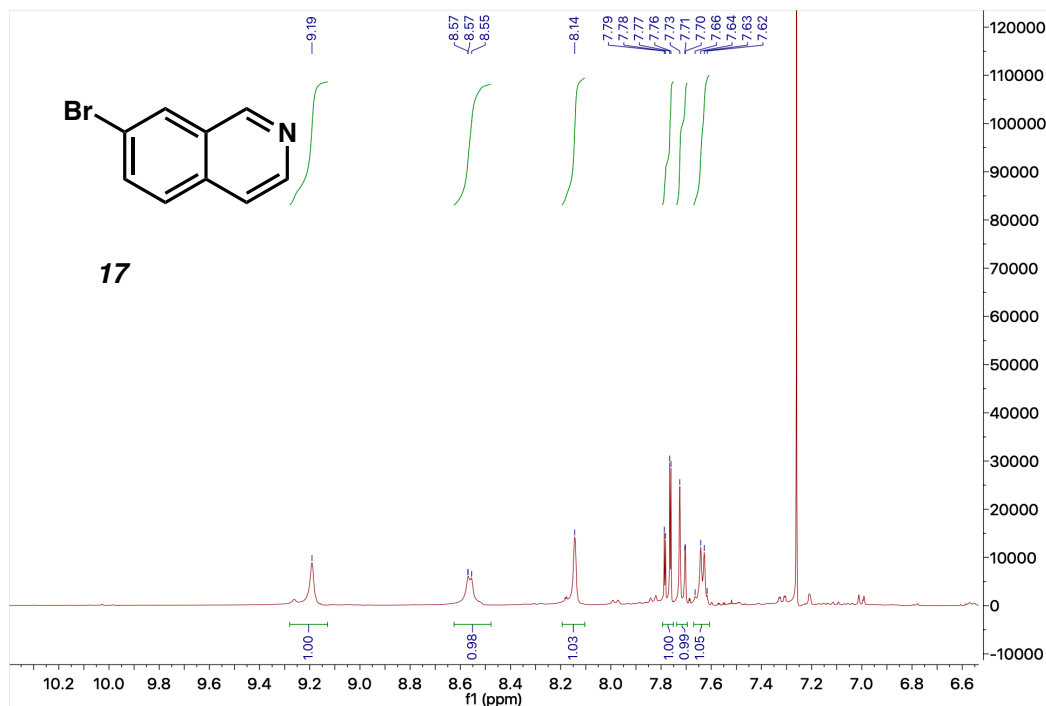
Figure A1.16 *Table 2.6 Entry 4 ^{1}H NMR (400 MHz, Chloroform-d) of Crude Reaction, Yield Calculated with Cis-1,4-Diacetoxy-2-Butene Standard*
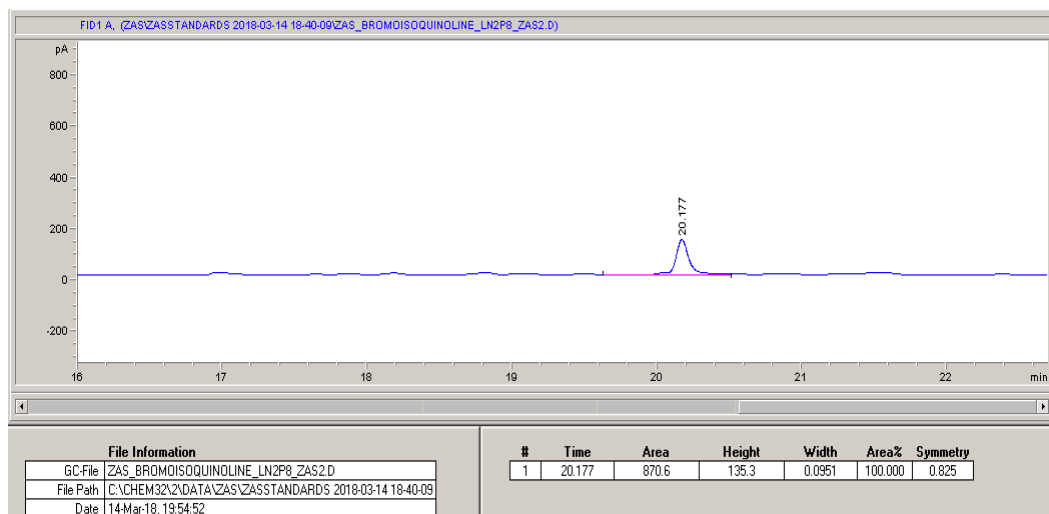
Figure A1.17 *GC Spectra of **16** Crude Reaction: Showing Full Conversion: **17**@20.18, **16** rt is Typically@19.51 Using ZAS2 Method in Table A1.1*
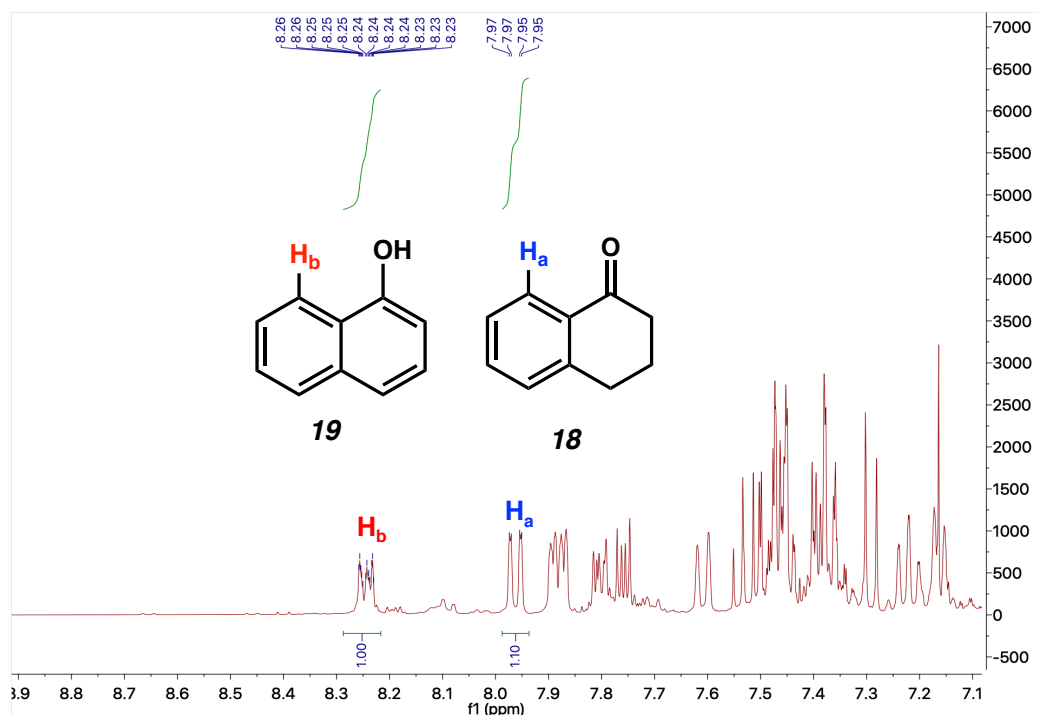
Figure A1.18 *Table 2.7 Entry 4 ¹H NMR (400 MHz, Chloroform-d) of Crude Reaction*
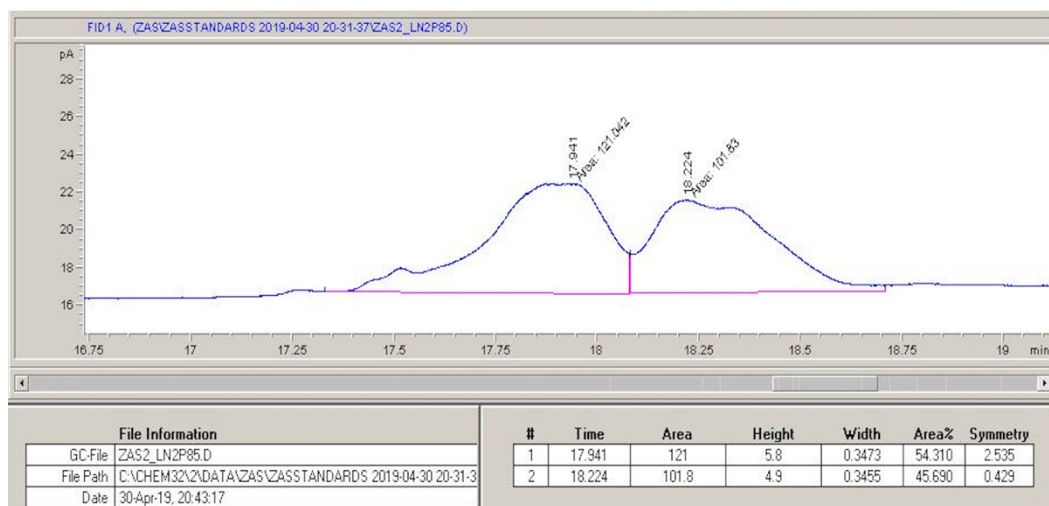
Figure A1.19 *GC Spectra of **18** Crude Reaction: **18**@17.94 and **19**@18.22 Using ZAS2 Method in Table A1.1*
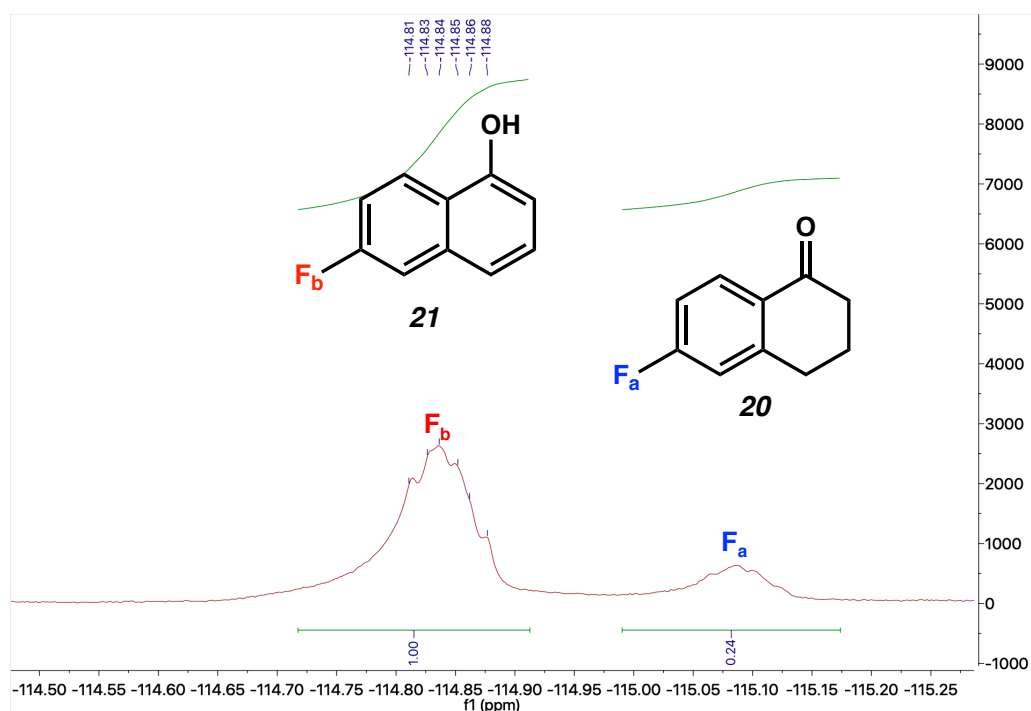
Figure A1.20 *Table 2.8 Entry 9 ^{19}F NMR (376 MHz, neat reaction) of Crude Reaction, Yield Calculated with α,α,α-Trifluorotoluene as in Internal Standard*
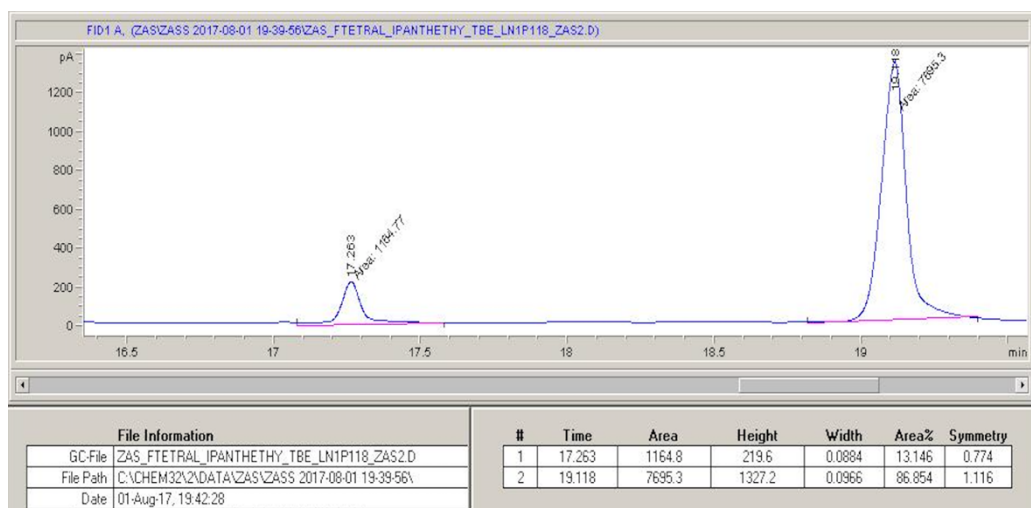
Figure A1.21 *GC Spectra of **20** Crude Reaction: **20**@17.26 and **21**@19.12 Using ZAS2 Method in Table A1.1*
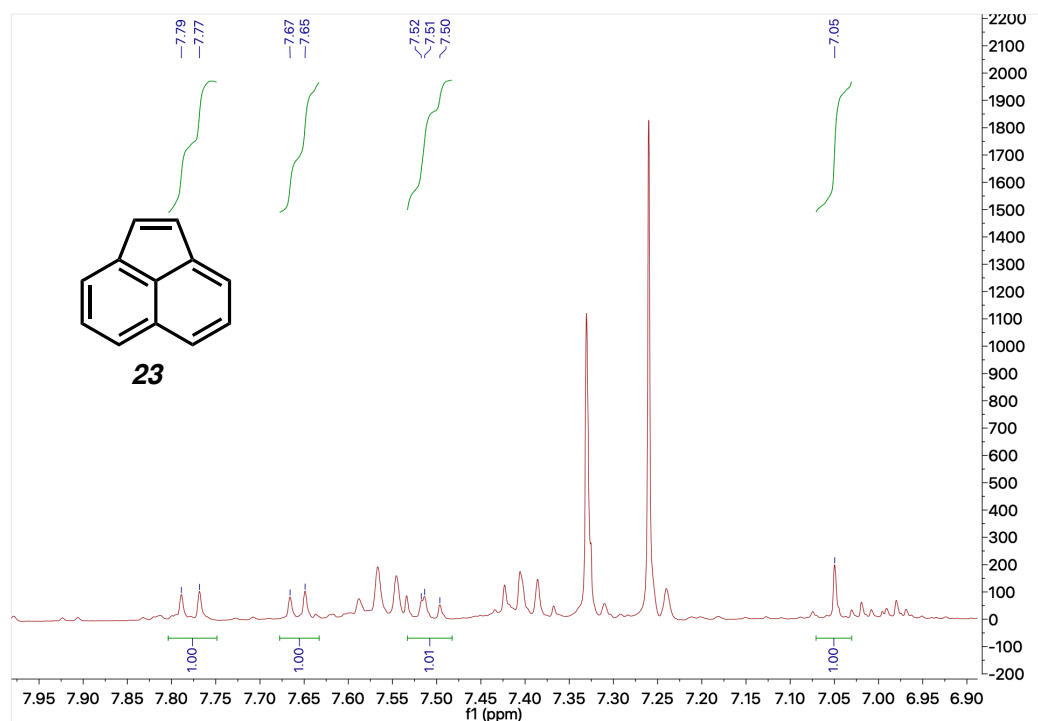
Figure A1.22 *Table 2.9 Entry 3 ^{1}H NMR (400 MHz, Chloroform-d) of Crude Reaction, Yield Calculated with Cis-1,4-Diacetoxy-2-Butene Standard*
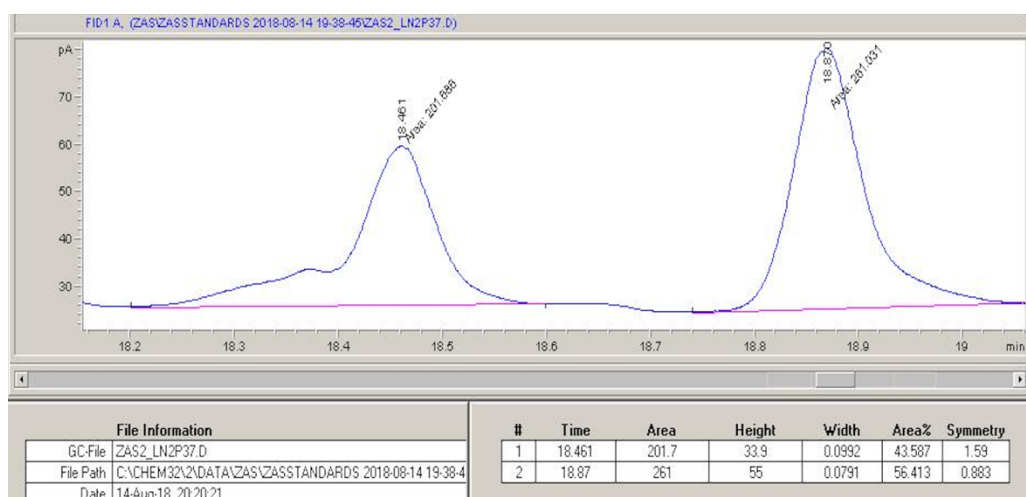
Figure A1.23 *GC Spectra of **22** Crude Reaction: **23**@18.46 and **22**@18.87 Using ZAS2 Method Table A1.1*

APPENDIX 2

C(SP³)–H DEHYDROGENATION ATTEMPTS OF CHALLENGING HETEROCYCLIC ALKANES BY IRIDIUM PINCER LIGATED COMPLEXES

A2.1   INTRODUCTION

In Chapter 2, we successfully demonstrated Ir pincer-catalyzed C(sp³)–H transfer dehydrogenation of a diverse collection of substrates bearing functional groups that are typically known to strongly coordinate to transition-metal centers and inhibit catalysis. In efforts to expand the application of Ir pincer ligated complexes as transfer dehydrogenation catalysts and explore their reactivity, we extended the investigated heterocyclic substrate scope to additional functionalities containing sulfur and chlorine heteroatoms, and silane and cyano groups . That being said, the dehydrogenative transformation of these substrates proved to be challenging. In this appendix, we present our attempts in dehydrogenating these

additional heterocyclic substrates by Ir pincer ligated complexes and provide

insights to the substrates with functionalities that could be promising in optimizing

this transformation.

A2.2   ATTEMPTS TO TRANSFER DEHYDROGENATE PIPERIDINE

AND N-METHYLPIPERIDINE

Pyridine and its derivatives are of great synthetic interest owing to their

properties and applications in organometallic chemistry, biologically active systems,

and materials.[1]   Goldman in 2003 and Huang in 2014 reported the transfer

dehydrogenation of secondary and tertiary amines using Ir pincer ligated complexes

($^{t\text{-}Bu4}$POCOP)–Ir **c13** and ($^{i\text{-}Pr4}$PSCOP)–Ir **c22** in moderate to excellent yields

(Scheme 2.3 in Chapter 2).[2,3]   Given the importance of pyridine and the promising

relevant reported examples, we were interested in investigating the application of Ir

pincer ligated complexes as potential catalysts for the direct transfer

dehydroaromatization of piperidine (**24**) to pyridine (**25**).   We commenced the

investigation using complex ($^{t\text{-}Bu4}$POCOP)–Ir **c13** and **TBE** as the H_2 acceptor (Table

A2.1, entries 1-4).   The reactions were carried out neat at 200 °C under an argon

atmosphere after drying and distilling all reagents.   We observed that **c13** was not

catalytically active and only trace amounts were generated even when increasing the

catalyst loading from 0.21 to 0.63 mol.% and reaction time from 21 h to 48 h.

Alternatively, we investigated the dehydrogenation of **24** using complexes

($^{i\text{-}Pr4}$PSCOP)–Ir **c22** and ($^{i\text{-}Pr4}$anthraphos)–Ir **c24** with **TBE** as the H_2 acceptor (Table

A2.1 entry 5 and 6).   However, we observed that complexes **c22** and **c24** were also

not catalytically active in transfer dehydrogenating **24** to **25**.

Table A2.1 *Investigated Conditions of Piperidine Transfer Dehydrogenation Attempts by*

Ir Pincer Ligated Complexes
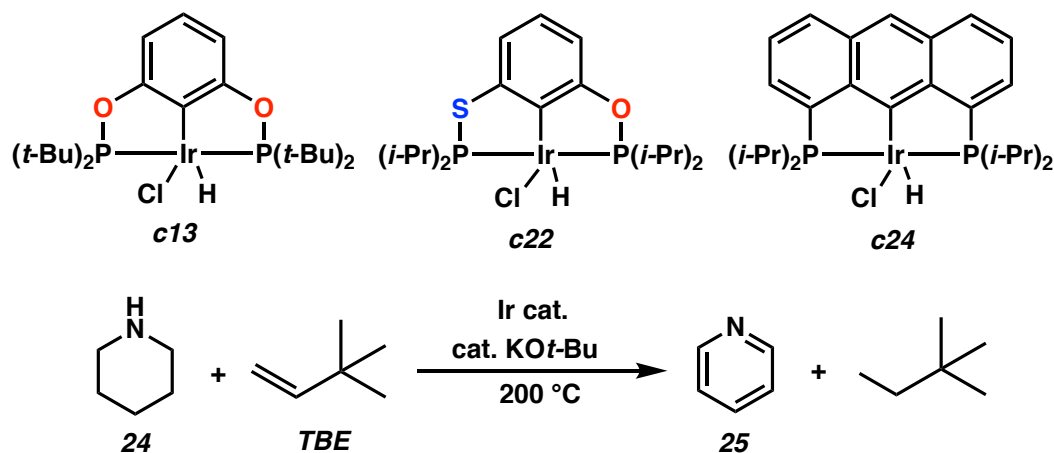
entry	cat./(mol.%)	equiv. of acceptor	reaction time	25 yield[b]	TON[c]
1	c13/0.22	1.0	21 h	-	-
2	c13/0.21	1.0	48 h	1.2%	6
3	c13[d]/0.42	1.0	25 h	0.5%	1
4	c13[d]/0.63	2.5	24 h	-	-
5	c22/0.16	1.8	48 h	-	-
6	c24/0.16	1.5	42 h	0.7%	4

[a] Conditions: 3.2-4.0 mmol of **24**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ^{1}H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation.

We believe **24** likely inhibits catalysis due to its Lewis basic nature in the form of an unprotected secondary amine. Hence, we then investigated the transfer dehydrogenation of *N*-methylpiperidine (**26**) to methylpyridine (**27**) using complex **c13** and **TBE** as the H_2 acceptor (Scheme A2.1).

Scheme A2.1 *Attempts to Transfer Dehydrogenate N-Methylpiperidine by Complex*

(*t-Bu4*POCOP)–Ir **c13**
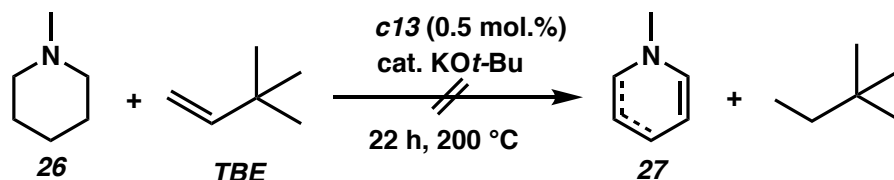
Unfortunately, we found that **c13** was not catalytically active and did not

observe any activation of **26**. This result is in agreement with previous reposts by

Goldman where no catalytic activity was observed when attempting the

dehydrogenation of **26** by complex (*t-Bu4*PCP)–Ir **c3** (Figure A2.1).[3]
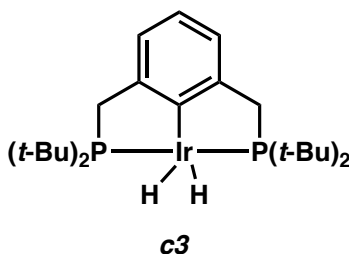
Figure A2.1 *Complex* (*t-Bu4*PCP)–Ir **c3** *Chemical Structure*

A2.3 ATTEMPTS TO TRANSFER DEHYDROGENATE FIVE-MEMBERED RING DERIVATIVES

Pentene and five-membered ring skeletons are found especially in

organometallic applications.[4,5] Owing to their importance, we were interested to

investigate the dehydrogenation of a diverse collection of five-membered ring

derivatives using Ir pincer ligated complexes to provide facile and complimentary

methods to the current approaches. In this section we discuss our attempts in dehydrogenating 5-methoxy-1-indanone, 1-chlorocyclopentene, 5-iodo-2,3,-dihydrobenzofuran, and 4-aminoindan.

A2.3.1 Investigations of 5-Methoxy-1-Indanone Transfer Dehydrogenation

We began our investigation of the transfer dehydrogenation of 5-methoxy-1-indanone (**28**) using complex (*t*-Bu4POCOP)–Ir **c13** and **TBE** as the H_2 acceptor (Scheme A2.2). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We did not observe any product and we believe **28** was decomposing since we did not observe any indicative aromatic peaks in the ¹H NMR spectrum. We also investigated using **HEX** as an alternative acceptor but observed similar findings and no dehydrogenated product was generated.

Scheme A2.2 *Attempts to Transfer Dehydrogenate 5-Methoxy-1-Indanone by Complex* (*t-Bu4POCOP*)–Ir **c13**
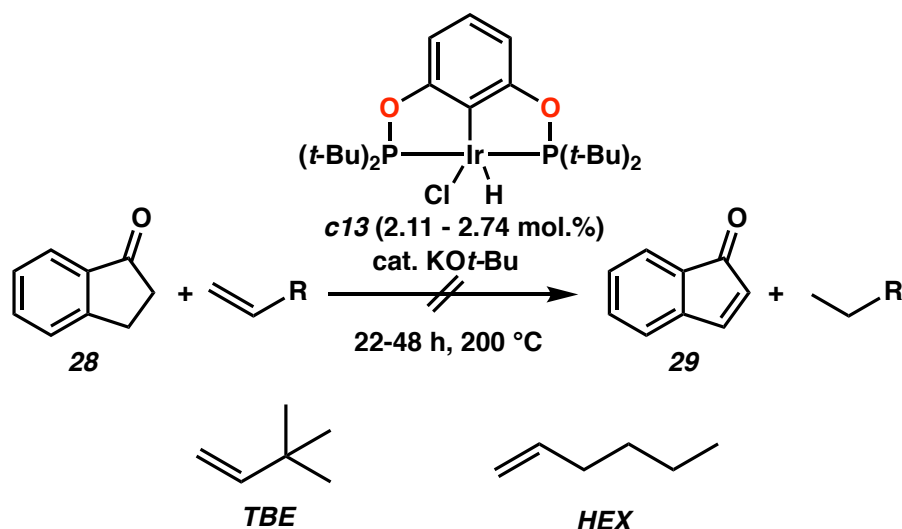
A2.3.2 Investigations of 1-Chlorocyclopentene Transfer Dehydrogenation

We began our investigation of the transfer dehydrogenation of
1-chlorocyclopentene (**30**) using complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** and **TBE** as the H_2
acceptor (Scheme A2.3). The reactions were carried out neat at 180 °C under an
argon atmosphere after drying and distilling all reagents. We did not observe the
desired product 1-clorocyclopentadiene (**31**). The substrate **30** was unreactive and
may have inhibited catalysis by coordinating to the Ir metal center. We also
investigated the disproportionation of **30** to **31** and 1-chlorocyclopentane without
using an H_2 acceptor but we did not observe any conversion.

Scheme A2.3 *Attempts to Transfer Dehydrogenate 1-Chlorocyclopentene by Complex*
($^{t\text{-Bu4}}$*POCOP)–Ir* **c13**
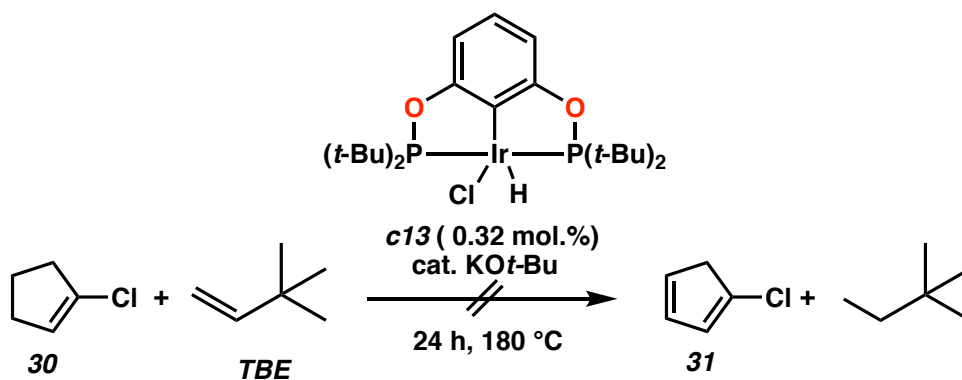
**A2.3.3   Investigations   of   5-Iodo-2,3-Dihydrobenzofuran   Transfer
Dehydrogenation**

We began our investigation of the transfer dehydrogenation of
5-iodo-2,3-dihydrobenzofuran (**32**) using complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** and **TBE** as
the H_2 acceptor (Table A2.2). The reactions were carried out neat at 200 °C under
an argon atmosphere after drying and distilling all reagents. We believe the reaction

generated 5-iodobenzofuran (**33**) in modest yield (30%). We observed other

unidentified products in the aromatic region in the ^{1}H NMR spectrum. Although this

transformation seems promising, further investigations are required to validate the

observed findings and optimize reaction conditions upon successful confirmation.

Table A2.2 *Investigated Conditions of 5-Iodo-2,3-Dihydrobenzofuran Transfer*

Dehydrogenation by Ir Pincer Ligated Complexes
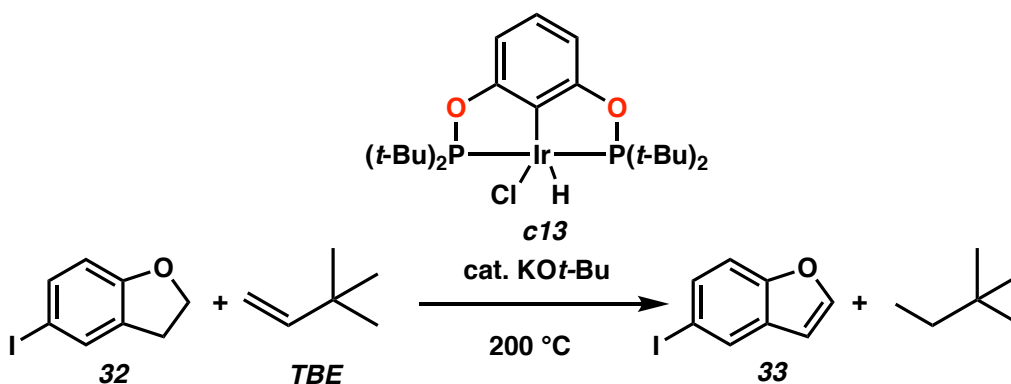
entry	cat./(mol.%)	equiv. of acceptor	reaction time	33 yield[b]	TON[c]
1	c13/5.50%	exs	21 h	25.9%	5
2	c13/7.26%	exs	24 h	30.0%	4

[a] Conditions: 3.2-4.0 mmol of **32**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ^{1}H NMR using cis-1,4-diacetoxy-2-butene as an internal standard. [c] TON per dehydrogenation.

A2.3.4 Investigations of 4-Aminoindan Transfer Dehydrogenation

We investigated the transfer dehydrogenation of 4-aminoindan (**34**) using

complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** and **TBE** as the H$_2$ acceptor (Scheme A2.4). The

reactions were carried out neat at 200 °C under an argon atmosphere after drying and

distilling all reagents. We believe the dehydrogenated substrate **35** was generated in

yields up to 15%. However, we observed other unidentified products in the aromatic

region in the ^{1}H NMR spectrum and we could not identify which isomer was generated. Further investigations are necessary to confirm the obtained isomer of the product and optimize reaction conditions upon successful confirmation.

Scheme A2.4. *Attempts to Transfer Dehydrogenate 4-Aminoindan by Complex* (*t-Bu4*POCOP)–Ir **c13**
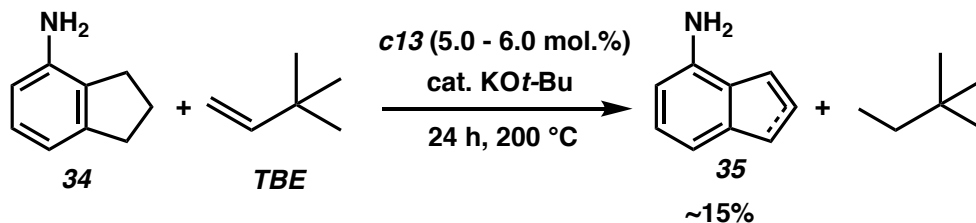
A2.4   ATTEMPTS TO TRANSFER DEHYDROGENATE CARBONYL CONTAINING CYCLIC ALKANE DERIVATIVES

Aromatic and olefinic carbonyl skeletons constitute a common substructure of a large variety of biologically active substances and materials with unique properties.[6-9] In addition, carbonyl derivatives can participate in nucleophilic addition reactions, the Wittig reaction, condensation reactions, and silylation reactions, and hence are a useful functional handle for a variety of organic reactions.[10-13] Owing to their properties and synthetic utility, it is of interest to dehydrogenate cyclic carbonyl derivatives using Ir pincer ligated complexes as dehydrogenation catalysts, in attempt to provide an alternative and complementary method to the current approaches. In this section we discuss our attempts at dehydrogenating 7-bromo-1-tetralone, tetrahydrothiopyran-4-one,

4-methoxy-5,6,7,8-tetrahydronaphthalene-1-carbaldehyde,8-fluoro-1-benzosuberoe,

5,6,7,8-tetrahydro-2-naphthoic   acid,   1-acetylcyclohexene,   3-(4-bromo-2-

fluorophenyl)cyclohexan-1-one, and 6-methoxy-3,4-dihydronaphthalen-1(2H)-one.

A2.4.1 Investigations of 7-Bromo-1-Tetralone Transfer Dehydrogenation

We began our investigation of the transfer dehydrogenation of

7-bromo-1-tetralone (**36**) using complex ($^{t\text{-}Bu4}$POCOP)–Ir **c13** and using both **TBE**

and **HEX** as H_2 acceptors (Scheme A2.5). The reactions were carried out neat at 200

°C under an argon atmosphere after drying and distilling all reagents. We found that

an aromatic product was generated based on the ^{1}H NMR spectrum observed ppm

shifts, however it was not the desired 7-bromo-1-naphthol (**37**) dehydrogenated

product. After further investigation, we found that a debrominated naphthol **19** is

generated instead, along with the decomposed **36** to 1-tetralone (**18**) (Scheme A2.6).

Scheme A2.5 *Attempts to Transfer Dehydrogenate 7-Bromo-1-Tetralone by Complex*
($^{t\text{-}Bu4}$POCOP)–Ir **c13**
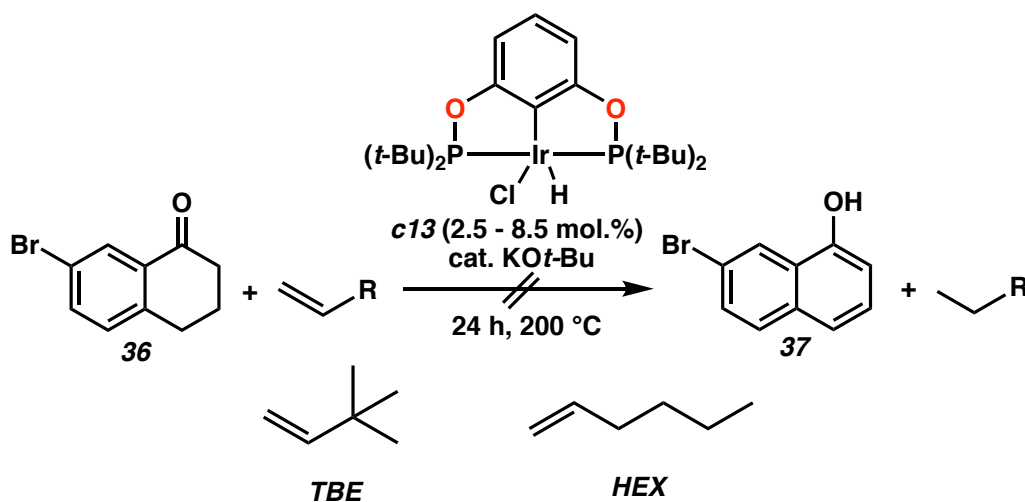
Scheme A2.6 *Debromination of 7-Bromo-1-Tetralone and Transfer Dehydrogenation*

by Complex (t-Bu4POCOP)–Ir **c13**
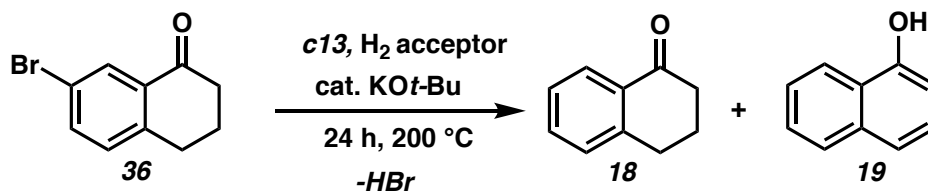
A2.4.2 Investigations of Tetrahydrothiopyran-4-one Transfer Dehydrogenation

We investigated the transfer dehydrogenation of tetrahydrothiopyran-4-one

(**38**) using complex ($^{t\text{-}Bu4}$POCOP)–Ir **c13** and **TBE** as the H_2 acceptor (Scheme A2.7).

The reactions were carried out neat at 200 °C under an argon atmosphere after drying

and distilling all reagents. We did not observe the desired product **39** and we believe

38 likely inhibited catalysis by coordinating to the Ir metal center via the thioether.

Scheme A2.7 *Attempts to Transfer Dehydrogenate Tetrahydrothiopyran-4-one by*

Complex (t-Bu4POCOP)–Ir **c13**
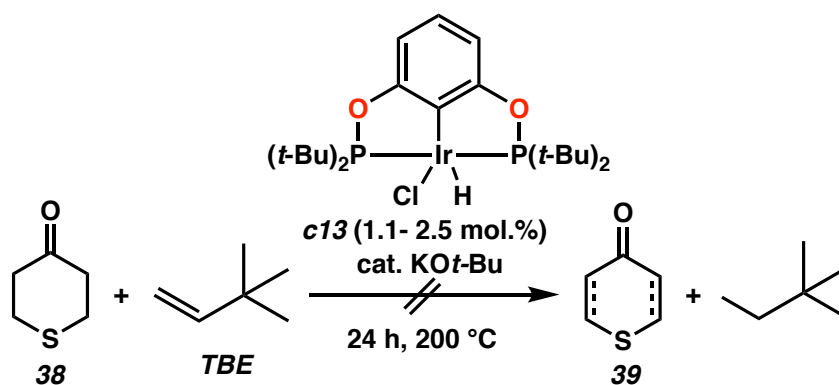
A2.4.3 Investigations of 4-Methoxy-5,6,7,8-Tetrahydronaphthalene-1-Carbaldehyde Transfer Dehydrogenation

We investigated the transfer dehydrogenation of 4-methoxy-5,6,7,8-tetrahydronaphthalene-1-carbaldehyde (**40**) using complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** and both **TBE** and **HEX** as H_2 acceptors (Scheme A2.8). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We did not observe the desired product **41** and we believe **40** likely inhibited catalysis by coordinating to the Ir metal center.

A2.4.4 Investigations of 8-Fluoro-1-Benzosuberone Transfer Dehydrogenation

We investigated the transfer dehydrogenation of 8-fluoro-1-benzosuberone (**42**) using complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** and both **TBE** and **HEX** as H_2 acceptors (Scheme A2.9). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We believe we observed trace amounts of **43**, however further investigations are required to validate our findings and confirm that the desired product was obtained. Upon successful confirmation, reaction conditions will be optimized to achieve higher yields of **43**.

Scheme A2.8 *Attempts to Transfer Dehydrogenate*

4-Methoxy-5,6,7,8-Tetrahydronaphthalene-1-Carbaldehyde by Complex (t-Bu4POCOP)–

Ir **c13**

Scheme A2.9 *Attempts to Transfer Dehydrogenate 8-Fluoro-1-Benzosuberone by*

Complex (t-Bu4POCOP)–Ir **c13**
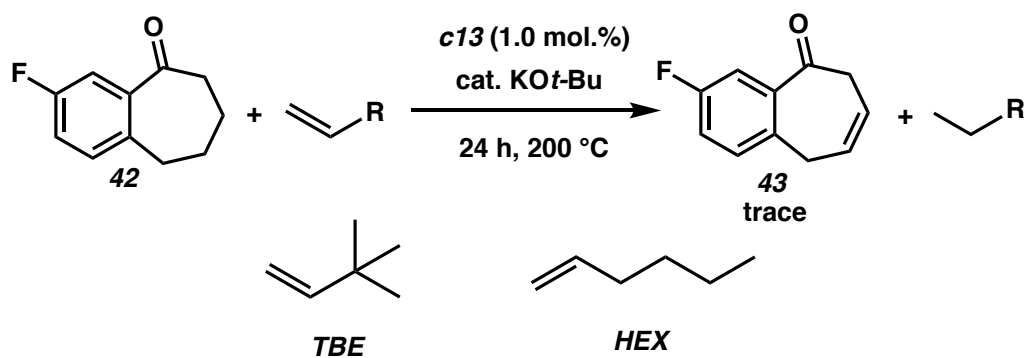
A2.4.5 Investigations of 5,6,7,8-Tetrahydro-2-Naphthoic Acid Transfer Dehydrogenation

We investigated the transfer dehydrogenation of 5,6,7,8-tetrahydro-2-naphthoic acid (**44**) using complex (*$^{t\text{-Bu}4}$*POCOP)–Ir **c13** and both **TBE** and **HEX** as H_2 acceptors (Scheme A2.10). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We did not observe the desired dehydrogenated product **45**. We are not surprised by this result as this substrate contains a carboxylic acid moiety; however, we wanted to explore complex **c13** catalytic activity in harsh environments given that we successfully transfer dehydrogenated substrates containing acidic functionalities in excellent yields, as presented in Chapter 2.

Scheme A2.10 *Attempts to Transfer Dehydrogenate 5,6,7,8-Tetrahydro-2-Naphthoic Acid by Complex (*$^{t\text{-Bu}4}$*POCOP)–Ir* **c13**
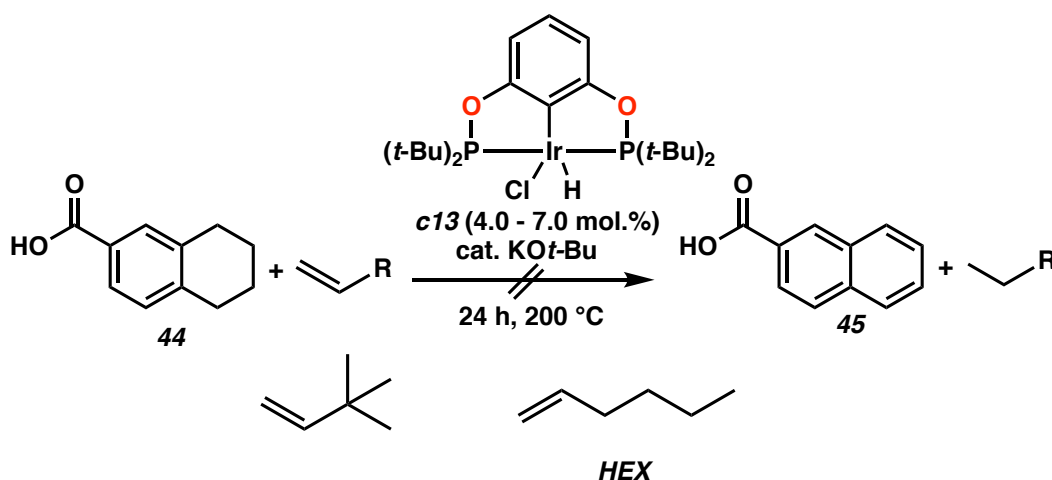
A2.4.6 Investigations of 1-Acetylcyclohexene Transfer Dehydrogenation

We investigated the transfer dehydrogenation of 1-acetylcyclohexene (**46**) using complex ($^{t\text{-}Bu4}$POCOP)–Ir **c13** and both **TBE** and **HEX** as H_2 acceptors (Scheme A2.11). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We varied the catalyst loading between 1.0 to 2.0 mol.% but we did not observe the desired dehydrogenated product methylbenzoate (**47**). We also investigated the disproportionation of **46** to **47** without using an olefinic acceptor but did not observe any conversion. It is likely that **46** inhibit catalysis by coordinating to the Ir metal center.

Scheme A2.11 *Attempts to Transfer Dehydrogenate 1-Acetylcyclohexene by Complex*
($^{t\text{-}Bu4}$*POCOP)–Ir* **c13**
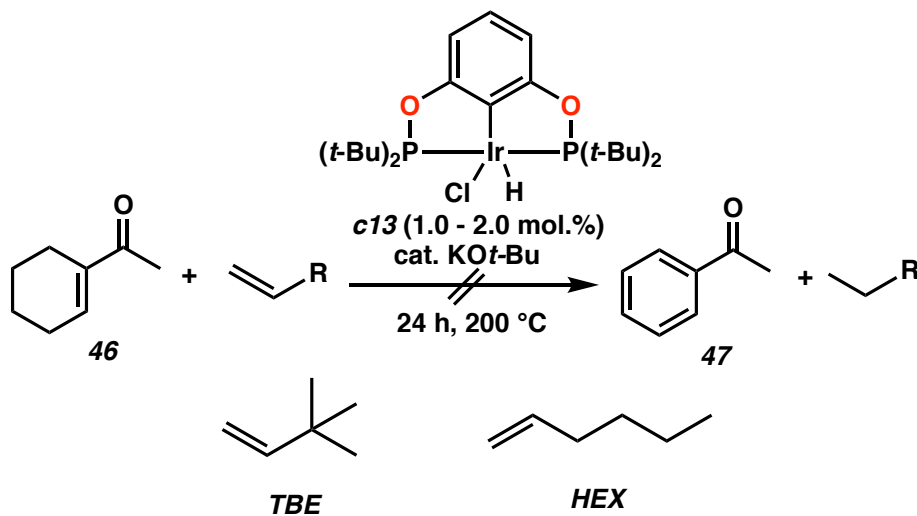
A2.4.7 Synthesis of 3-(4-Bromo-2-Fluorophenyl)Cyclohexan-1-one and Transfer Dehydrogenation Attempts

We were interested in transfer dehydrogenating a substrate with multiple functionalities to investigate the tolerance of Ir pincer ligated complexes in such systems. Hence, we synthesized 3-(4-bromo-2-fluorophenyl)cyclohexan-1-one (**50**) from 4-bromo-2-fluorobenzeneboronic acid (**48**) and 2-cyclohexenone (**49**) utilizing rhodium catalyzed 1,4-conjugate addition following literature procedures.[14,15]

Scheme A2.12 *3-(4-Bromo-2-Fluorophenyl)Cyclohexan-1-one Synthesis via Rhodium Catalyzed 1,4-Conjugate Addition*
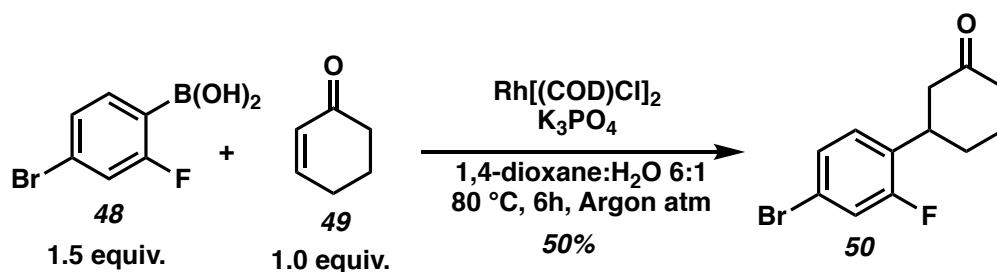
After successfully synthesizing **50** we investigated its transfer dehydrogenation using complex ($^{t\text{-}Bu4}$POCOP)–Ir **c13** and **TBE** as the H_2 acceptor to 4'-bromo-2'-fluoro-[1,1'-biphenyl]-3-ol (**51**) (Scheme A2.13). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We could not identify the product as there were several peaks observed in the aromatic region in the ^{1}H NMR spectrum. However, the diagnostic peak of **50** at 3.20 ppm was no longer observed, indicating full conversion of the starting material. Further investigations are necessary to identify the products and optimize reaction conditions upon successful confirmation.

Scheme **A2.13** 3-(4-Bromo-2-Fluorophenyl)Cyclohexan-1-one Transfer

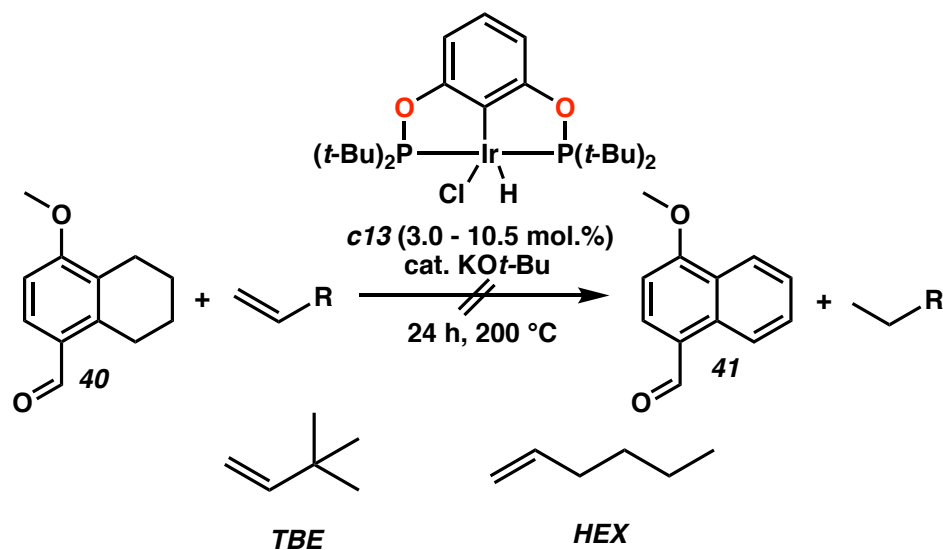Dehydrogenation Attempts by Complex (*t-Bu4*POCOP)–Ir **c13**
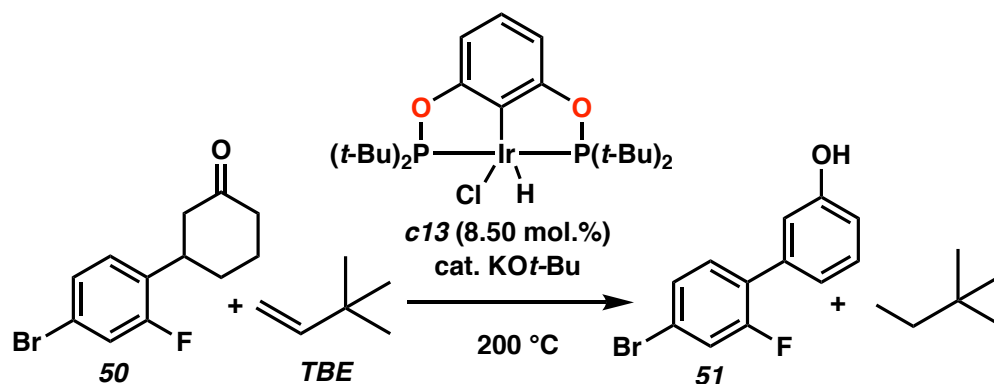
A2.4.8 Investigations of 6-Methoxy-3,4-Dihydronaphthalen-1(2H)-one Transfer

Dehydrogenation

We investigated the transfer dehydrogenation of
6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**52**) using complex (*t-Bu4*POCOP)–Ir
c13 and **TBE** as the H_2 acceptor (Scheme A2.14). The reactions were carried out
neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We
did not observe the desired dehydrogenated product **53**. That being said, we believe
this reaction is promising and increasing the catalyst loading and or experimenting
with other Ir pincer ligated complexes may generate conversion given that we've
seen high catalytic activity of investigated Ir pincer ligated complexes when
dehydrogenating tetralone derivatives in Chapter 2. Hence, further investigations are
required to study this system.

Scheme **A2.14** 6-Methoxy-3,4-Dihydronaphthalen-1(2H)-one Transfer

Dehydrogenation Attempts by Complex (*t-Bu4*POCOP)–Ir **c13**
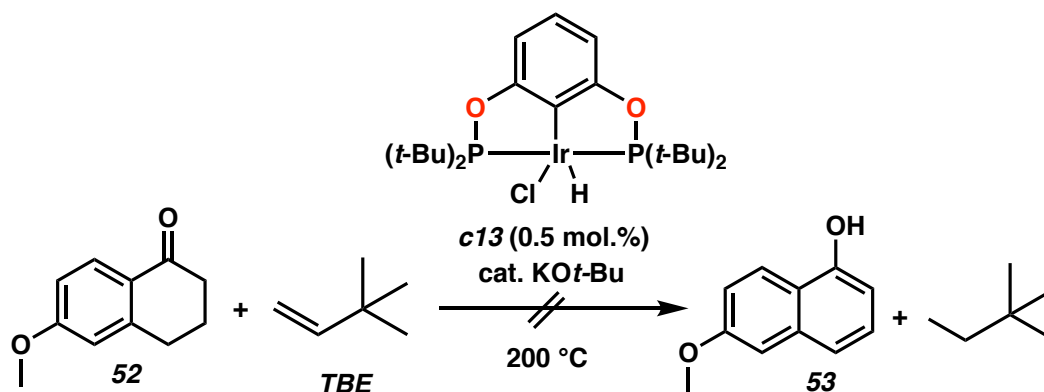
A2.5   ATTEMPTS TO TRANSFER DEHYDROGENATE CYCLOHEXYL DERIVATIVES

Functionalized arenes and olefins are found as substructures in many organic compounds that are synthetically useful and have biological and physical properties.[16-21] Hence it is of interest to use Ir pincer ligated complexes as dehydrogenation catalysts to dehydrogenate cyclohexyl derivatives to functionalized arenes and olefins as a new and complementary method to the current approaches. in this section, we present our attempts in transfer dehydrogenating 1,4-thioxane, 2-cyclohexene-1-acetonitrile, phenylcyclohexane, 1-bromo-4-cyclohexylbenzene, 3-bromocyclohexene, chlorocyclohexane, 1-(trimethylsiloxy)cyclohexene, julolidine, and paroxetine by Ir pincer ligated complexes.

A2.5.1 Investigations of 1,4-Thioxane Transfer Dehydrogenation

We investigated the transfer dehydrogenation of 1,4-thioxane (**54**) using complex (*$^{t\text{-Bu4}}$*POCOP)–Ir **c13** and **TBE** as the H_2 acceptor (Scheme A2.15). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We observed trace amounts of the olefinic product **55**, however further investigations are required to validate our findings and optimize reaction conditions upon successful confirmation of the desired product. In all cases, we did not observe what would be the fully dehydrogenated product 1,4-oxathiline.

Scheme A2.15 *1,4-Thioxane Transfer Dehydrogenation Attempts by Complex (*$^{t\text{-Bu4}}$*POCOP)–Ir **c13***
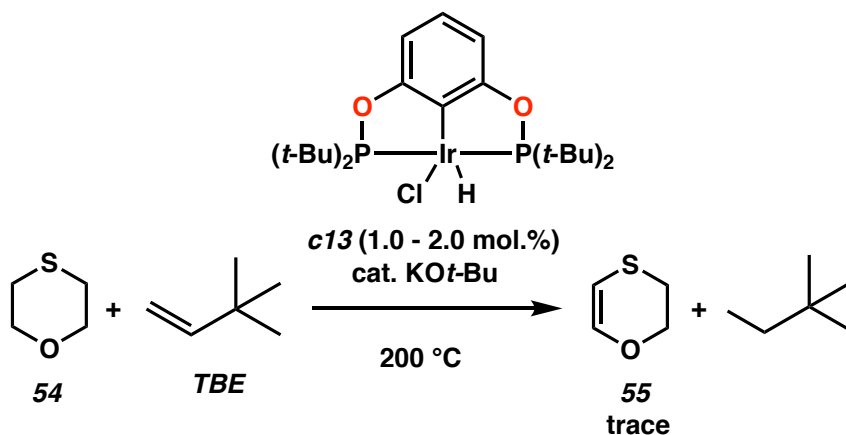
A2.5.2   Investigations   of   2-Cyclohexene-1-Acetonitrile   Transfer Dehydrogenation

We investigated the transfer dehydrogenation of 2-cyclohexene-1-acetonitrile (**56**) using complex (*t*-Bu4POCOP)–Ir **c13** and using both **TBE** and **HEX** as H_2 acceptors (Scheme A2.16). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. In all cases, we did not observe the desired dehydrogenated product **57**. Instead, we observed isomerization of **56**. We also investigated the disproportionation of **56** to **57** and similarly observed isomerization of **56**. It is likely that operating the reaction at the required high temperatures for dehydrogenation is causing isomerization, and hence this substrate is not ideal for such transformation.

Scheme A2.16 *2-Cyclohexene-1-Acetonitrile Transfer Dehydrogenation Attempts by Complex (t-Bu4POCOP)–Ir **c13***
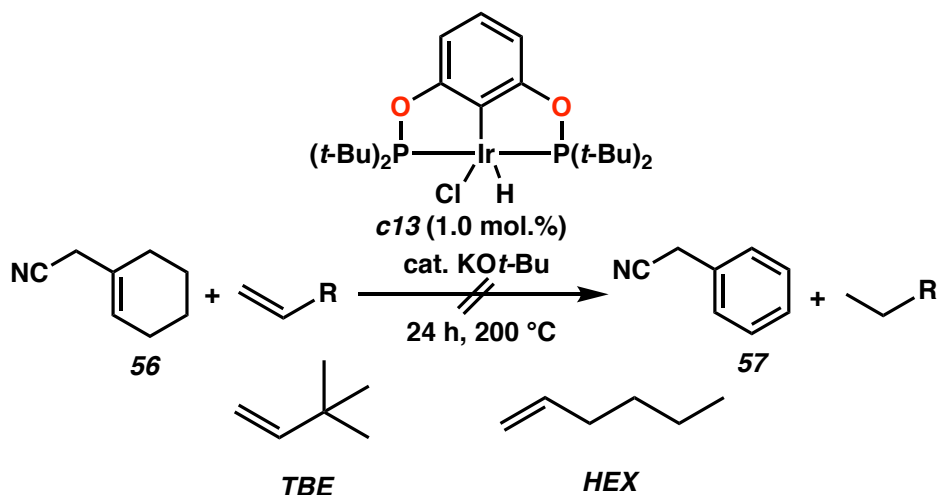
A2.5.3 Investigations of Phenylcyclohexane Transfer Dehydrogenation

We investigated the transfer dehydrogenating of phenylcyclohexane (**58**) to

biphenyl (**59**) using complex (*t*-Bu4POCOP)–Ir **c13** and using both **TBE** and **HEX** as

H_2 acceptors (Scheme A2.17). The reactions were carried out neat at 200 °C under

an argon atmosphere after drying and distilling all reagents. In all cases, we did not

observe the desired biphenyl (**59**) product and **58** was unreactive.

Scheme A2.17 *Phenylcyclohexane Transfer Dehydrogenation Attempts by Complex*
(t-Bu4POCOP)–Ir c13
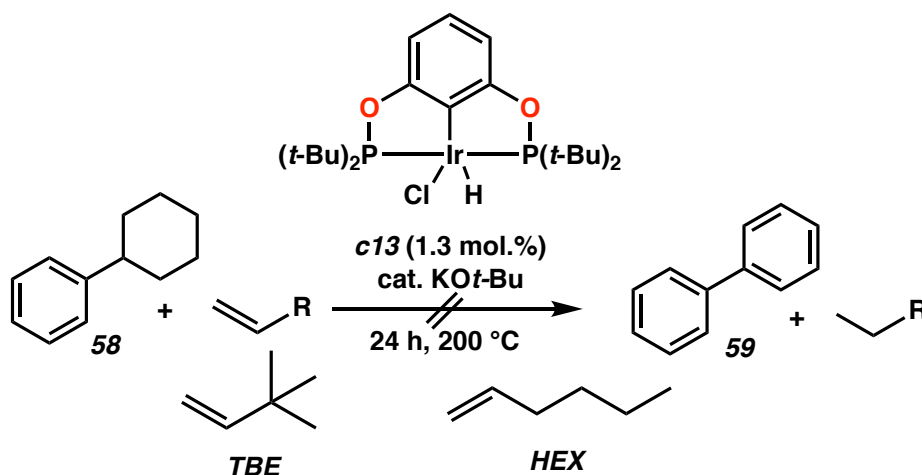
A2.5.4 Investigations of 1-Bromo-4-Cyclohexylbenzene Transfer Dehydrogenation

We investigated the transfer dehydrogenation of

1-bromo-4-cyclohexylbenzene (**60**) to 4-bromo-biphenyl (**61**) using complex

(*t*-Bu4POCOP)–Ir **c13** and using both **TBE** and **HEX** as H_2 acceptors (Scheme A2.18).

The reactions were carried out neat at 200 °C under an argon atmosphere after drying

and distilling all reagents. We did not observe the desired dehydrogenated product

61, and **60** was unreactive.

Scheme A2.18 1-Bromo-4-Cyclohexylbenzene Transfer Dehydrogenation Attempts by

Complex (*t-Bu4*POCOP)–Ir **c13**
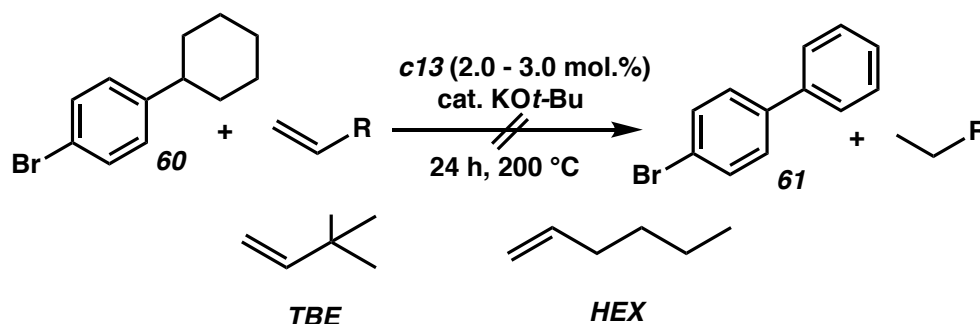
A2.5.5 Investigations of 3-Bromo-Cyclohexene Transfer Dehydrogenation

We investigated the transfer dehydrogenation of 3-bromocyclohexene (**62**) to

1-bromobenzene (**63**) using complex (*t-Bu4*POCOP)–Ir **c13** and using **TBE** as the H$_2$

acceptor (Scheme A2.19). The reactions were carried out neat at 200 °C under an

argon atmosphere after drying and distilling all reagents. We did no observe **63** and

instead we observed phenylcyclohexane (**58**), benzene, and 1-bromocyclohexane

(**64**). We investigated the disproportionation of **62** using complex (*t-Bu4*POCOP)–Ir

c13 and observed similar results. In addition, we carried out a 1:1 reaction mixture

of **62** and benzene at 200 °C without the addition of an Ir complex or KO*t*-Bu and

observed similar results (Scheme A2.20). Hence, the generated phenylcyclohexane

(**58**) is likely not catalyzed by complex **c13** and possibly occurred *via* a Friedel-Craft

type alkylation *via* electrophilic aromatic substitution followed by H atom transfer.

Scheme A2.19 *3-Bromocyclohexene Transfer Dehydrogenation Attempts by Complex*

(*t-Bu4*POCOP)–Ir **c13**
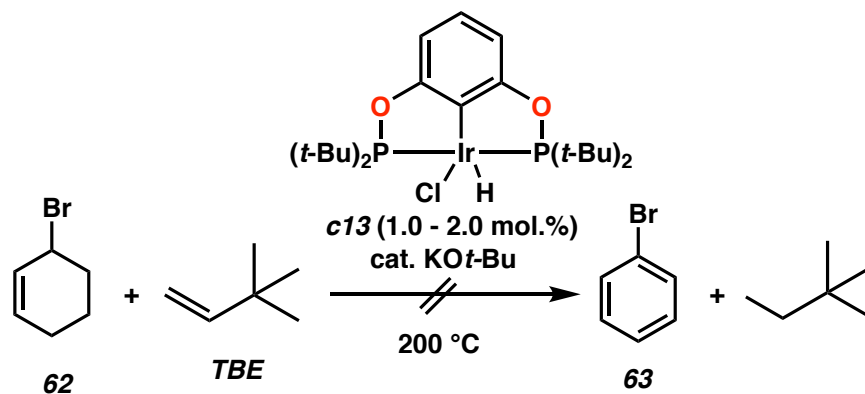
Scheme A2.20 *3-Bromocyclohexene Reaction with Benzene without an Ir Complex*
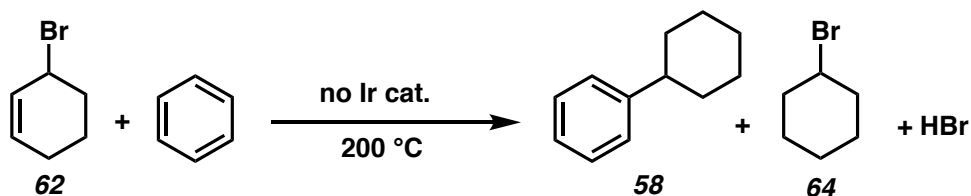
A2.5.6 Investigations of Chlorocyclohexane Transfer Dehydrogenation

We investigated the transfer dehydrogenation of chlorocyclohexane (**65**) to

chlorobenzene (**66**) using complex (*t-Bu4*POCOP)–Ir **c13** and using both **TBE** and

HEX as H_2 acceptors (Scheme A2.21). The reactions were carried out neat at 200

°C under an argon atmosphere after drying and distilling all reagents. In all cases we

did not observe the desired dehydrogenated product **66**. Instead we observed

1-cyclohexene, cyclohexane, and benzene (Scheme 2.22). 1-Cyclohexene is likely

generated from elimination of the chloride, and cyclohexane and benzene are likely

generated from 1-cyclohexene disproportionation as we will demonstrate in Chapter

3.

Scheme A2.21 *Chlorocyclohexane Transfer Dehydrogenation Attempts by Complex*

(*t-Bu4*POCOP)–Ir **c13**
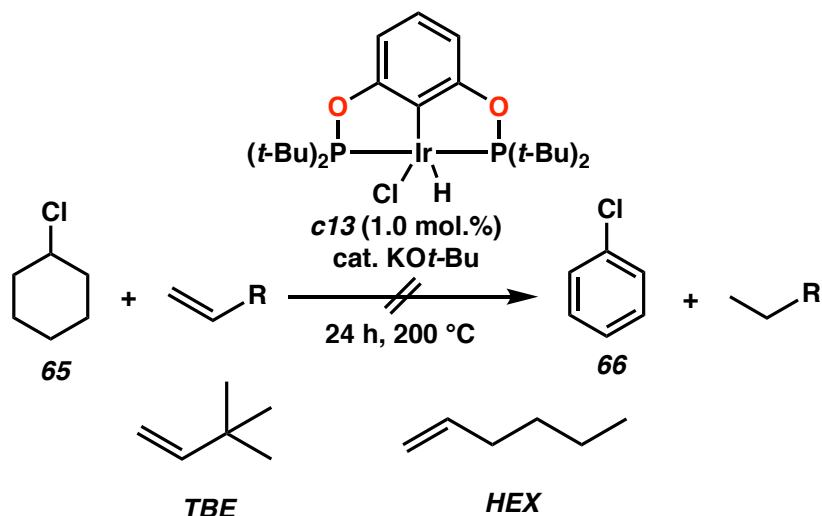
Scheme A2.22 *Chlorocyclohexane Decomposition to 1-Cyclohexene During Transfer*

Dehydrogenation Attempts
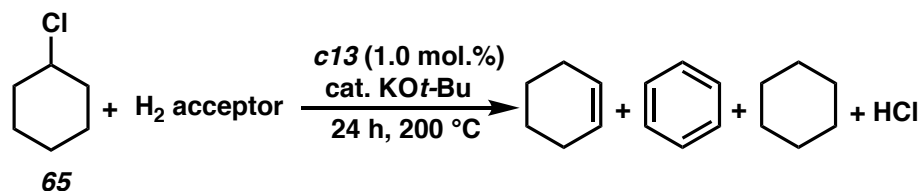
A2.5.7   Investigations   of   1-(Trimethylsiloxy)Cyclohexene   Transfer

Dehydrogenation

We investigated the transfer dehydrogenation of 1-(trimethylsiloxy)cyclohexene (**67**) to trimethyl(phenoxy)silane (**68**) using complex (*t-Bu4*POCOP)–Ir **c13** and using **TBE** as the H₂ acceptor (Scheme A2.23). The reactions were carried out neat at 200 °C under an argon atmosphere after drying and distilling all reagents. We did no observe **68** and **67** was not activated and unreactive toward complex **c13**.

Scheme A2.23 *1-(Trimethylsiloxy)Cyclohexene Transfer Dehydrogenation Attempts by*

*Complex (*ᵗ⁻ᴮᵘ⁴*POCOP)–Ir* **c13**
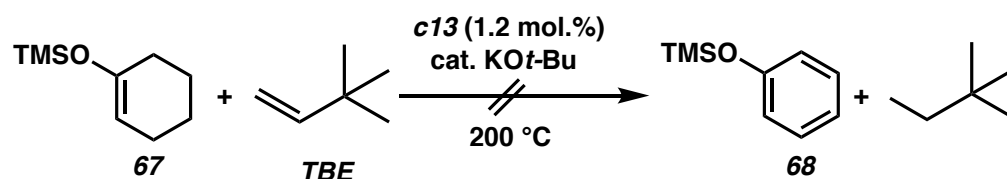
A2.5.8 Investigations of Julolidine Transfer Dehydrogenation

Julolidine (**69**) is a natural product that has been shown to have photoconductive and other useful properties along with its derivatives.[22,23] We wanted to extend the application of Ir pincer ligated complexes as dehydrogenation catalysts on a natural product to demonstrate late stage dehydrogenation ability. We investigated the transfer dehydrogenating of **69** using complex (ᵗ⁻ᴮᵘ⁴POCOP)–Ir **c13** and using both **TBE** and **HEX** as H₂ acceptors (Scheme A2.24). However, we did not observe any olefinic product possibly due to steric hinderance of the investigated substrate and its unreactive nature toward complex **c13**.

A2.5.9 Investigations of Paroxetine Transfer Dehydrogenation

Paroxetine (**71**) is a widely used drug to treat depression and other medical conditions.[24,25] We wanted to extend the application of Ir pincer ligated complexes as dehydrogenation catalysts on drug-like molecules to demonstrate the efficacy of late stage dehydrogenation. We investigated the transfer dehydrogenating of **71** using complex (ᵗ⁻ᴮᵘ⁴POCOP)–Ir **c13** and using both **TBE** and **HEX** as H₂ acceptors (Scheme A2.25). We believe we observed trace amounts of the dehydrogenated product **72**, further investigations are required to validate our findings. Upon

successful confirmation, optimization conditions will be carried out to achieve higher

yields of **72**.

Scheme A2.24 *Julolidine Transfer Dehydrogenation Attempts by Complex*
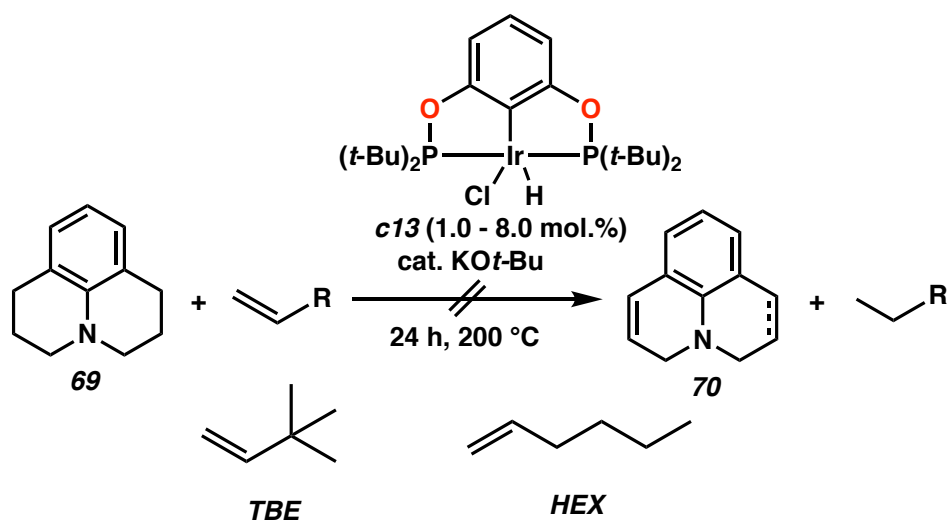
($^{t\text{-}Bu4}$*POCOP*)*–Ir* **c13**

Scheme A2.25 *Paroxetine Transfer Dehydrogenation Attempts by Complex*

($^{t\text{-}Bu4}$*POCOP*)*–Ir* **c13**
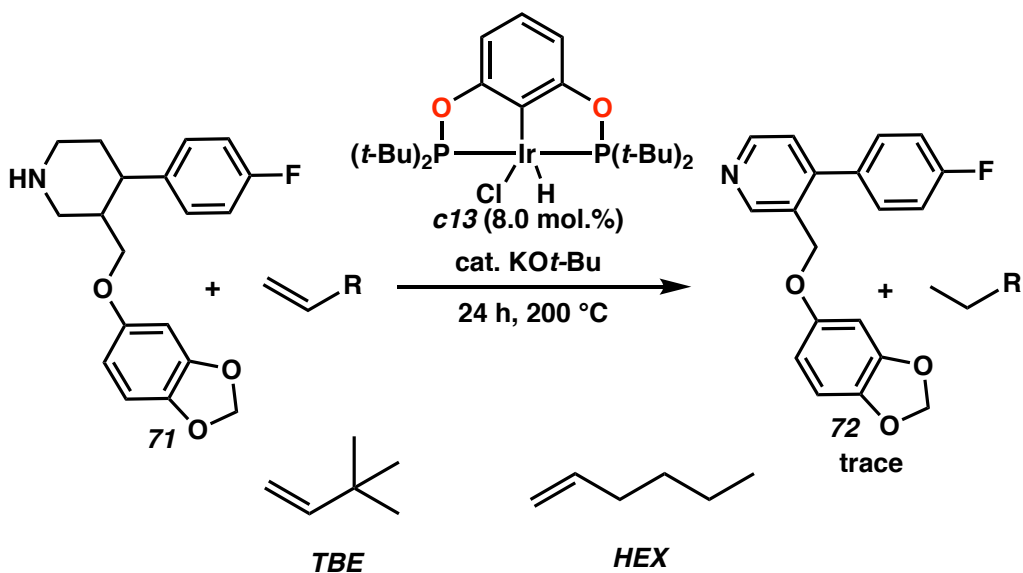
A2.6   SUMMARY AND CONCLUSIONS

Functional aromatics and olefins constitute common substructures in a large variety of complex molecules, materials, and polymers. Hence, there is a great interest in developing methods for the synthesis of substituted and unsubstituted aromatics Utilizing Ir pincer ligated complexes to dehydrogenate functional cycloalkanes is attractive and can be a complementary method toward current approaches. In Chapter 2, we demonstrated the successful transfer dehydrogenation of a diverse collection of heterocyclic alkanes containing functionalities known to strongly coordinate to metal centers and inhibit catalysis. In efforts to expand our scope of work we extended our studies to investigate heterocyclic substrates containing functionalities with halides, carbonyls, five- and six- memebered heterocyclic rings, and thiols (Figure A2.2). However, the direct dehydrogenation of $C(sp^3)$–H alkanes may seem conceptually sipmle but in fact is a challenging trasnformation and in some cases not feasible, especially when dehydrogenating heteroatomic substrates. In the case of **26**, **28**, **30**, **36**, **38**, **40**, **44**, **46**, **52**, **56**, **58**, **60**, **62**, **65**, **67** and **69**, it was not possible to generate a dehydrogenated product due to binding to the Ir metal center, steric hindrance, the basic or acidic nature of the substrate, decomposition of the substrate, isomerization of the substrate, and or unreactivity toward the investigated Ir pincer ligated complexes.

On the other hand, transfer dehydrogenating **24**, **32**, **34**, **42**, **50**, **54**, and **71**, is potentially promising and further investigations are required to validate the obtained product. Upon successful confirmation of the desired product, reaction

conditions will be optimized to achieve higher yields. All in all, the obtained results

showcased the limited capability of Ir pincer ligated complexes as dehydrogenation

catalysts for functionalized heterocyclic substrates.
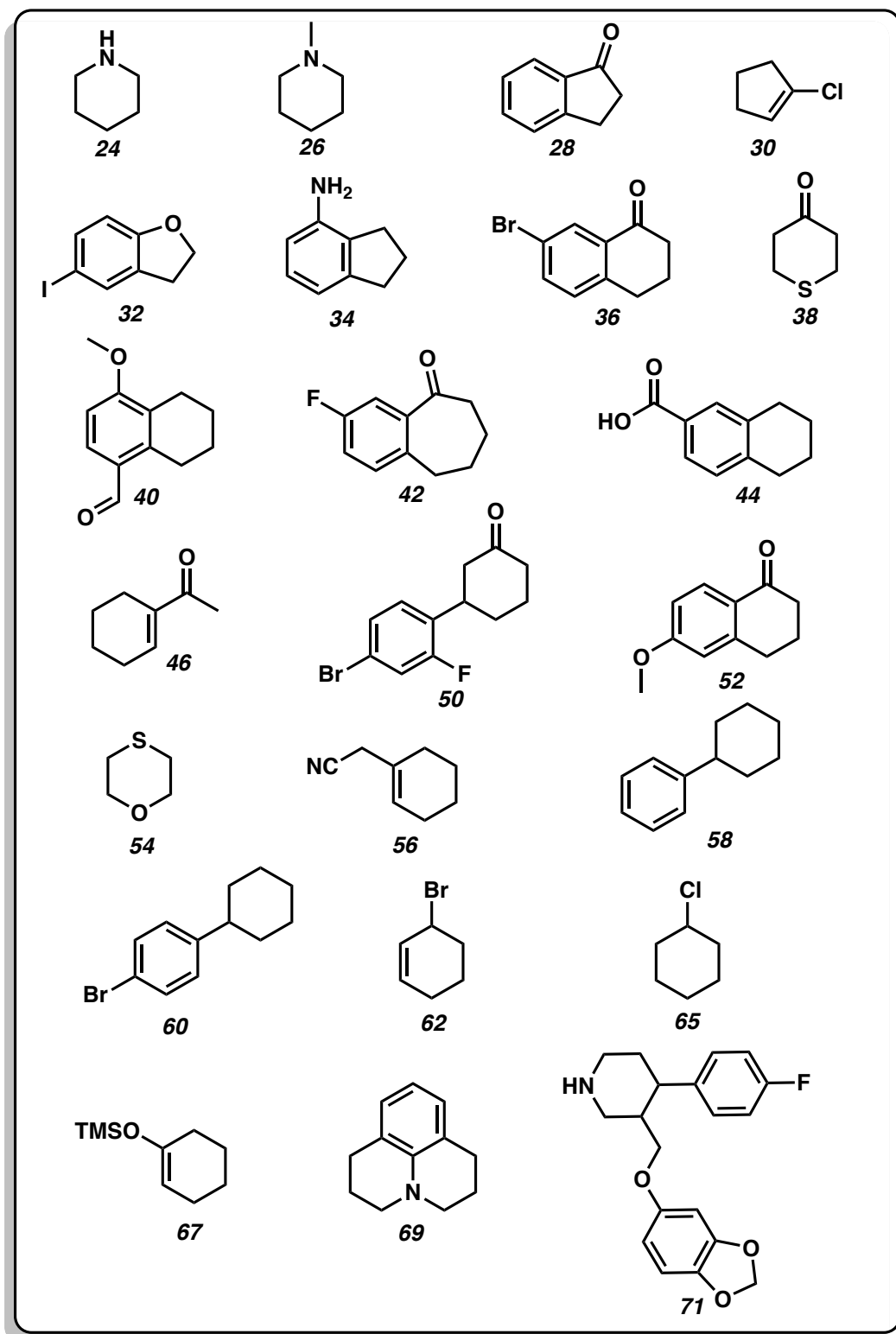
Figure A2.2 *Summary of Investigated Substrate Scope in Appendix 2*

A2.7 NOTES AND REFERENCES

1. Fraser, H. L.; Floyd, M. B.; Barrios Sosa, A. C. In *Prog. Heterocycl. Chem.*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: 2005; Vol. 17, p 261.

2. Yao, W.; Zhang, Y.; Jia, X.; Huang, Z. *Angewandte Chemie International Edition* **2014**, *53*, 1390.

3. Zhang, X.; Fried, A.; Knapp, S.; Goldman, A. S. *Chem. Commun.* **2003**, 2060.

4. Ke, Z.; Tsui, G. C.; Peng, X.-S.; Yeung, Y.-Y. In *Prog. Heterocycl. Chem.*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: 2016; Vol. 28, p 219.

5. Omae, I. *Coord. Chem. Rev.* **2004**, *248*, 995.

6. Fan, Z.; Nakayama, K.; Sawanobori, T.; Hiraoka, M. *Pflügers Archiv* **1992**, *421*, 409.

7. Zhang, X.; Xie, T.; Cui, M.; Yang, L.; Sun, X.; Jiang, J.; Zhang, G. *ACS Appl. Mater. Interfaces* **2014**, *6*, 2279.

8. Somersall, A. C.; Guillet, J. E. *Macromolecules* **1972**, *5*, 410.

9. Denmark, S. E.; Fu, J. *Chemical Reviews* **2003**, *103*, 2763.

10. Kidonakis, M.; Mullaj, A.; Stratakis, M. *The Journal of Organic Chemistry* **2018**, *83*, 15553.

11. Jayaram, V.; Sridhar, T.; Sharma, G. V. M.; Berrée, F.; Carboni, B. *The Journal of Organic Chemistry* **2018**, *83*, 843.

12. Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry: Part A: Structure and Mechanisms*; Carey, F. A., Sundberg, R. J., Eds.; Springer US: Boston, MA, 1977, p 325.

13.   Ranu, B. C.; Jana, R. *Eur. J. Org. Chem.* **2006**, *2006*, 3767.

14.   Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chemical Society Reviews* **2010**, *39*, 2093.

15.   Hayashi, T.; Yamasaki, K. *Chemical Reviews* **2003**, *103*, 2829.

16.   Pahlavan, F.; Hosseinnezhad, S.; Samieadel, A.; Hung, A.; Fini, E. *Industrial & Engineering Chemistry Research* **2019**, *58*, 11939.

17.   Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. *Journal of the American Chemical Society* **2016**, *138*, 3294.

18.   Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A. *Adv. Synth. Catal.* **2013**, *355*, 2203.

19.   Rossi, R.; Lessi, M.; Manzini, C.; Marianetti, G.; Bellina, F. *Synthesis* **2016**, *48*, 3821.

20.   Zhan, Z.-P.; Yang, R.-F.; Lang, K. *Tetrahedron Letters* **2005**, *46*, 3859.

21.   Binder, J. B.; Raines, R. T. *Curr. Opin. Chem. Biol.* **2008**, *12*, 767.

22.   Varejão, J. O. S.; Varejão, E. V. V.; Fernandes, S. A. *Eur. J. Org. Chem.* **2019**, *2019*, 4273.

23.   Enoki, T.; Matsuo, K.; Ohshita, J.; Ooyama, Y. *Phys. Chem. Chem. Phys.* **2017**, *19*, 3565.

24.   Despiau, C. F.; Dominey, A. P.; Harrowven, D. C.; Linclau, B. *Eur. J. Org. Chem.* **2014**, *2014*, 4335.

25.   Vardanyan, R. In *Piperidine-Based Drug Discovery*; Vardanyan, R., Ed.; Elsevier: 2017, p 299.

APPENDIX 3

EXPERIMENTAL SECTION AND SPECTRA RELEVANT TO
APPENDIX 2

A3.1 MATERIALS AND METHODS

Unless noted in the specific procedure, reactions were performed in oven-dried glassware. All dehydrogenation reactions were degassed by freeze-pump-thaw x 5 cycles and were carried out under air-free conditions in dry glassware. All liquid reagents were purified by distillation and dried using molecular sieves, NaH, or Na-K alloy. For all the investigated dehydrogenation systems, the substrate was mixed with the H_2 acceptor in a 4 mL sealed Schlenk pressure flask under an argon atmosphere. Then synthesized Ir pincer complexes were added to the reaction mixture with at least 1.2 equivalents of the Ir pincer complexes of KO*t*-Bu when the Ir–HCl version of catalyst is used.

^{1}H NMR spectra were recorded on Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, and are reported in

terms of chemical shift relative to residual CHCl$_3$ (δ 7.26). Dehydrogenation conversions were determined using ^{1}H NMR with cis-1,4-diacetoxy-2-butene standard.

In addition, the conversions were determined using an Agilent 6850 GC-FID equipped with a Supelco column (SPB^{TM}-1, fused silica capillary column, 30 m x 0.25 μm film thickness) and using methods with temperature programs shown in Table A3.1 and inlet program shown in Table A3.2.

Table A3.1 *ZAS2 General Method Temperature Ramping Program for The Investigated Substrates in Appendix 2*

Oven Ramp	°C/min	Next °C	Hold min
Initial	-	38	1.50
Ramp 1	10.00	150	0.00
Ramp 2	20.00	250	5.00

Table A3.2 *Inlet Parameters used in All Methods*

Inlet	Setting
Mode	Split
Gas	He
Heater	250 °C
Pressure	9.52 psi
Total Flow	82.2
Split Ratio	100:1
Split Flow	78.5 mL/min

A3.2 GENERAL PROCEDURE FOR DEHYDROGENATION REACTIONS

For all the investigated dehydrogenation systems, 3.2 to 4.0 mmol of the substrate was mixed with the state equivalence of the H_2 acceptor in a 4 mL sealed Schlenk pressure flask under an argon atmosphere. Then the synthesized Ir pincer ligated complex was added to the reaction mixture with at least 1.2 catalytic equivalents of KO*t*-Bu under an argon atmosphere. The reaction mixture was then dried by freeze-pump-thaw method x five cycles and then backfilled with argon gas. Lastly, the Schlenk flask was placed in heated silicone oil stirring for the duration of reaction and specified temperature.

A3.3   SYNTHESIS   PROCEDURE   OF

3-(4-BROMO-2-FLUOROPHENYL)CYCLOHEXAN-1-ONE
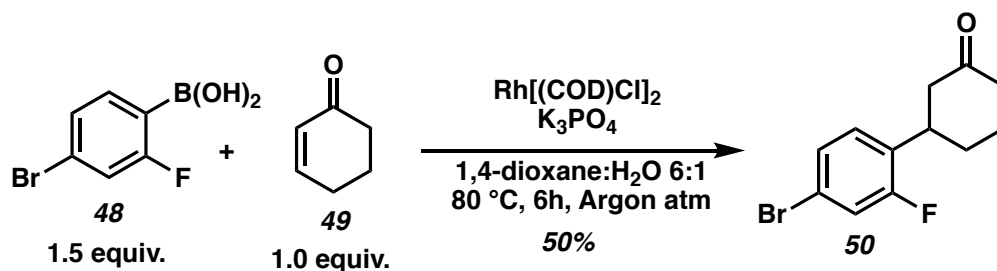
An 8 mL vial was charged with 0.40 g (1.8 mmol) of 4-bromo-2-fluorobenzeneboronic acid (**48**), 0.14 mL (1.2 mmol) of 2-cyclohexenone (**49**), 50 mg of [Rh(COD)Cl]$_2$, 0.66 g (3 mmol, 3 Molar) of K$_3$PO$_4$ in 1 mL DI H$_2$O, and 5 mL dioxane and an argon atmosphere. Then the reaction mixture was heated at 80 ºC for 6 h. After cooling the reaction mixture, the generated product **50** was extracted *via* a silica column using a 1:4 mixture of diethyl ether and pentane and then dried under vacuum. The obtained product was a colorless viscous liquid.

4'-bromo-2'-fluoro-[1,1'-biphenyl]-3-ol (**51**) : ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.18 (m, 1H), 7.16 (dd, *J* = 9.9, 2.0 Hz, 1H), 7.06 – 7.00 (m, 1H), 3.20 (tdd, *J* = 11.0, 5.8, 3.5 Hz, 1H), 2.50 – 2.23 (m, 4H), 2.14 – 1.88 (m, 2H), 1.89 – 1.62 (m, 2H).

A3.4 ¹H NMR SPECTRA OF REACTIONS
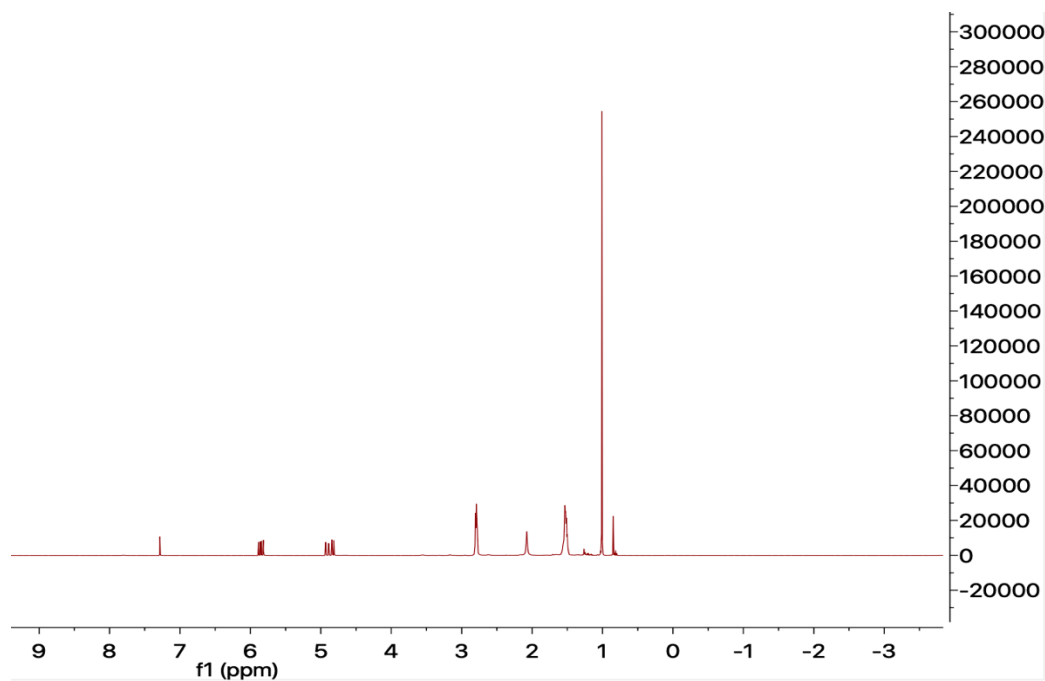
Figure A3.1 *Table A2.1 Entry 1: Crude Reaction of Piperidine (**24**) Showing No Conversion*
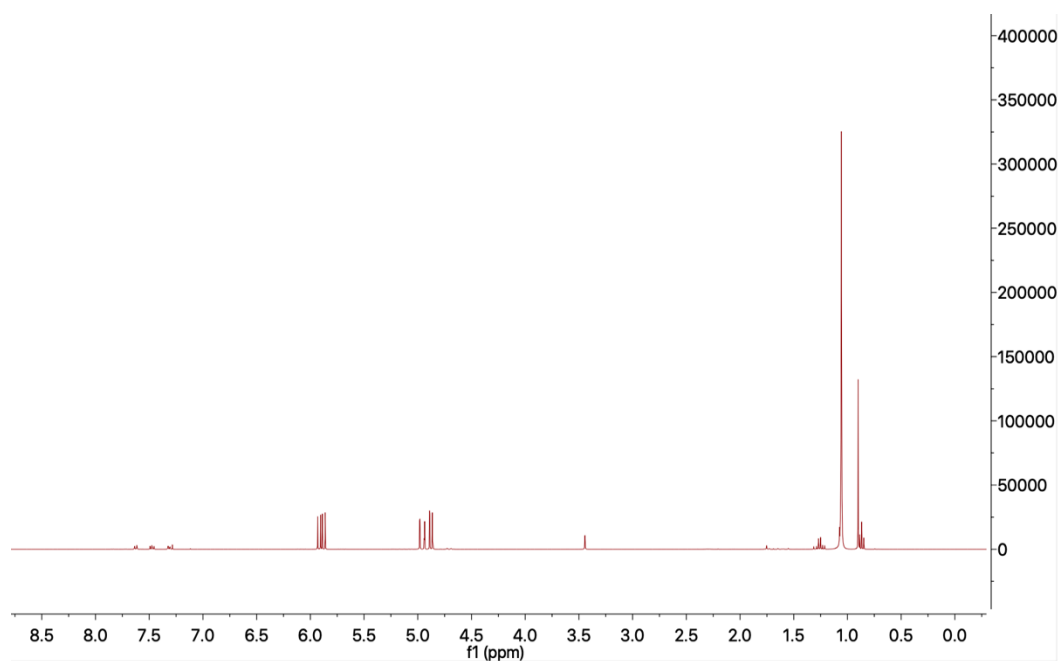
Figure A3.2 *Table A2.1 Entry 5: Crude Reaction of Piperidine (**24**) Showing No Conversion*
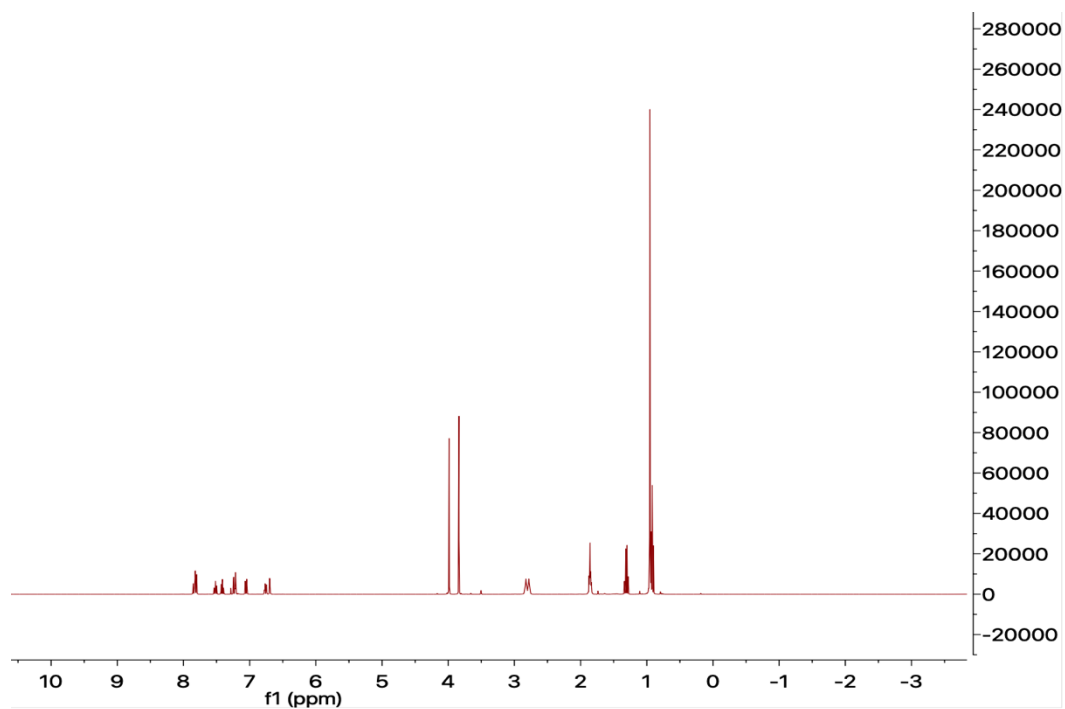
Figure A3.3 *Table A2.1 Entry 6: Crude Reaction of Piperidine (24) Showing Low Conversion*
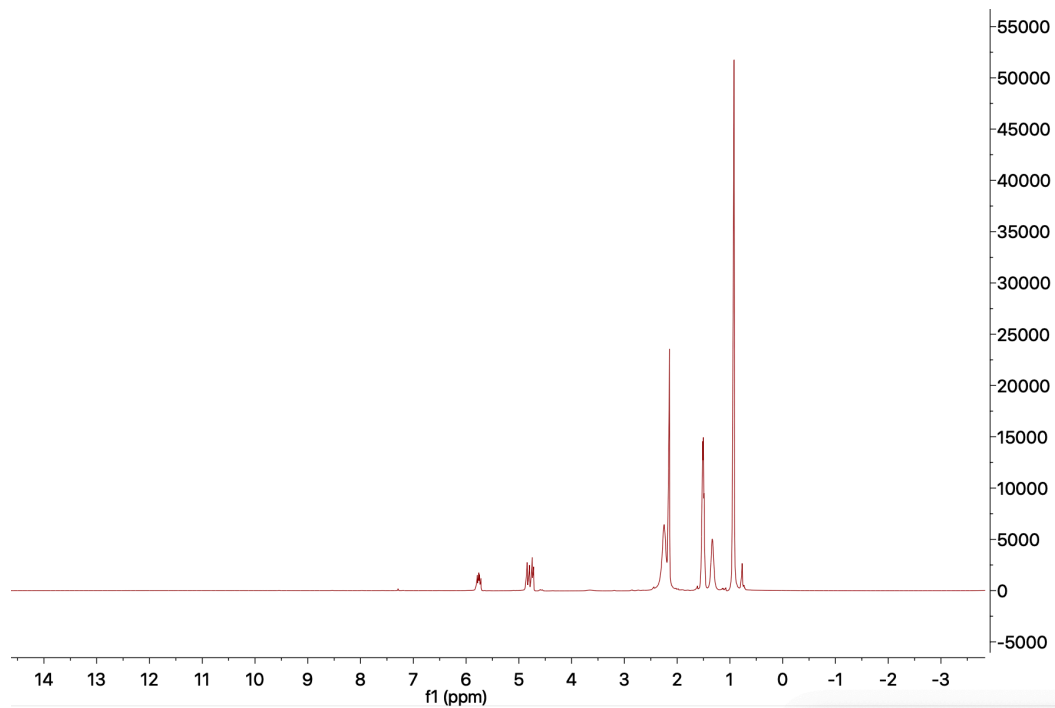
Figure A3.4 *Scheme A2.1: Crude Reaction of N-Methylpiperidine (26) Showing No Conversion*
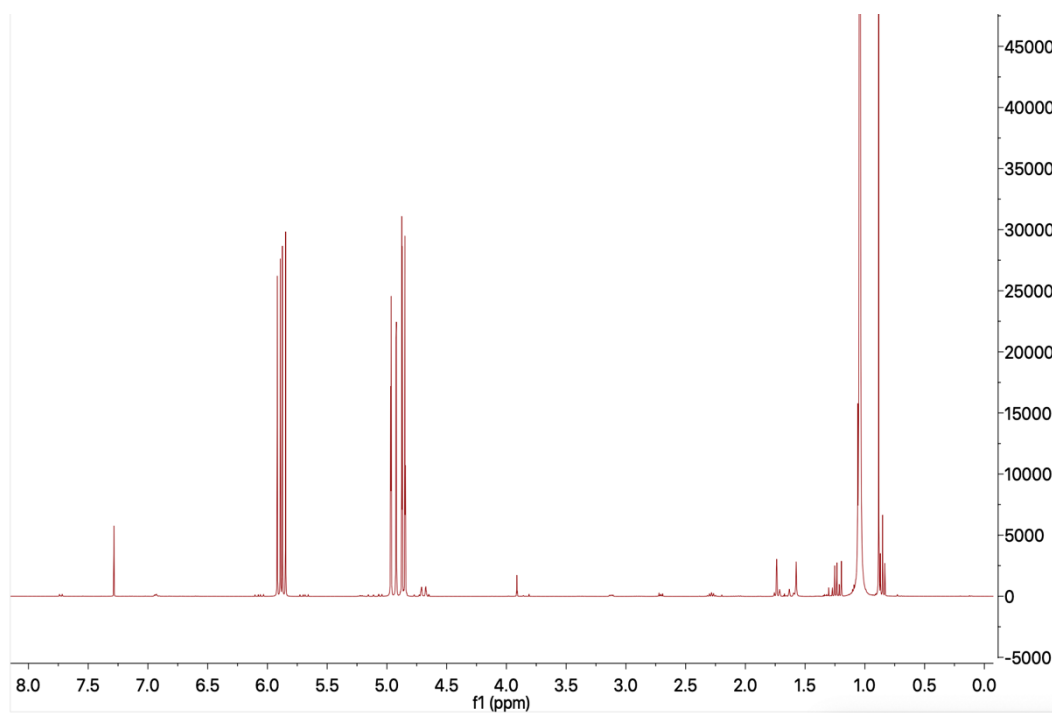
Figure A3.5 *Scheme A2.2: Crude Reaction of 5-Methoxy-1-Indanone (**28**) Showing*

Decomposition
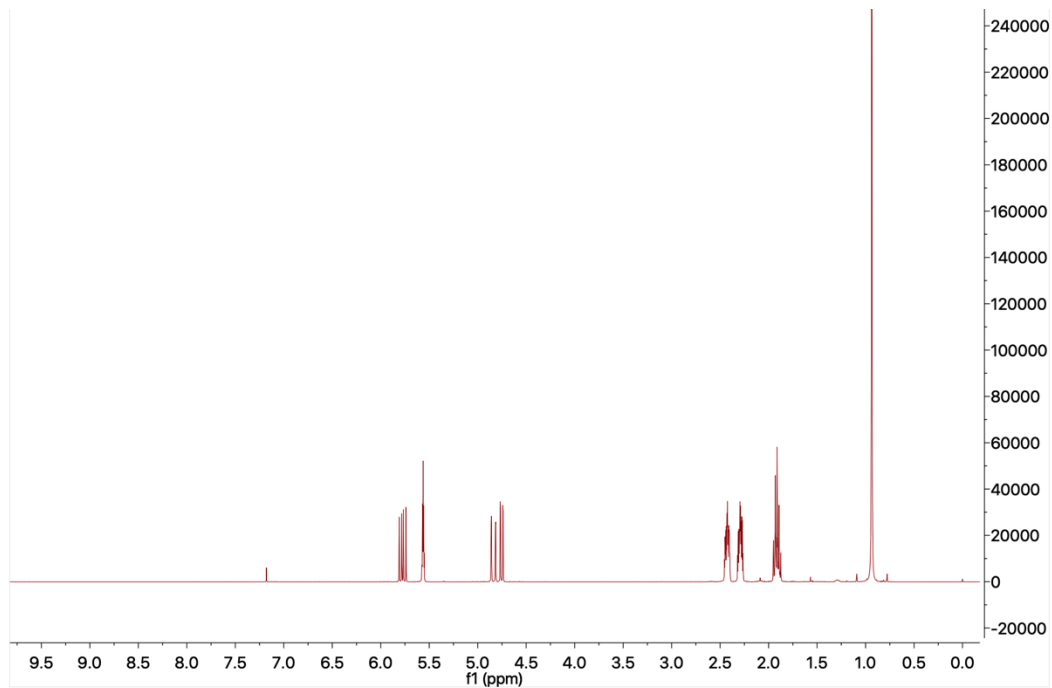
Figure A3.6 *Scheme A2.3: Crude Reaction of 1-Chlorocyclopentene (**30**) Showing No*

Conversion
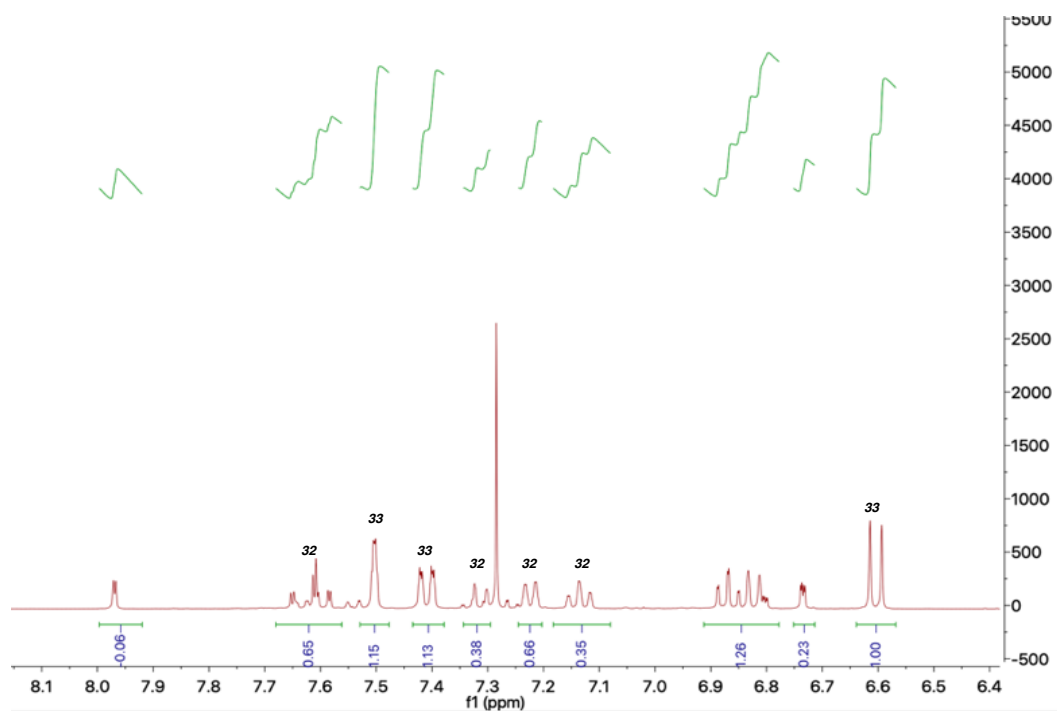
Figure A3.7 Table A2.2 Entry 1: Crude Reaction of 5-Iodo-2,3-Dihydrobenzofuran (**32**)

Showing Conversion to 5-Iodobenzofuran (**33**)
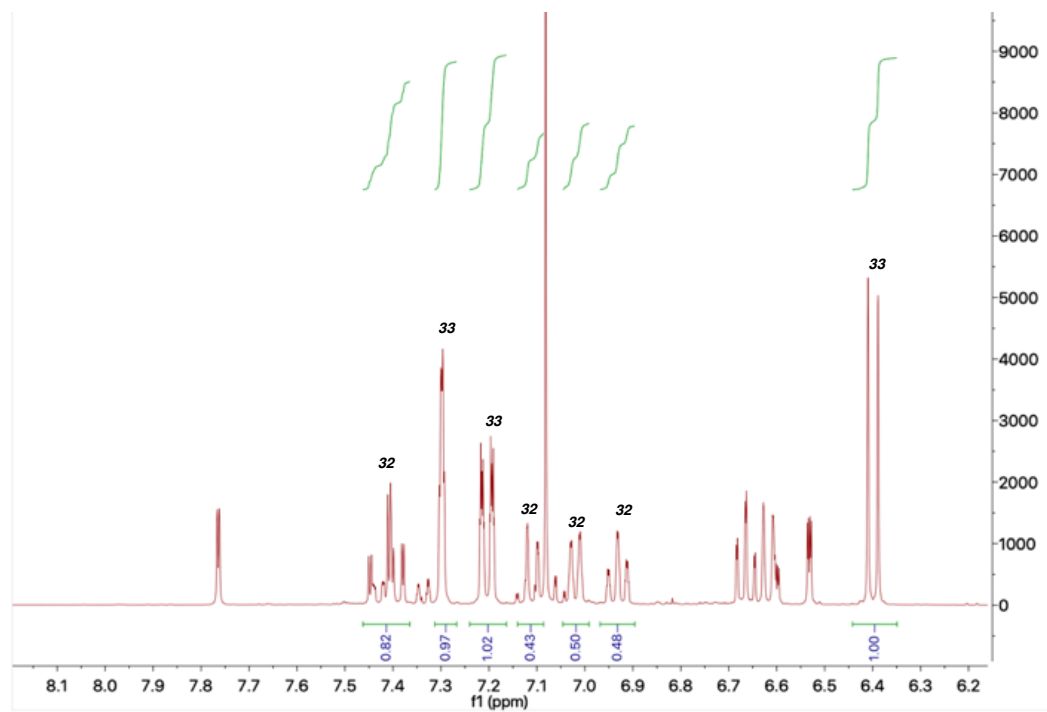
Figure A3.8 Table A2.2 Entry 2: Crude Reaction of 5-Iodo-2,3-Dihydrobenzofuran (**32**)

Showing Conversion to 5-Iodobenzofuran (**33**)
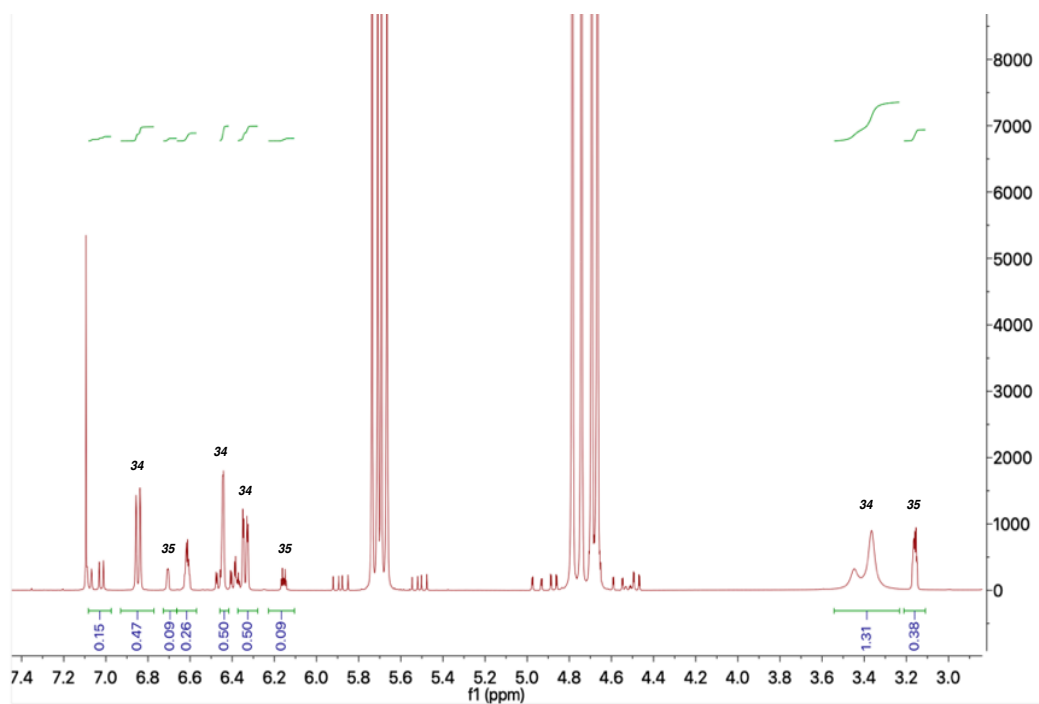
Figure A3.9 *Scheme A2.4: Crude Reaction of 4-Aminoindan (**34**) Showing Low conversion to **35***
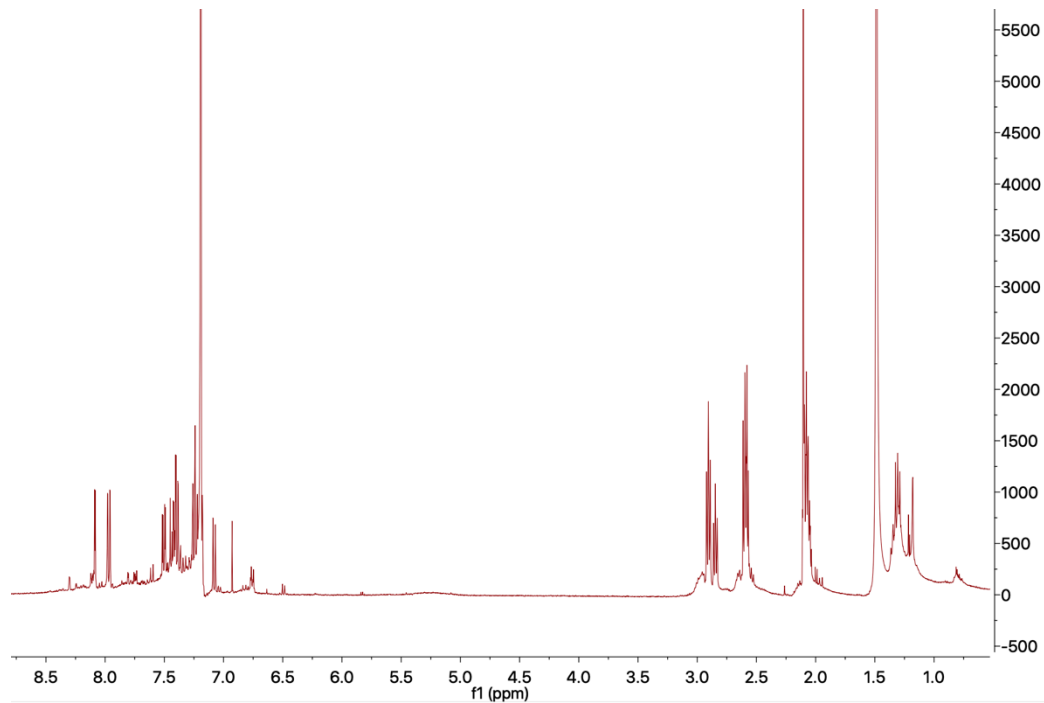
Figure A3.10 *Scheme A2.5: Crude Reaction of 7-Bromo-1-Tetralone (**36**) Showing Debromination to 1-Tetralone (**18**) and Some Conversion to Naphthol (**19**)*
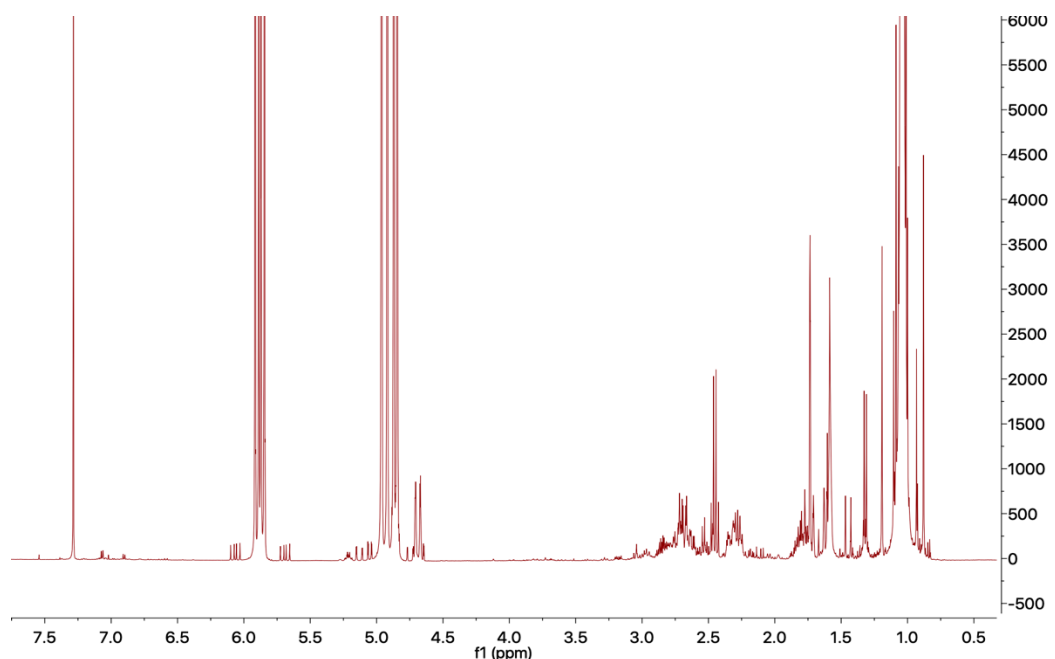
Figure A3.11 *Scheme A2.7: Crude Reaction of Tetrahydrothiopyran-4-one* **(38)** *Showing No Conversion*
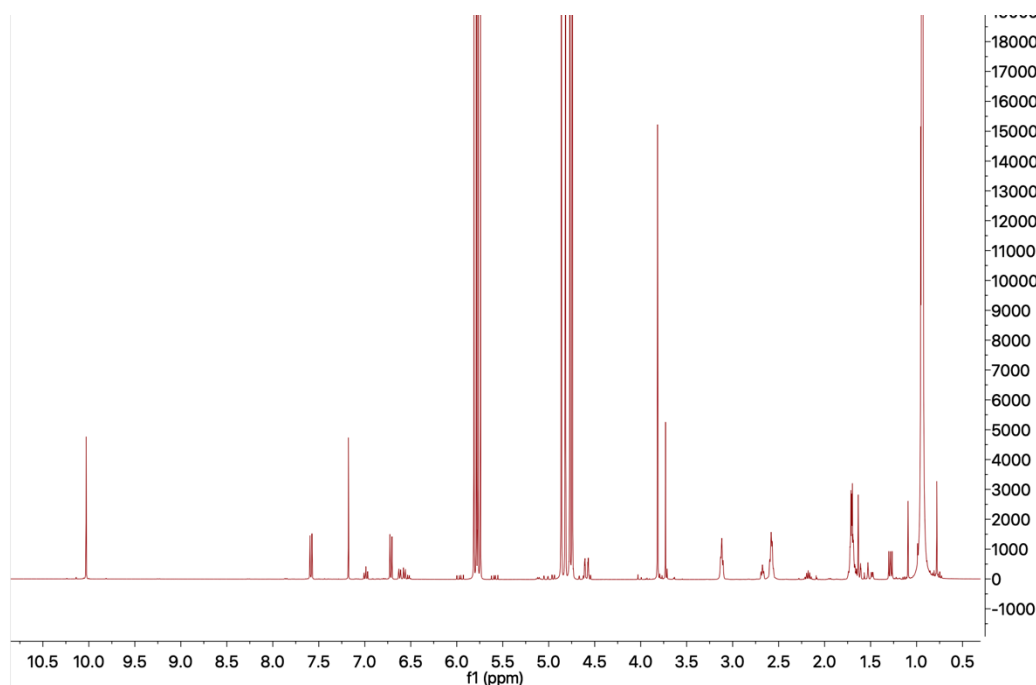
Figure **A3.12** *Scheme* *A2.8:* *Crude* *Reaction* *of* *4-Methoxy-5,6,7,8-Tetrahydronaphthalene-1-Carbaldehyde* **(40)** *Showing* *No* *Conversion*
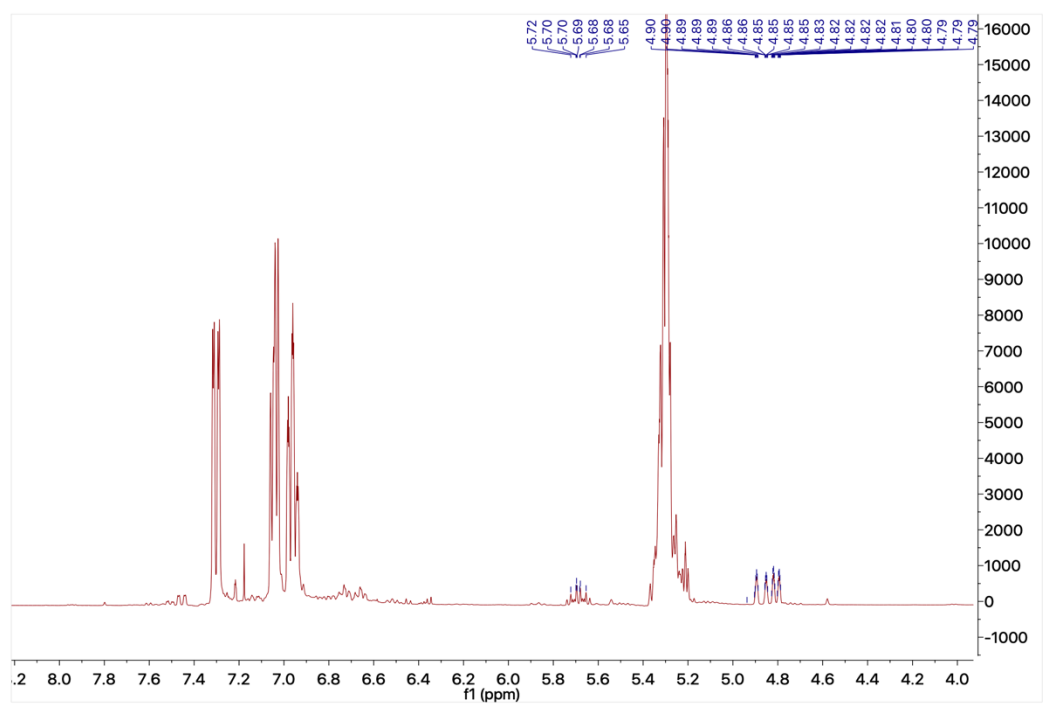
Figure A3.13 *Scheme A2.9: Crude Reaction of 8-Fluoro-1-Benzosuberone (**42**)*

*Showing Possible Trace of **43** with Olefinic Peaks at 5.69 ppm and 4.83 ppm*
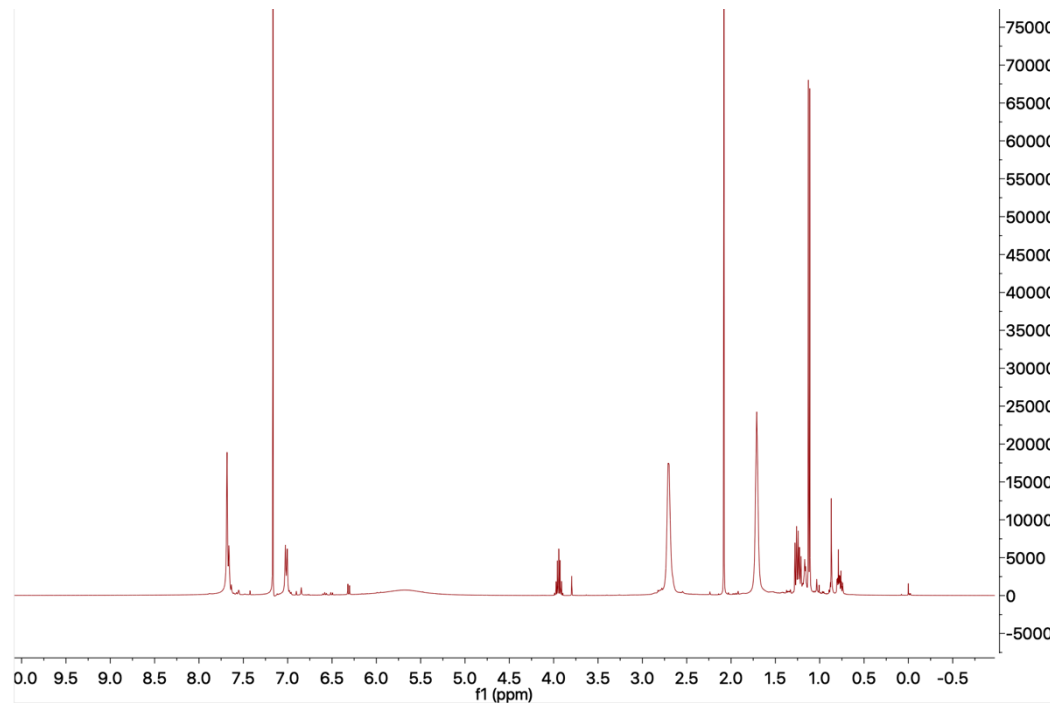
Figure A3.14 *Scheme A2.10: Crude Reaction of 5,6,7,8-Tetrahydro-2-Naphthoic Acid*

*(**44**) Showing No Conversion*
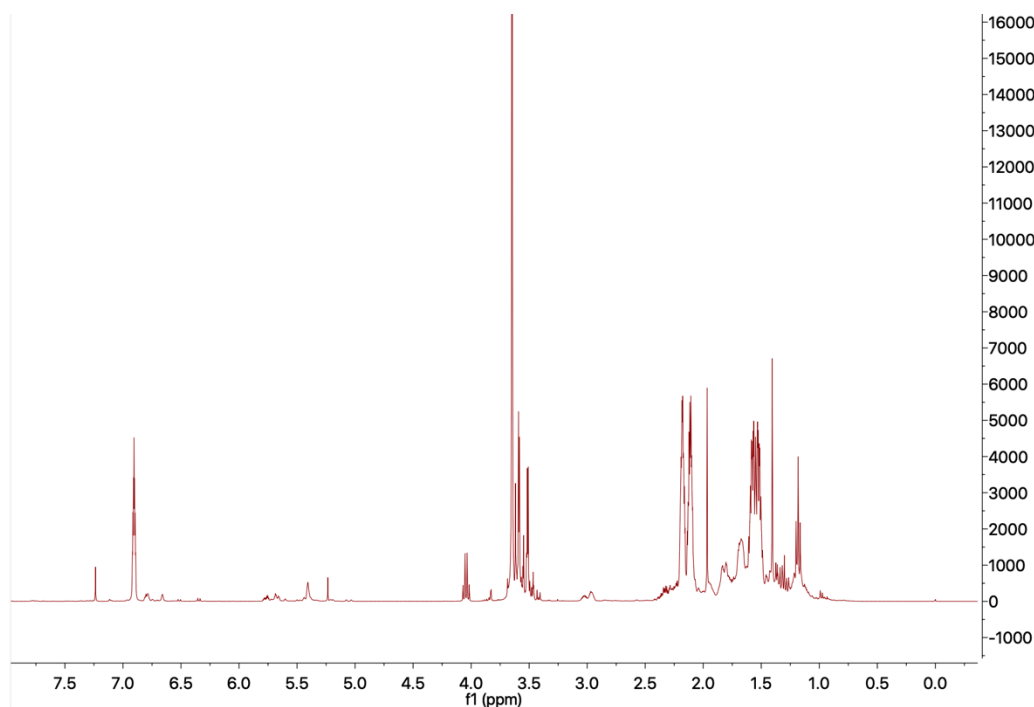
Figure A3.15 *Scheme A2.11: Crude Reaction of 1-Acetylcyclohexene (**46**) Showing No Conversion*
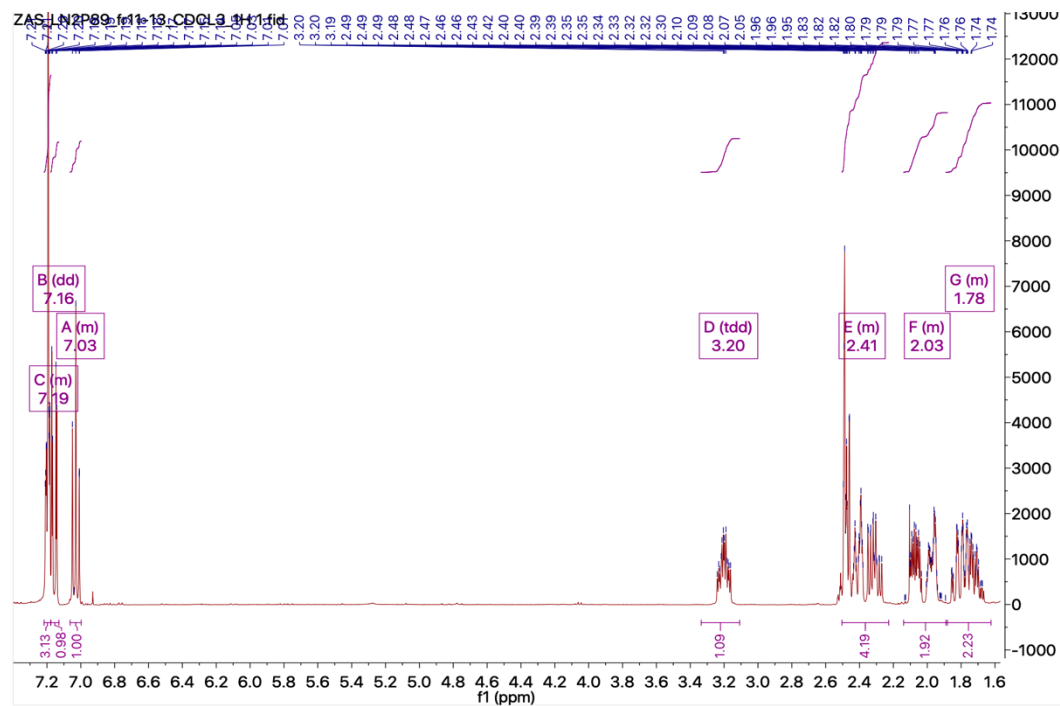
Figure A3.16 *Scheme A2.12: ¹H NMR of Synthesized 3-(4-Bromo-2-Fluorophenyl)Cyclohexan-1-one (**50**)*
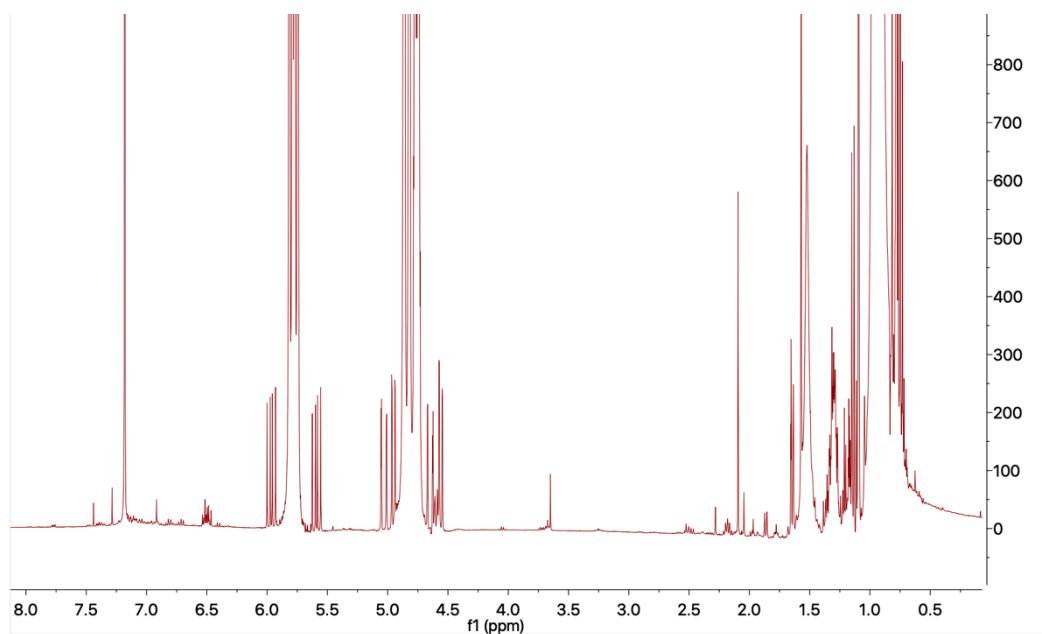
Figure A3.17 *Scheme A2.13: Crude Reaction of 3-(4-Bromo-2-Fluorophenyl)Cyclohexan-1-one (50) Showing Disappearance of Diagnostic ¹H NMR Shift at 3.20 ppm*
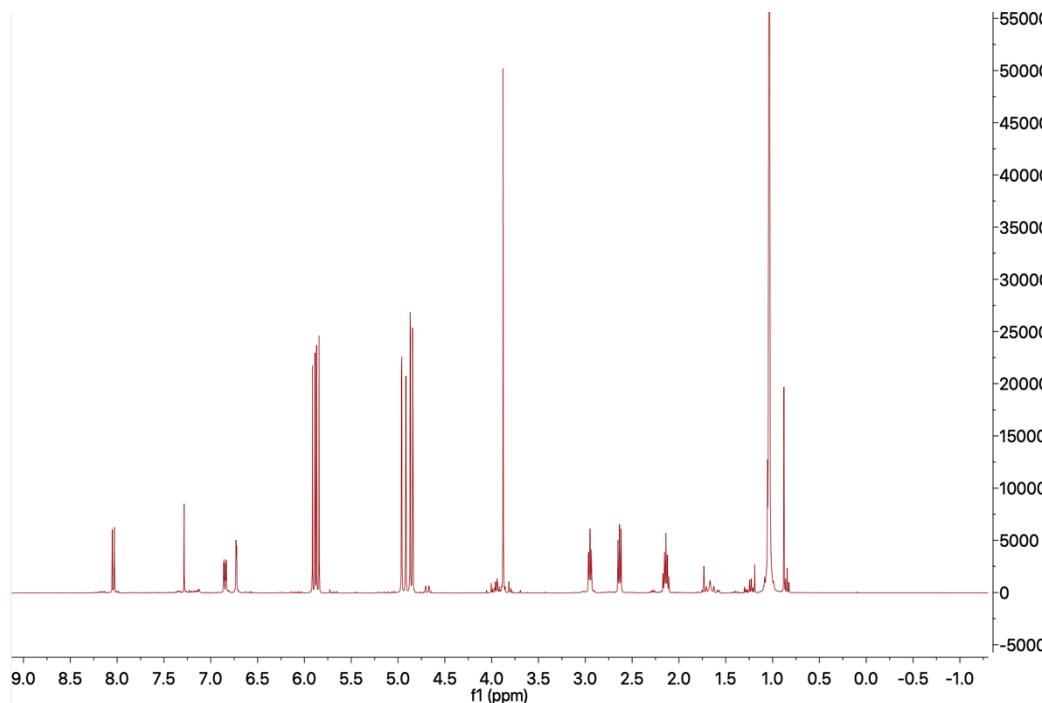
Figure A3.18 *Scheme A2.14: Crude Reaction of 6-Methoxy-3,4-Dihydronaphthalen-1(2H)-one (52) Showing No Conversion*
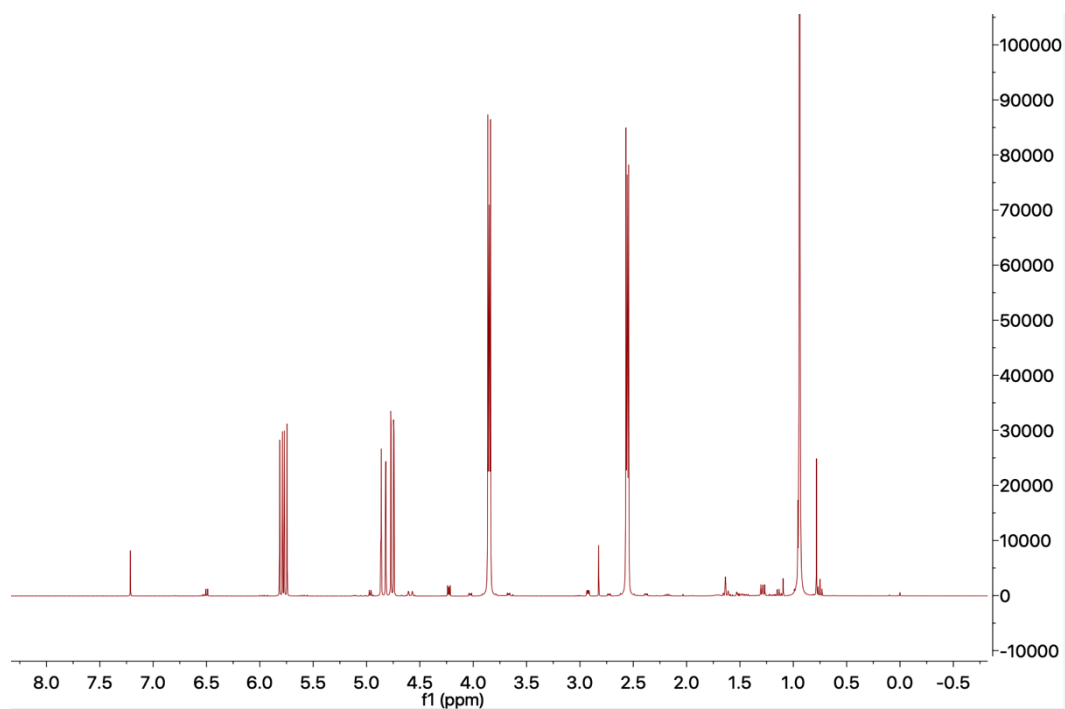
Figure A3.19 *Scheme A2.15: Crude Reaction of 1,4-Thioxane (**54**) Showing Trace*

*Conversion to **55***
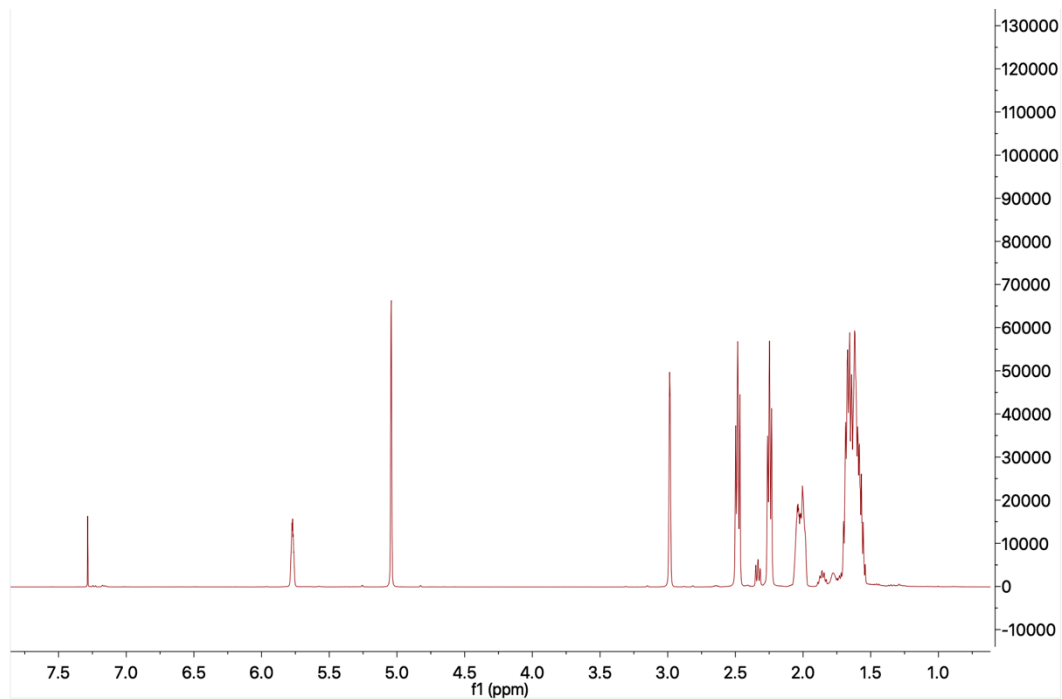
Figure A3.20 *Scheme A2.16: Crude Reaction of 2-Cyclohexene-1-Acetonitrile (**56**)*

*Showing Isomerization of **56***
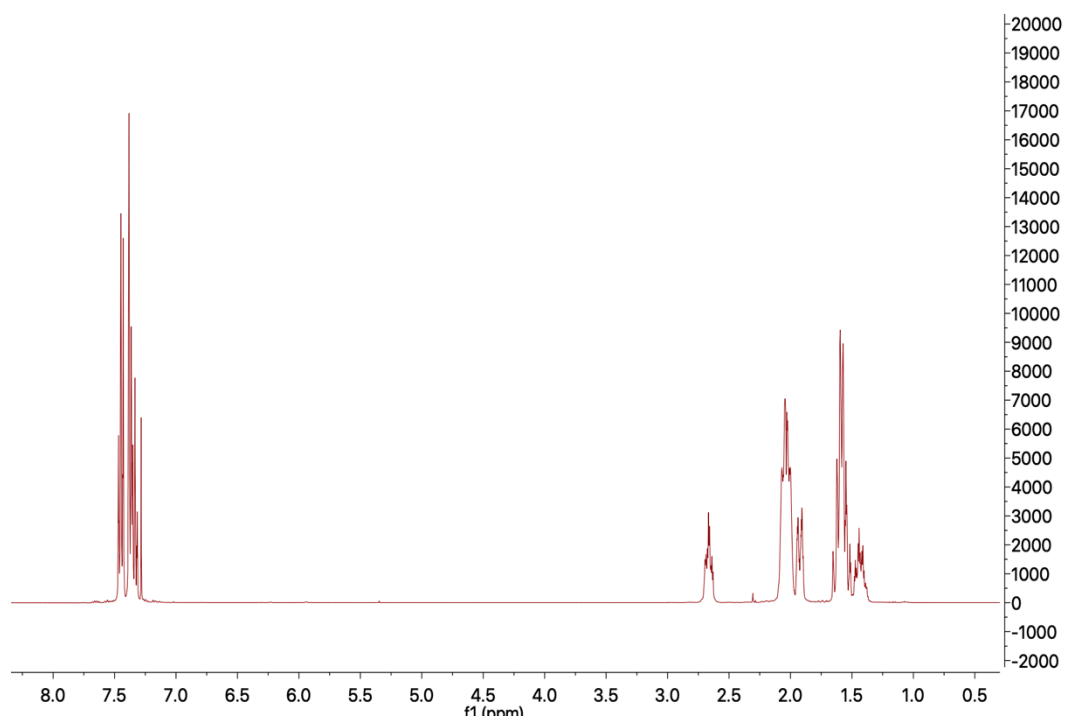
Figure A3.21 *Scheme A2.17: Crude Reaction of Phenylcyclohexane (**58**) Showing No*

Conversion
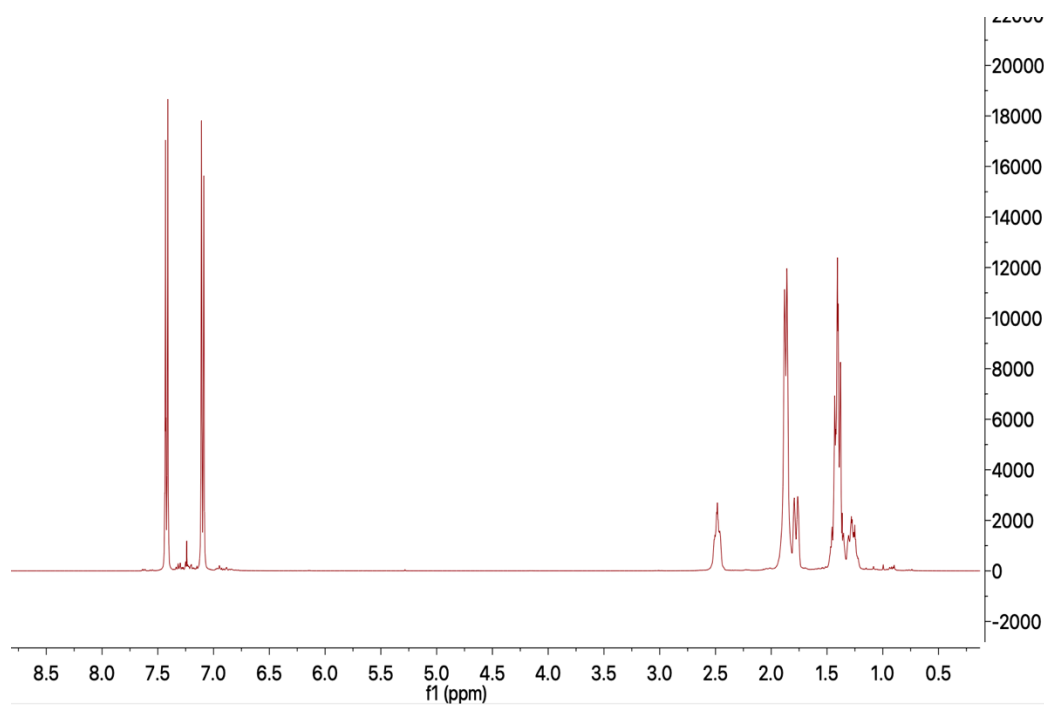
Figure A3.22 *Scheme A2.18: Crude Reaction of 1-Bromo-4-Cyclohexylbenzene (**60**)*

Showing No Conversion
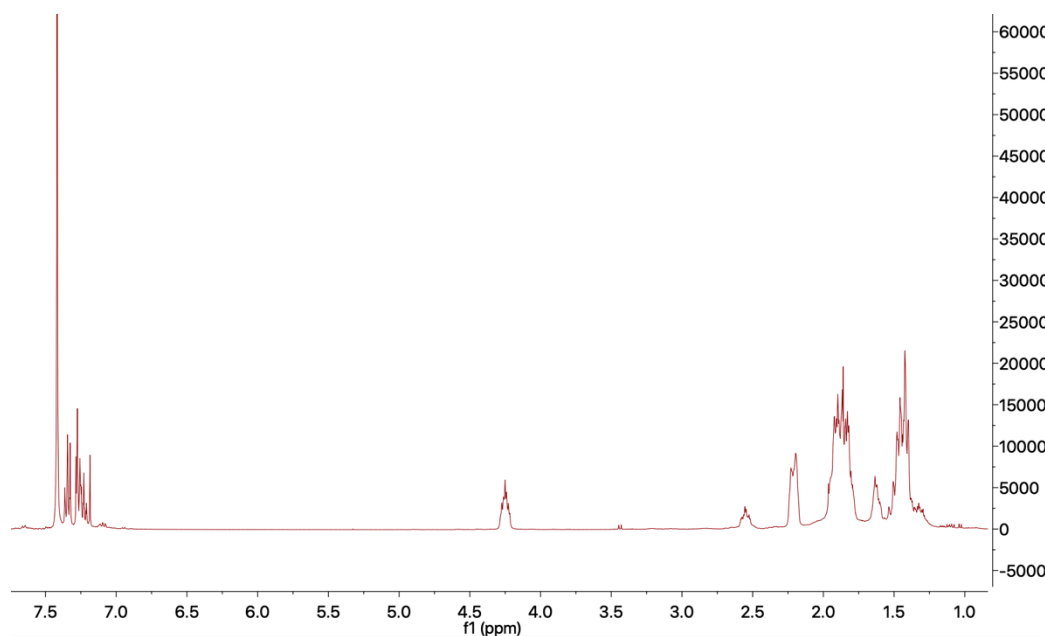
Figure A3.23 *Scheme A2.19: Crude Reaction of 3-Bromocyclohexene (**62**) Showing Conversion to **64** and **58***
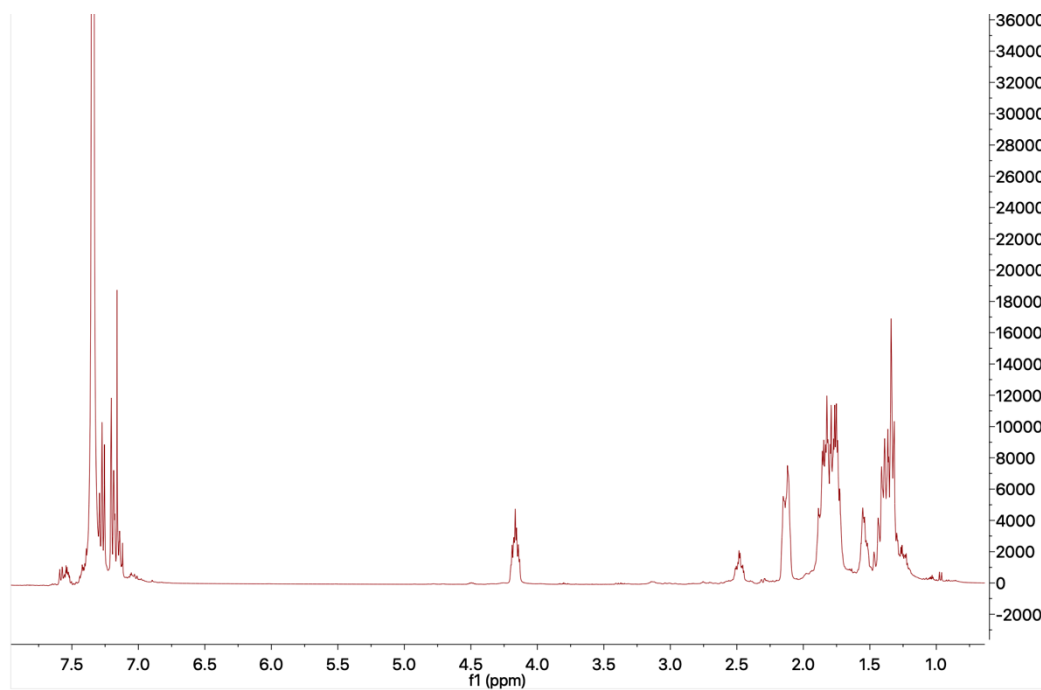
Figure A3.24 *Scheme A2.20: Crude Reaction of 3-Bromocyclohexene (**62**) Showing Conversion to **64** and **58***
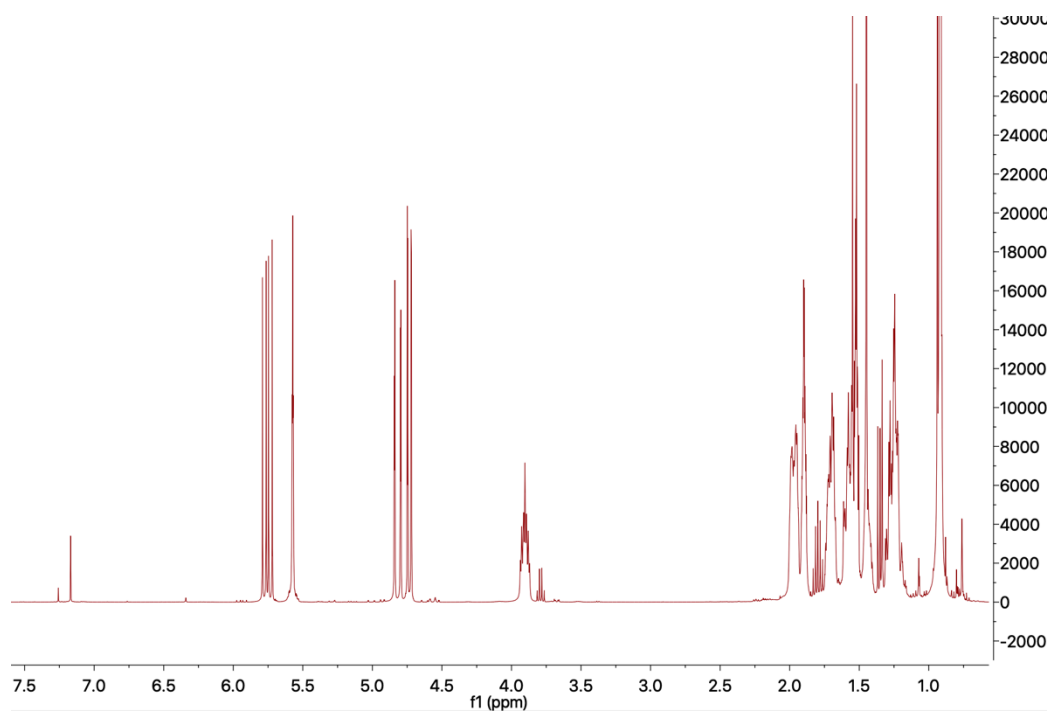
Figure A3.25 *Schemes A2.21 and A2.22: Crude Reaction of Chlorocyclohexane (**65**)*

Decomposition to 1-Cyclohexene, Cyclohexane, and Benzene
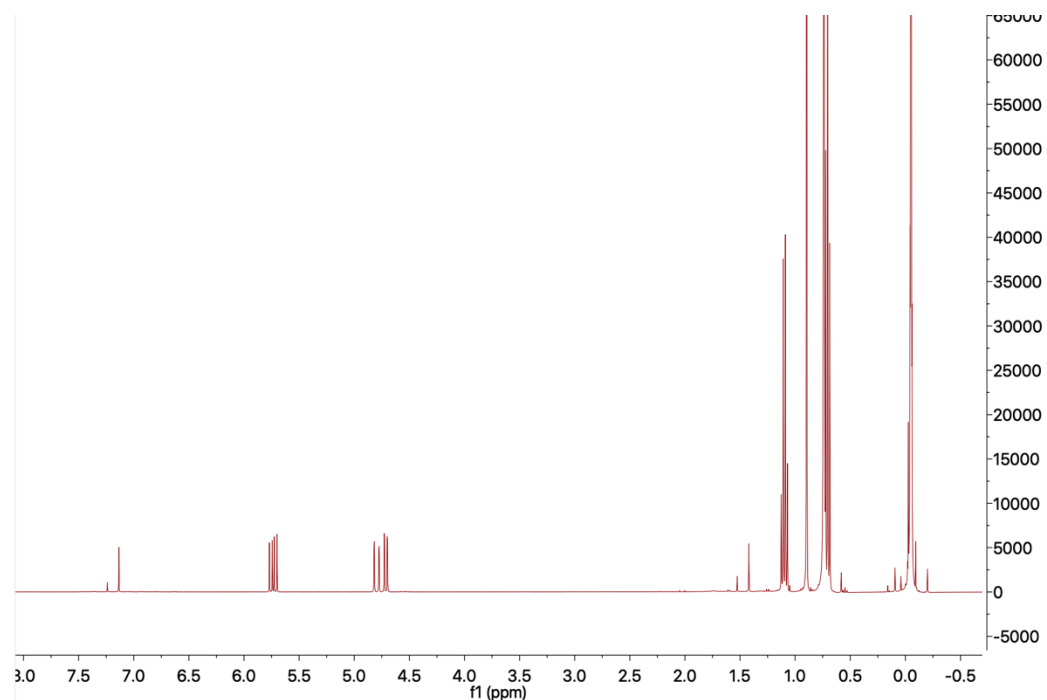
Figure A3.26 *Schemes A2.23: 1-(Trimethylsiloxy)Cyclohexene (**67**) Showing No*

Conversion
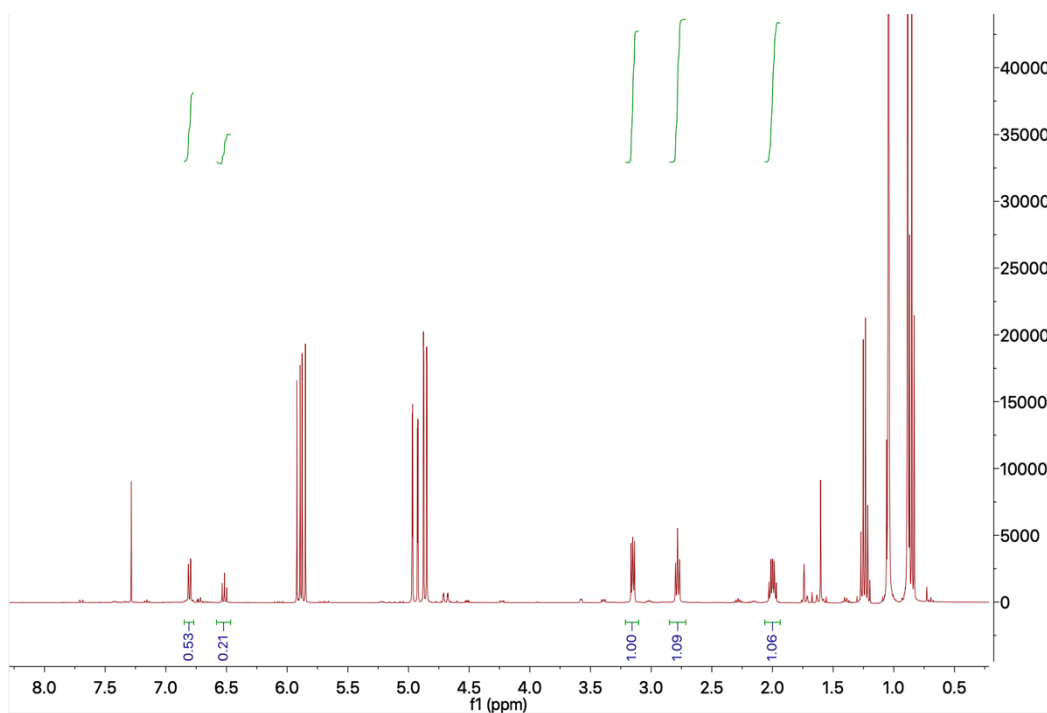
Figure A3.27 *Scheme A2.24: Crude Reaction of Unreacted Julolidine (**69**) and No Conversion*
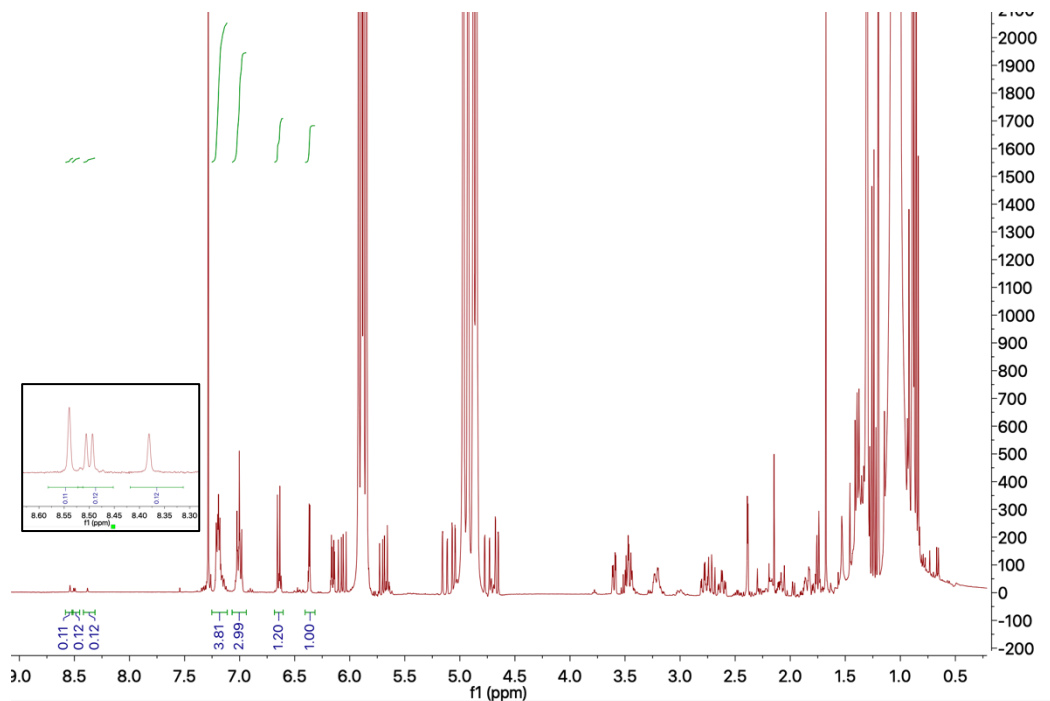
Figure A3.28 *Scheme A2.25: Crude Reaction of Paroxetine (**71**) Showing Trace Conversion to **72***

APPENDIX 4

*PROGRESS TOWARD THE SYNTHESIS OF A NOVEL
ASYMMETRIC NHC-PHOSPHONITE HYBRID PINCER LIGAND*

A4.1   INTRODUCTION

Most of the early examples of studied complexes showed poor thermal stability at the temperatures needed to achieve reasonable reaction rates. Pincer ligated complexes, however, were found to be thermally stable at these elevated temperatures, making them useful for this transformation.[1] These complexes are stable due to the tridentate coordination of ligands with the metal center. In 1996, Jensen and co-workers reported the first thermally stable pincer ligated complex, ($^{t\text{-}Bu4}$PCP)–Ir **c3**.[2-4] Since then, variations of complex **c3** have been reported with different aryl backbones, various linkers, and ligating groups (Figure A4.1).[5-6]
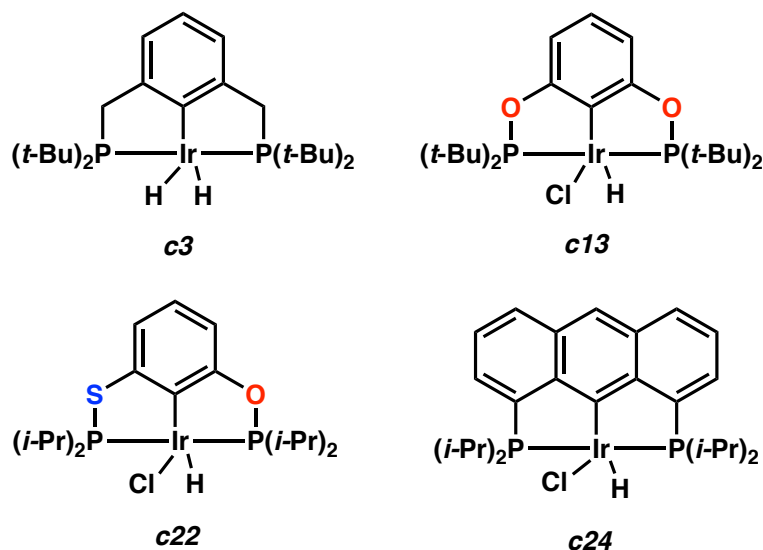
Figure A4.1 *Various Reported Ir Pincer Ligated Complexes*

That being said, it was found that varying the electronics around the Ir metal center is not as effective as varying the geometry and steric effects in improving catalytic activity.[7] We have also demonstrated the different reactivities of ($^{t\text{-}Bu4}$POCOP)–Ir **c13**, ($^{i\text{-}Pr4}$PSCOP)–Ir **c22**, and ($^{i\text{-}Pr4}$anthraphos)–Ir **c24** when dehydrogenating heterocyclic substrates and the varying tolerance to different functionalities. The results we obtained indicated varying steric hinderance around the Ir metal center contributed a major role in the observed variant reactivities.

Hence, we were interested to synthesize a novel asymmetric NHC-phosphinite ligand and metalate it generating complex ($^{t\text{-}Bu2}$Mes-NHCCOP)–Ir **c31** (Figure A4.2). We hypothesize this complex could potentially increase Ir catalytic activity in dehydrogenating heterocyclic substrates to functionalized arenes

and unsubstituted cyclic alkanes to aromatics due to the increased steric effects and

the geometry around the metal center from the NHC.
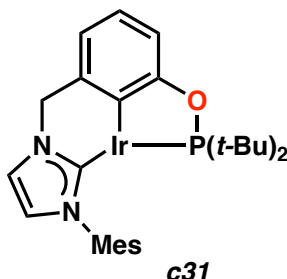
proposed novel hybrid NHC-phosphonite complex

Figure A4.2 *Proposed Novel Asymmetric NHC-Phosphonite Complex*
(t-Bu2Mes-NHCCOP)–Ir c31

A4.2   RELATED LITERATURE

Braunstein and co-workers reported the first hybrid imidazolium-phosphinite
*(t-Bu2n-*Bu-NHCCOP)–Ir **c32** complex in 2013 and employed it as a dehydrogenation

catalyst when transfer dehydrogenating the **COA/TBE** system in a preliminary

investigation (Scheme A4.1).[8] They found that complex **c32** exhibited low catalytic

activity and only 0.48% of cyclooctene was obtained.

Scheme A4.1 *Reported NHC-Phosphonite Complex (t-Bu2n-Bu-NHCCOP)–Ir* **c32** *by*

Braunstein
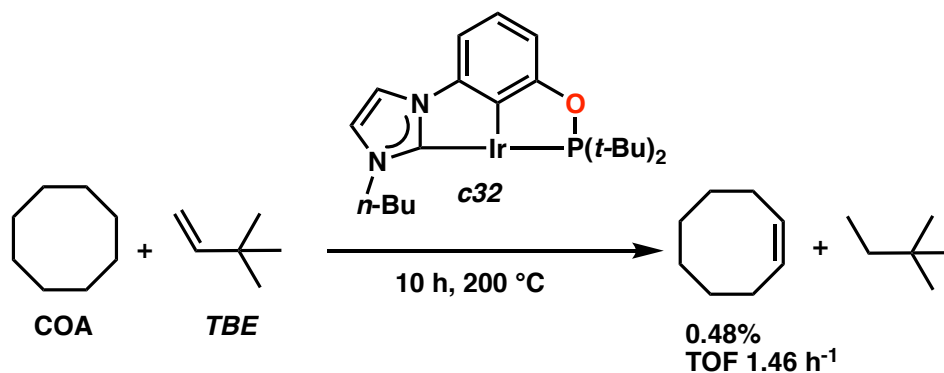
Braunstein 2013

Although Braunstein and co-workers reported low catalytic activity for their

catalyst, they explained that the low insolubility of complex **c32** in neat alkanes may

be a factor contributing to its poor performance in dehydrogenating **COA**. However,

we believe our proposed complex **c31** could be promising in this context for three

reasons. First, Braunstein noted that switching the NHC side group from a methyl to

an n-Bu increased catalytic activity. In our proposed complex **c31**, we propose to

use a mesityl (Mes) NHC which would enhance solubility in neat alkanes. Second,

it was noted that the stronger σ-donor properties of the NHC ligands should facilitate

the C–H oxidative addition step of the alkane while disfavoring the reductive

elimination of the product. We anticipate that changing the geometry around the Ir

metal center and increasing the bulk on the NHC ligand from the Mes group could

potentially enhance its catalytic activity by making the reductive elimination of the

product more favorable relatively. Third, NHC ligands generally exhibit higher

thermal stability than their phosphine analogues, hence higher temperatures could be

investigated in transfer dehydrogenation systems using our proposed complex **c31**.[9]

For these reasons we believe our proposed complex **c31** could be a good candidate for catalyzing dehydrogenation reactions

A4.3   Synthesis of $^{t\text{-}Bu2}$Mes-NHCCOP Ligand 91

Modifying the Braunstein and Heinekey published procedures, we first synthesized 3-hydroxybenzylbromide (**88**) by treating 3-hydroxybenzenealcohol (**87**) with PBr$_3$ according to Voegtle and co-workers procedure (Scheme A4.2).[8, 10-11] Then we treated **88** with an equivalent of 1-mesitylimidazole (**89**) affording 1-mesityl-3-(3-hydroxybenzyl) imidazole salt (**90**). The diagnostic ^{1}H NMR shift is the NC*H*N observed at 9.60 ppm with purity above 98%. The purified product was also analyzed by LC/MS and the exact mass (293.1 g/mol) was observed. The molecular weight was also confirmed with HRMS. We then treated **90** with (*t*-Bu)$_2$PCl and DBU which successfully afforded the desired novel imidazolium-phosphinite hybrid ligand **91**. However, attempts to isolate **91** and purify it were challenging due to the nature of insolubility of the ligand in organic solvents and lack of crystallinity of the ligand. The diagnostic phosphinite peak was observed at 155.24 ppm in the ^{31}P NMR spectrum.

Scheme A4.2 *Synthesis of Novel Asymmetric NHC-Phosphonite Complex*

(*t-Bu2*Mes-NHCCOP)–Ir **c32**
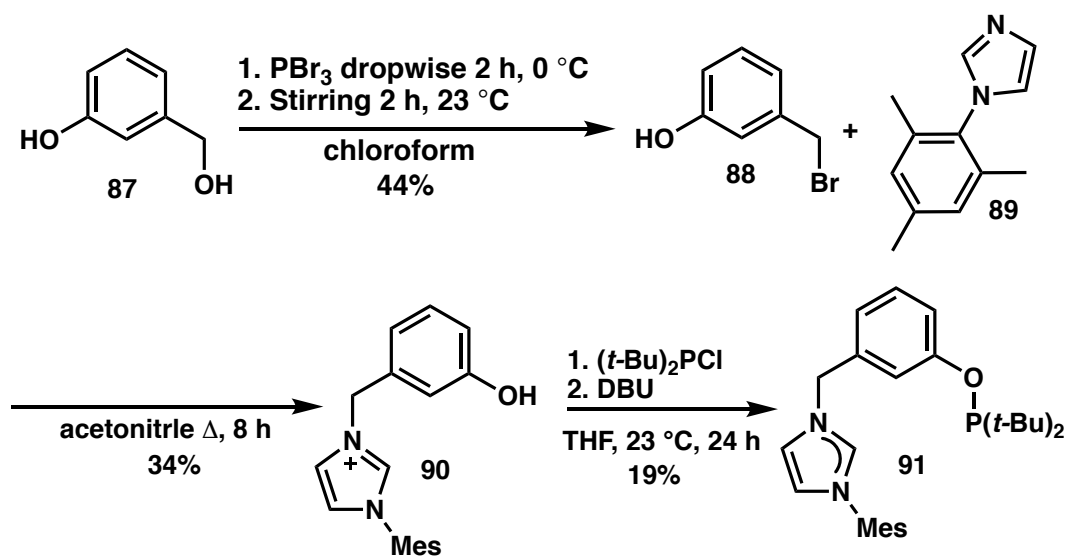
We will investigate several methods for isolating **91** including column chromatography by varying polar organic solvents ratios and we will investigate recrystallizing the ligand to purify it by the solvent diffusion method.

A4.4   SUMMARY AND FUTURE WORK

Varying the steric effects around Ir pincer ligated complexes have been shown to be effective in changing its catalytic activity when employed as dehydrogenation catalysts. NHC ligands have strong σ-donor properties and could facilitate the C–H oxidative addition step, which is typically rate determining in dehydrogenation mechanisms catalyzed by Ir pincer ligated complexes. We proposed a novel asymmetric NHC-phosphonite ligand that could be a good candidate for catalyzing dehydrogenation reactions. We successfully synthesized the

novel ligand; however, isolation and purification were challenging. Once the ligand

is purified and isolated, we envision metalation with half an equivalent [Ir(COD)Cl]$_2$

generating complex **c31** (Scheme A4.3). Upon successful synthesis of the desired Ir

complex, we will then investigate its dehydrogenation catalytic activity on the

COA/TBE system to evaluate its performance. Then, we will expand the scope to

include a wide array of substrates.
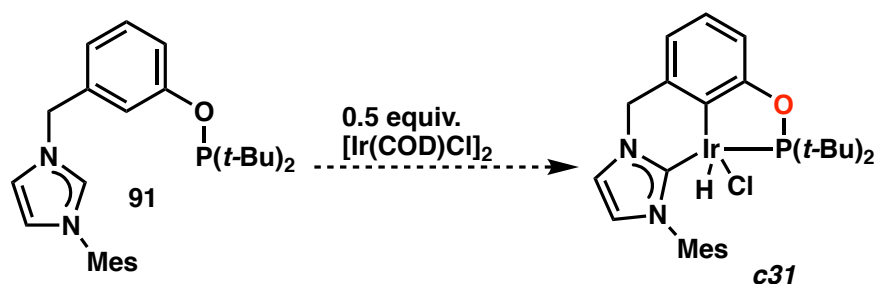
A4.5   NOTES AND REFERENCES

1.   M. Jensen, C., *Chem. Commun.* **1999,** (24), 2443-2449.

2.   Gupta, M.; C. Kaska, W.; M. Jensen, C., *Chem. Commun.* **1997,** (5), 461-462.

3.   Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M., *Journal of the American Chemical Society* **1997,** 119 (4), 840-841.

4.   Gupta, M.; Hagen, C.; Flesher, R. J.; Kaska, W. C.; Jensen, C. M., *Chem. Commun.* **1996,** (17), 2083-2084.

5.   Akshai Kumar, A. S. G. In *The Privileged Pincer-Metal Platform: Coordination Chemistry & Applications*, Gerard Van Koten, R. A. G., Ed. Springer, Cham: Cham, 2015; Vol. 54, pp 307-334.

6.   Kumar, A.; Bhatti, T. M.; Goldman, A. S., *Chemical Reviews* **2017,** 117 (19), 12357-12384.

7.   Kundu, S.; Choliy, Y.; Zhuo, G.; Ahuja, R.; Emge, T. J.; Warmuth, R.; Brookhart, M.; Krogh-Jespersen, K.; Goldman, A. S., *Organometallics* **2009,** 28 (18), 5432-5444.

8.   Liu, X.; Braunstein, P., *Inorg. Chem.* **2013,** 52 (13), 7367-7379.

9.   Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L., *Coord. Chem. Rev.* **2009,** 253 (5), 687-703.

10.   Przybilla, K. J.; Vögtle, F., *Chem. Ber.* **1989,** 122 (2), 347-355.

11.   Schultz, K. M.; Goldberg, K. I.; Gusev, D. G.; Heinekey, D. M., *Organometallics* **2011,** 30 (6), 1429-1437.

A4.6   EXPERIMENTAL SECTION AND SPECTRA

A4.6.1 Materials and Methods

Unless noted in the specific procedure, all liquid reagents were distilled and reactions were performed in an oven-dried glassware under an argon atmosphere . All dehydrogenation reactions were degassed by freeze-pump-thaw x 5 cycles and were carried out under air-free conditions in dry glassware. ^{1}H NMR and ^{31}P NMR spectra were recorded on Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, and are reported in terms of chemical shift relative to residual CHCl$_3$ (δ 7.26). LC/MS was acquired with an Agilent 6140 quadrupole LC/MS with an Agilent Eclipse Plus C$_{18}$ RHHD 1.8 um column (2.1x 50, 11,072 plates). The method used was a standard 10-minute gradient with 5% to 95% acetonitrile to water (0.1% acetic acid) ratio. HRMS were acquired using an Agilent 6200 Series TOF with a JEOL JMS-600H in fast atom bombardment (FAB+).

A4.6.2 General Procedure of *t*-Bu2Mes-NHCCOP Ligand 91 Synthesis
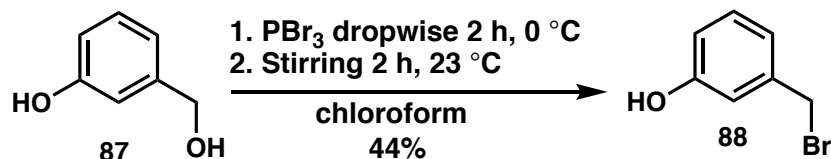
Synthesis of 3-(bromomethyl)phenol (88). 10.172 g of 3-hydroxybenzyl alcohol was suspended in 50 mL absolute chloroform. The suspension was cooled to 0 °C and then 4.0 mL of PBr$_3$ was added dropwise over a period of 2 h while stirring under argon. The reaction was subsequently stirred for another 2 h and then poured onto ice. The phases were separated and the organic phase was extracted twice with chloroform. The extract was dried in a rotavap obtaining a yellow oil similar to literature reports. However, upon ^{31}P NMR it was discovered that phosphine impurities existed. Further purification with silica gel column chromatography using 25% Et$_2$O in hexanes was required to obtain a white product with a cotton-like texture. The product is stable and can be refrigerated for a long time.[3] $R_f = 0.4$ (25% Et$_2$O in hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (t, $J = 7.9$ Hz, 1H, Ar-H), 6.99 (dd, $J = 7.7$, 1.2 Hz, 1H, Ar-H), 6.90 (dd, $J = 2.6$, 1.7 Hz, 1H, Ar-H), 6.79 (ddd, $J = 8.1$, 2.6, 0.9 Hz, 1H, Ar-H), 4.75 (s, br., 1H, OH), 4.46 (s, 2H, CH$_2$). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.62 (s, 1C, Ar-C-O), 139.44 (s, 1C, Ar-C-C), 130.08 (s, 1C, Ar-C), 121.51 (s, 1C, Ar-C), 115.91 (s, 1C, Ar-C), 115.53 (s, 1C, Ar-C), 33.12 (s, 1C, CH$_2$).
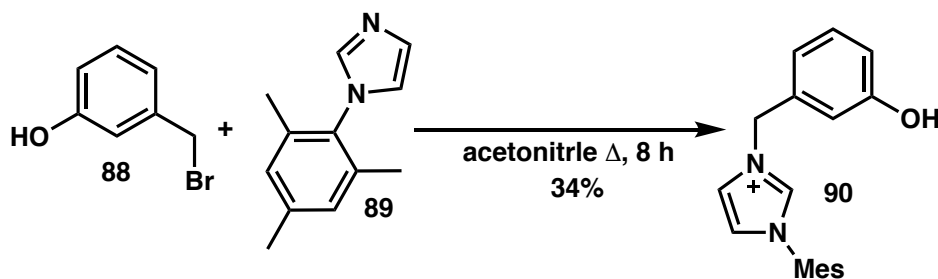
Synthesis of 3-(3-hydroxybenzyl)-1-mesityl-1H-imidazol-3-ium Salt 90.   This ligand precursor was prepared by a modification of the procedure reported by Braunstein and Heinekey.[5,6] 1.041 g of 3-(bromomethyl)phenol and 1.036 g of 1-mesitylimidazole were refluxed in 45 mL acetonitrile overnight. The solution was then dried under vacuum. The product was then purified in a silica gel column plug with 10% MeOH in DCM yielding the pure product as white solid. R_f = 0.6 (10% MeOH in DCM). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H, OH), 9.60 (t, J = 1.6 Hz, 1H, im-H), 8.07 (t, J = 1.8 Hz, 1H, im-H), 7.97 (t, J = 1.8 Hz, 1H, im-H), 7.29 – 7.22 (m, 1H, Ar-H), 7.16 (s, 2H, Mes-H), 6.85 – 6.76 (m, 3H, Ar-H), 5.45 (s, 2H, CH$_2$), 2.34 (s, 3H, p-Me-Mes), 2.02 (s, 6H, 2x o-Me-Mes). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.32 (1C, C-OH), 140.76(1C, Mes-C), 138.12 (1C, NCN), 136.54 (1C, Ar-C), 134.69 (2C, Mes), 131.60 (1C, Ar-H), 130.65 (1C, Ar-H), 129.73 (2C, Mes-C), 124.75 (1C, Mes-C-N), 123.83 (1C, im-C), 118.67 (1C, im-C), 116.11 (1C, Ar-C), 115.11 (1C, Ar-C), 52.77 (1C, CH$_2$), 21.07 (1C, p-Me-Mes), 17.38 (2C, o-Me-Mes). LC/MS MW = 293.1 g/mol. HRMS (FAB+) m/z calc'd for C$_{19}$H$_{21}$N$_2$O [M+H]+: 293.1654, found 293.1655.
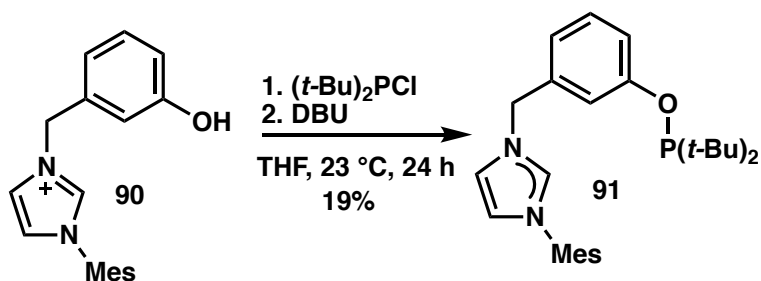
Synthesis of 3-(3-((di-tert-butylphosphanyl)oxy)benzyl)-1-mesityl-1H-imidazol-3-ium Ligand 91. 0.075 g of 3-(3-hydroxybenzyl)-1-mesityl-1*H*-imidazol-3-ium *23a* was dissolved in 15 mL THF. 51 mL (*t*-Bu)$_2$PCl was then added *via* a syringe slowly to the THF solution. 0.5 mL DBU (excess) was then added to the reaction mixture and it was stirred at room temperature for 21 h. The solution was dried under vacuum and then washed with Et$_2$O x 2. The desired phosphonite peak was observed at 155.24 ppm, however the product shows that it is 70% pure based on ^{1}H NMR. Purification of the product is still under progress. ^{31}P NMR (162 MHz, Benzene-d_6) δ 155.24.

A4.6.3 NMR Spectra
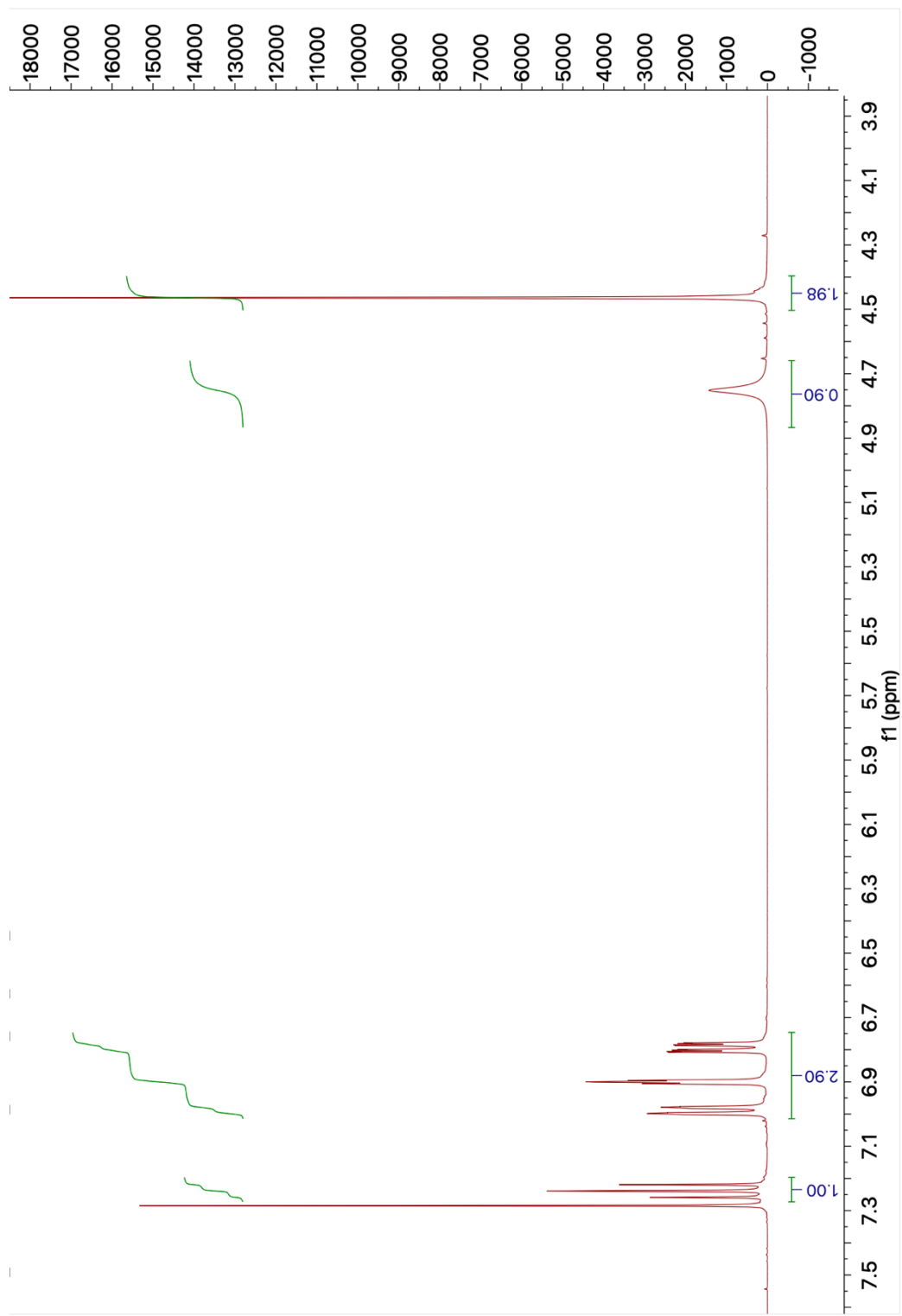
Figure A4.3 ^{1}*H NMR (400 MHz, Chloroform-d) of 88*
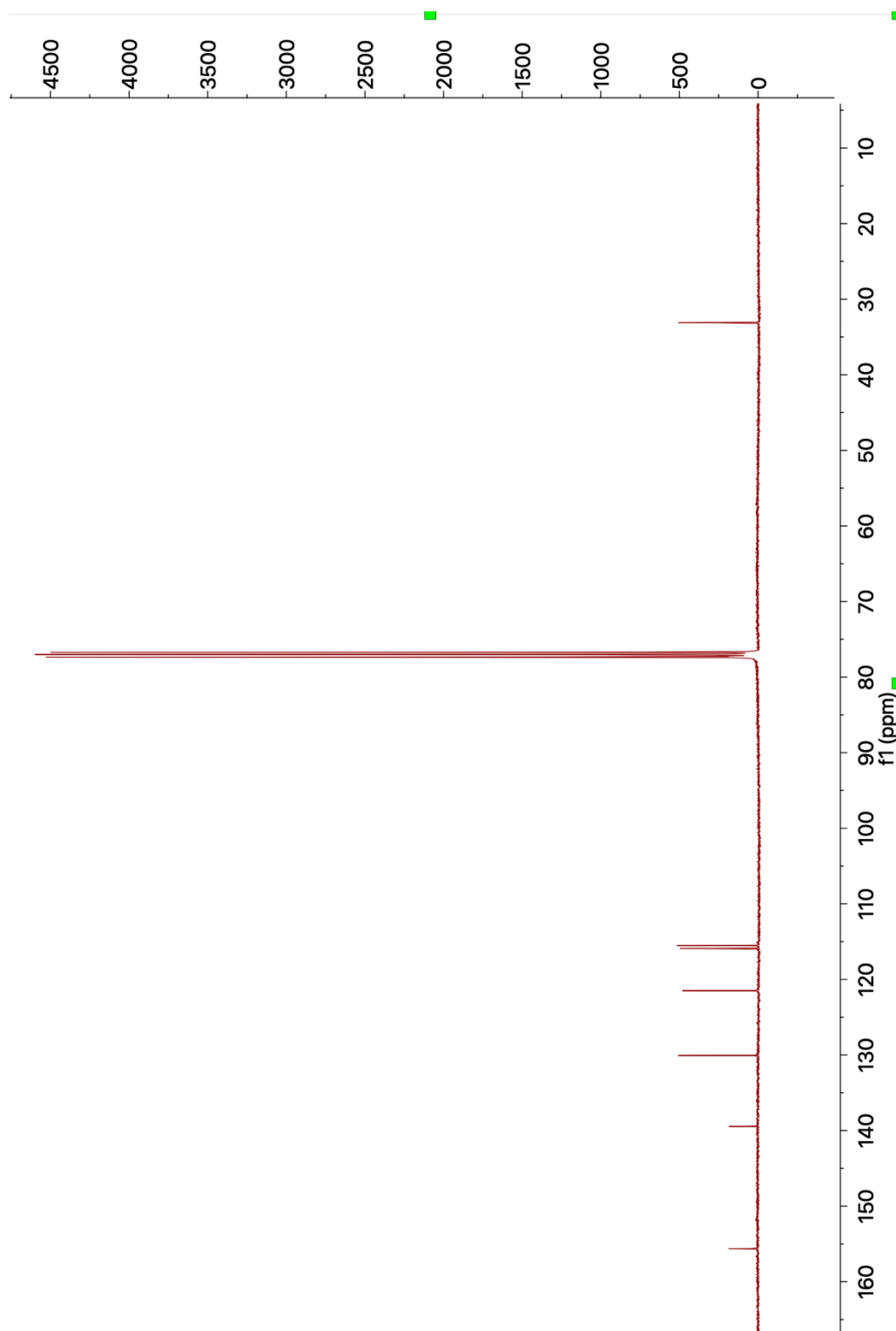
Figure A4.4 ^{13}C *NMR (101 MHz, Chloroform-d) of 88*
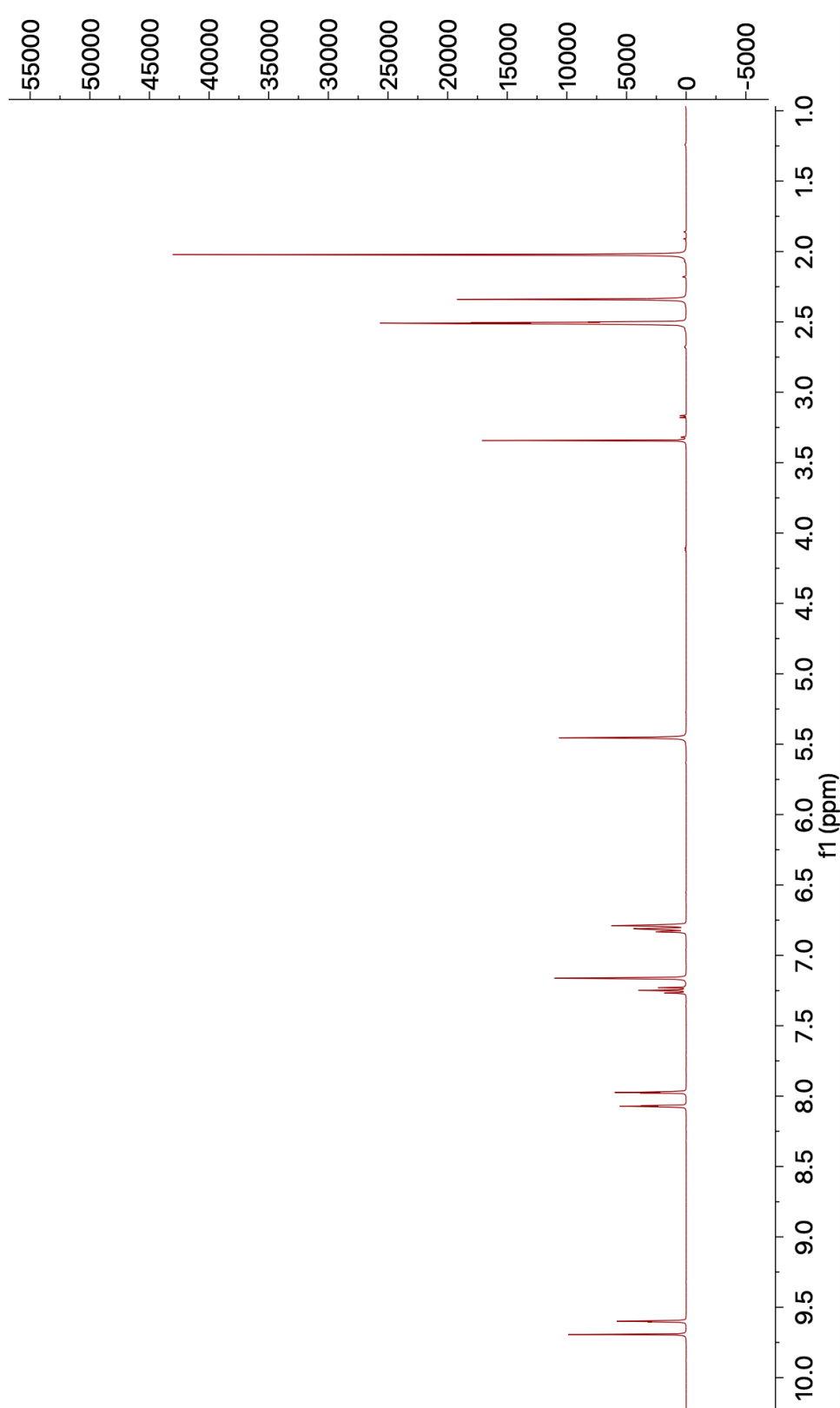
Figure A4.5 *¹H NMR (400 MHz, DMSO-d₆) of **90***
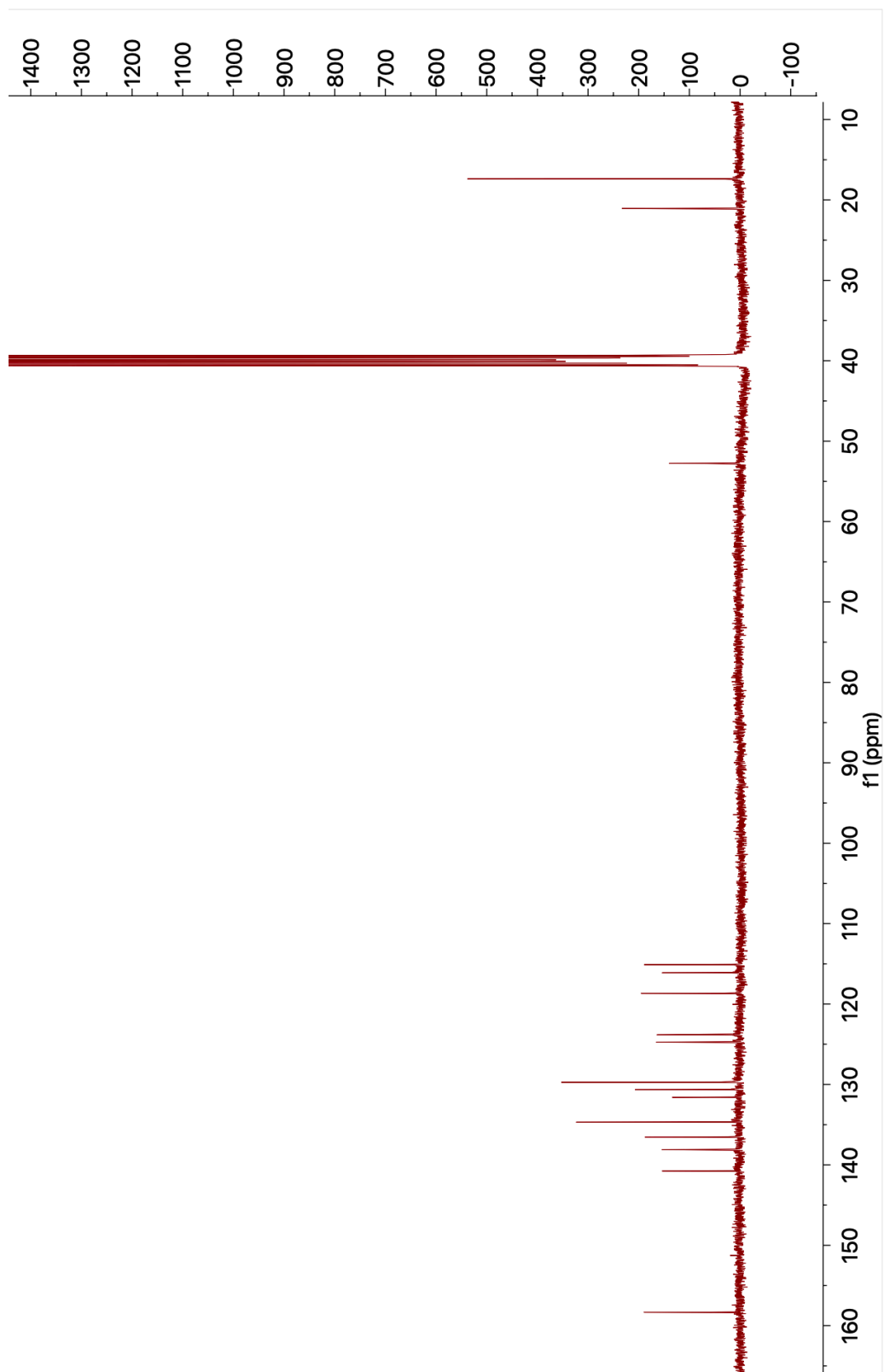
Figure A4.6 ^{13}C NMR (101 MHz, DMSO-d_6) of **90**
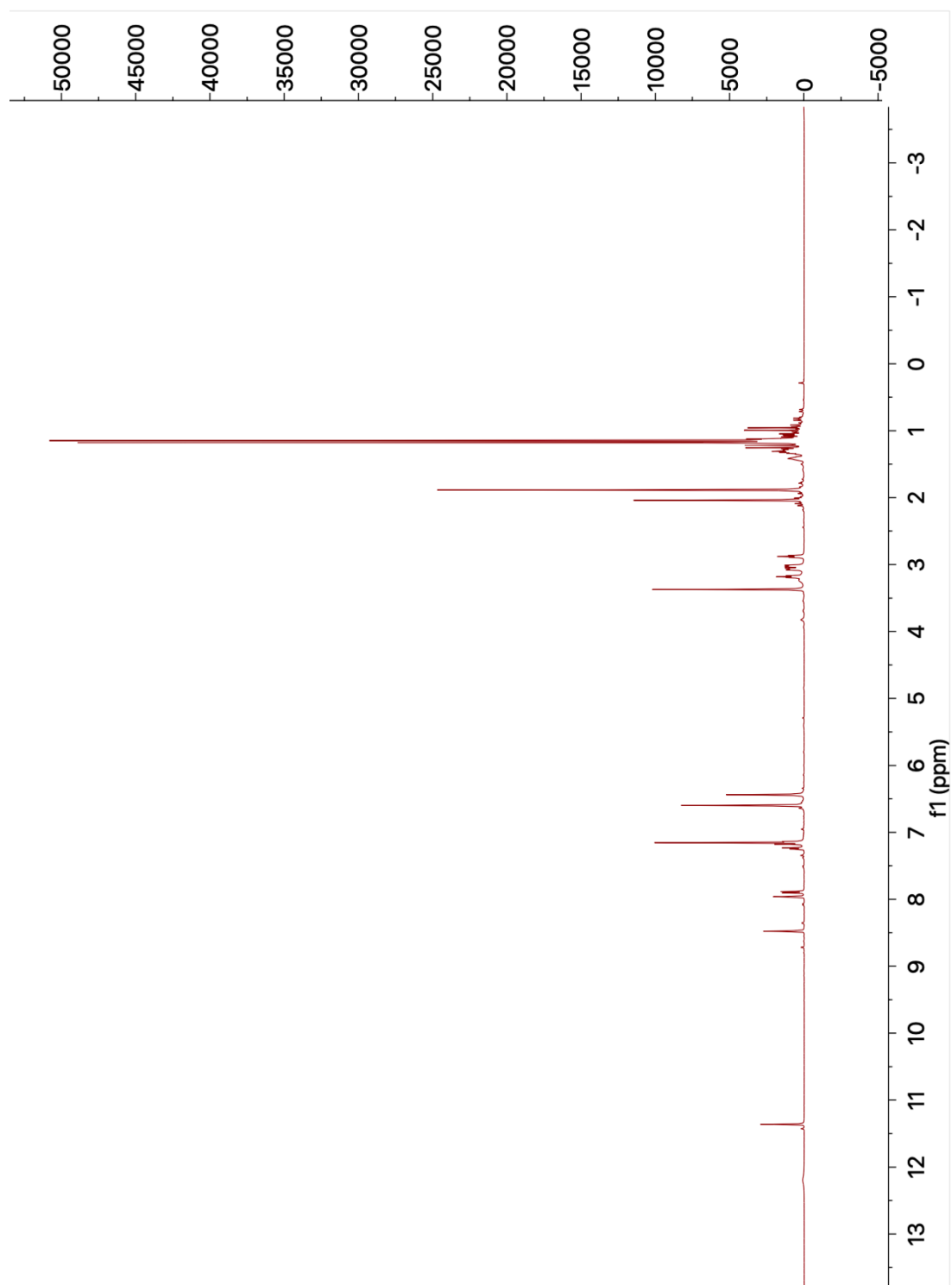
Figure A4.7 *^{1}H NMR (400 MHz, C6D6-d) of **91***
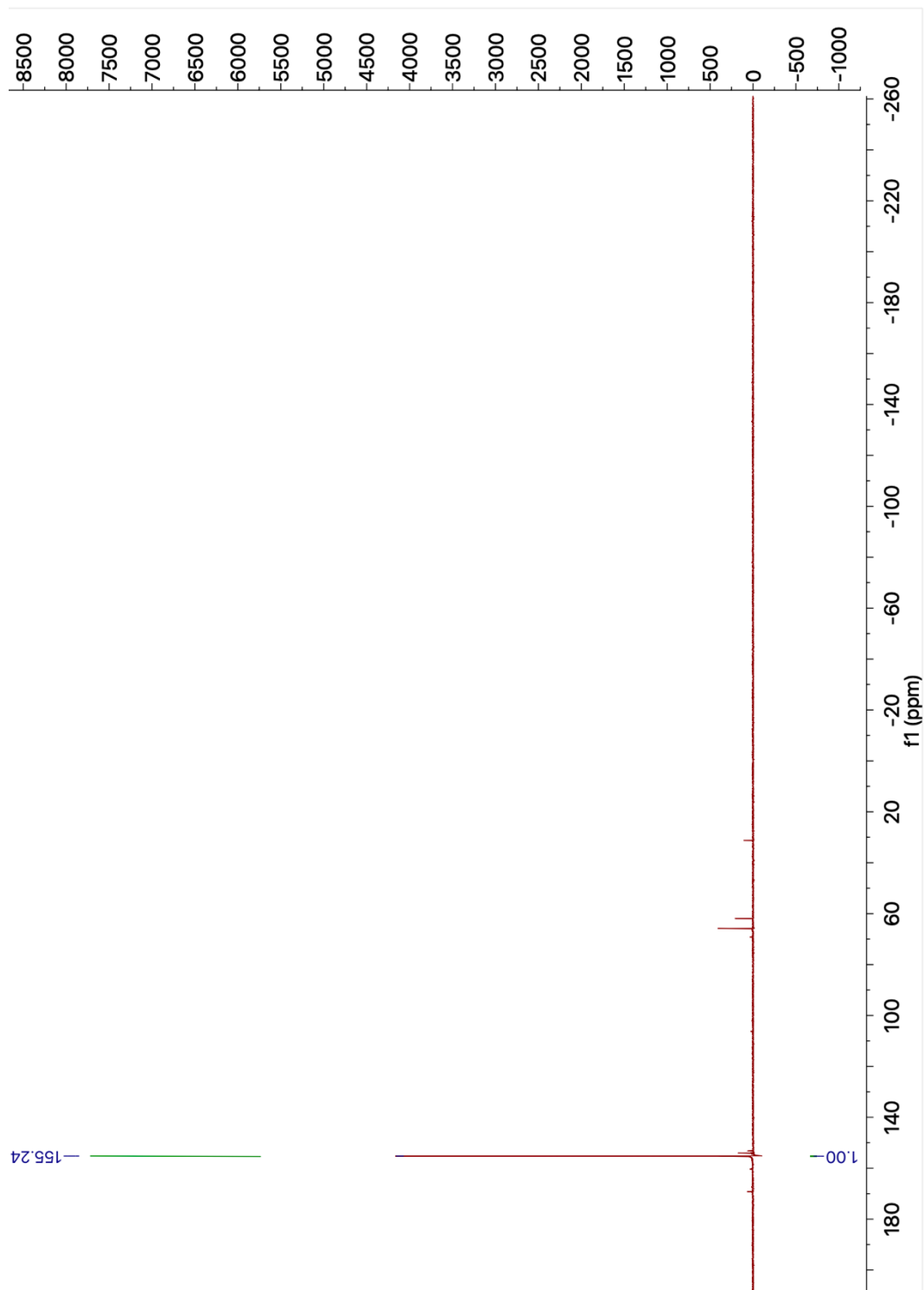
Figure A4.8 ^{31}P *NMR (162 MHz, Benzene-d$_6$) of 91*

CHAPTER 3

*C(SP³)–H DEHYDROAROMATIZATION OF 1-CYCLOHEXENE
AND 4-VINYL-1-CYCLOHEXENE VIA DISPROPORTIONATION
CATALYZED BY IRIDIUM PINCER LIGATED COMPLEXES*

3.1   INTRODUCTION

Alkanes are a ubiquitous class of chemicals that are extracted from crude oils *via* distillation and refining processes. They are typically considered to be inert, and as a result they find limited synthetic use. Small olefins and aromatics however, are more reactive and allow easier functionalization to serve as building blocks in various applications in the preparation of complex molecules, pharmaceuticals, and materials.[1-3] Amongst the most important industrial building blocks are benzene, ethylbenzene, and styrene. However, these do not naturally exist and the current industrial production of small aromatics is through dehydrogenating aliphatic hydrocarbons from crude oil using heterogeneous catalysts, which is a highly energy-intensive process operating at high pressures up to 60 bar and temperatures up to 900 °C (Scheme 3.1).[4]

Scheme 3.1 *Important Aromatics Industrial Production*
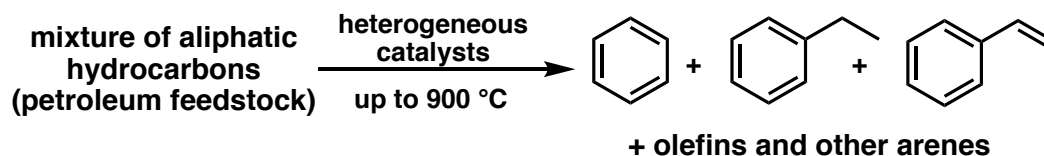
As shown in the previous chapters, the direct dehydrogenation of $C(sp^3)$–H alkanes may seem conceptually simple but in fact it is a challenging transformation and is in some cases not feasible. This transformation is difficult due to the distinct inert nature of alkanes and the endergonic nature of dehydrogenation, making it necessary to employ energy-intensive processes with high temperatures in order to amplify the entropic contributions to the equilibrium. With the diminishing oil supply, there is a commercial need to find new routes to convert less valuable materials into more useful building blocks. We were interested to investigate the catalytic activity of the Ir pincer complexes ($^{t\text{-Bu}4}$POCOP)–Ir **c13**, ($^{i\text{-Pr}4}$PSCOP)–Ir **c22**, and ($^{i\text{-Pr}4}$anthraphos)–Ir **c24** in disproportionating cyclohexenyl derivatives. The advantage of our proposed system is that we do not employ a sacrificial olefin as an H_2 acceptor, and the investigated substrates in this chapter act as both the H_2 donor and acceptor simultaneously.

3.2   RELATED LITERATURE

There is a great interest in developing and identifying methods for the synthesis of unsubstituted aromatics under milder conditions. Since the first reports of homogeneous transition metals as catalysts for alkane dehydrogenation by Crabtree and Felkin, substantial progress has been achieved in the field of

homogeneous catalytic alkane dehydrogenation using Ir pincer ligated complexes.[4-10] That being said, the direct dehydroaromatization of alkane precursors using Ir pincer ligated complexes remains limited due to the believed nature of arenes coordination to metal centers.[11-12]

For example, in 1997 Kaska and Jensen reported the transfer dehydrogenation of ethylbenzene to styrene using complex (*t-Bu4*PCP)–Ir **c3** and **TBE** as the H$_2$ acceptor reporting only up to 17% conversion (Scheme 3.2).[13]

Scheme 3.2 *Styrene Formation via Ethylbenzene Transfer Dehydrogenation by Complex (t-Bu4PCP)–Ir* **c3**
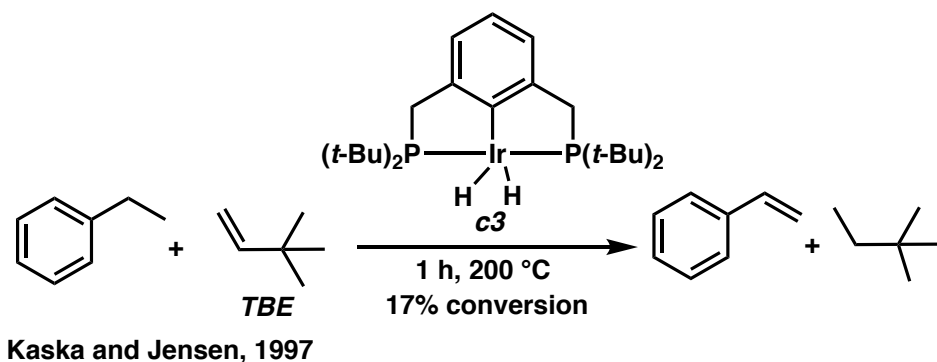
Brookhart and co-workers reported a one pot method to synthesize *p*-xylene from ethylene and 1-hexene transfer dehydrogenation followed by Diels Alder reactions using complex (*i-Pr4*anthraphos)–Ir **c24** (Scheme 3.3). However, *p*-xylene was a minor product and its yield was reported as a mixture of aromatics up to 10.3% after 192 h of reaction time.

Scheme 3.3 *p-Xylene Formation as a Minor Product via Dehydrogenation by Complex*

(*i-Pr4Anthraphos*)*–Ir* **c24**

Brookhart 2012
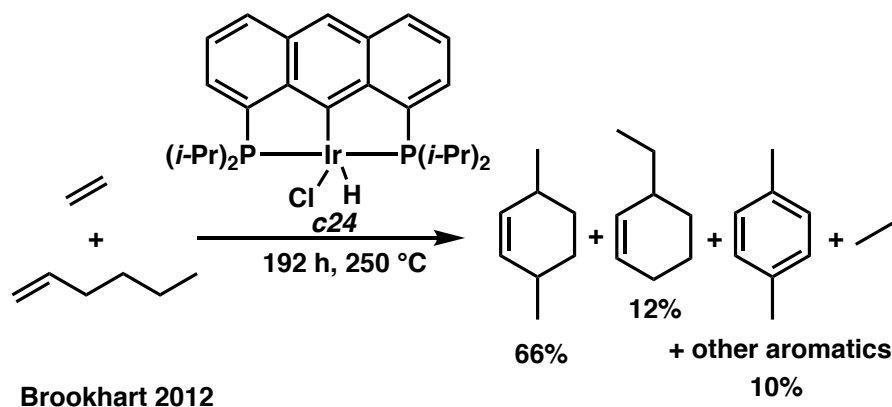
To date only four previous studies reported benzene formation *via* dehydrogenation catalyzed by Ir pincer ligated complexes (Scheme 3.4). Jensen and Kaska first reported the dehydrogenation of cyclohexane to benzene using **TBE** as the H_2 acceptor catalyzed by complex (*t-Bu4PCP*)–Ir **c3** (Scheme 3.4a).[12, 14] **TBE** was partially hydrogenation and found to inhibit catalysis at high concentrations. Later in 2004, Goldman observed the formation of small amounts of benzene when transfer dehydrogenating n-hexane using complex (*i-Pr4OMe-PCP*)–Ir **c9** and **NBE** as the H_2 acceptor (Scheme 3.4b).[15] More recently in 2011, Brookhart and Goldman reported the dehydroaromatization of n-hexane and n-dodecane using complex (*i-Pr4PCOP*)–Ir **c21** and **TBE** as the H_2 acceptor (Scheme 3.4c). In the latter example, at least 4 equivalents of **TBE** were required to render the reaction's thermodynamics favorable.[16] In addition, these reactions are not selective for benzene and a complex mixture of several products consisting of dienes, trienes, monenes, and aromatics was generated.

Scheme 3.4 *Reported Studies of Benzene Formation via Dehydrogenation by Ir Pincer*

Ligated Complexes
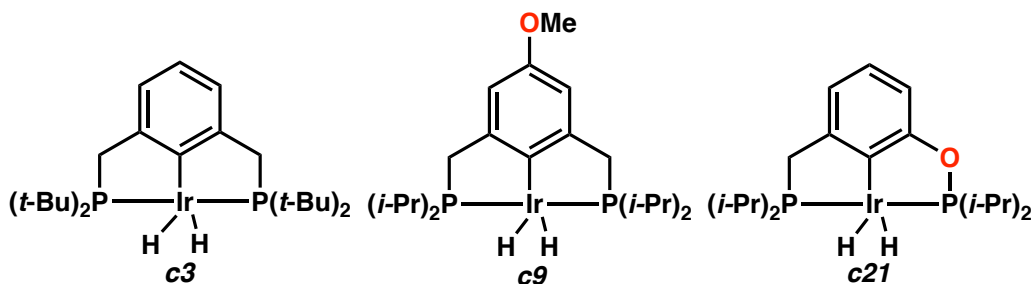
a. Kaska and Jensen, 1997
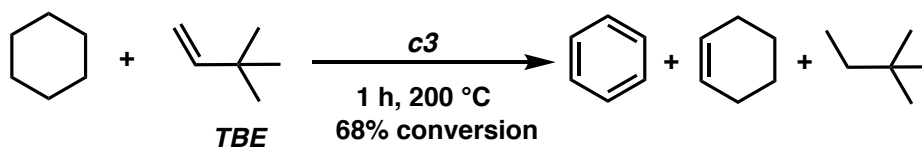
b. Goldman, 2004
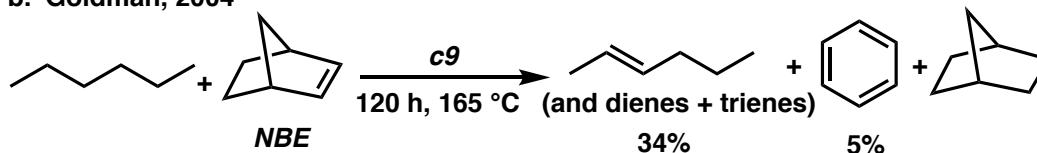
c. Brookhart and Goldman, 2011
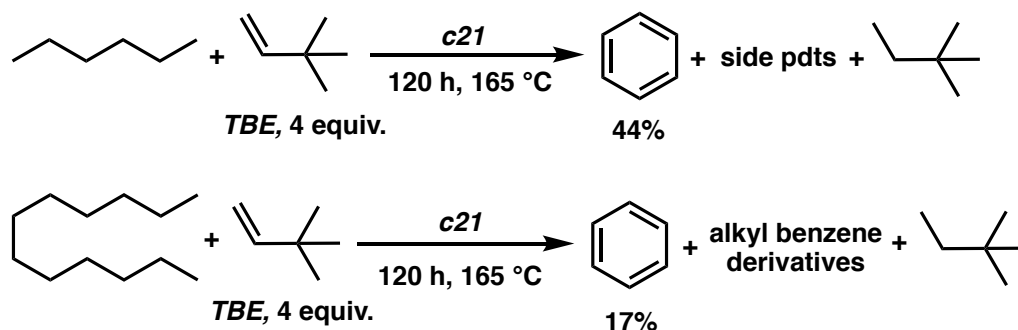
Ethylbenzene formation *via* Ir pincer ligated catalysts has also been limited

and only two studies were previously reported. Kaska and Jensen reported the

synthesis of ethylbenzene from cyclohexane transfer dehydrogenation using

complex ($^{t\text{-}Bu4}$PCP)–Ir **c3** and **TBE** as the H$_2$ acceptor (Scheme 3.5a).[13] Goldman

also reported the formation of ethylbenzene when studying *n*-octane transfer

dehydrogenation using complex ($^{i\text{-}Pr4}$PCOP)–Ir **c21** and **TBE** as the H$_2$ acceptor as

the minor product(Scheme 3.5b).

Scheme 3.5 *Only Reported Studies of Ethylbenzene Formation via Dehydrogenation by*

Ir Pincer Ligated Complexes

a. **Kaska and Jensen, 1997**

b. **Brookhart and Goldman, 2011**
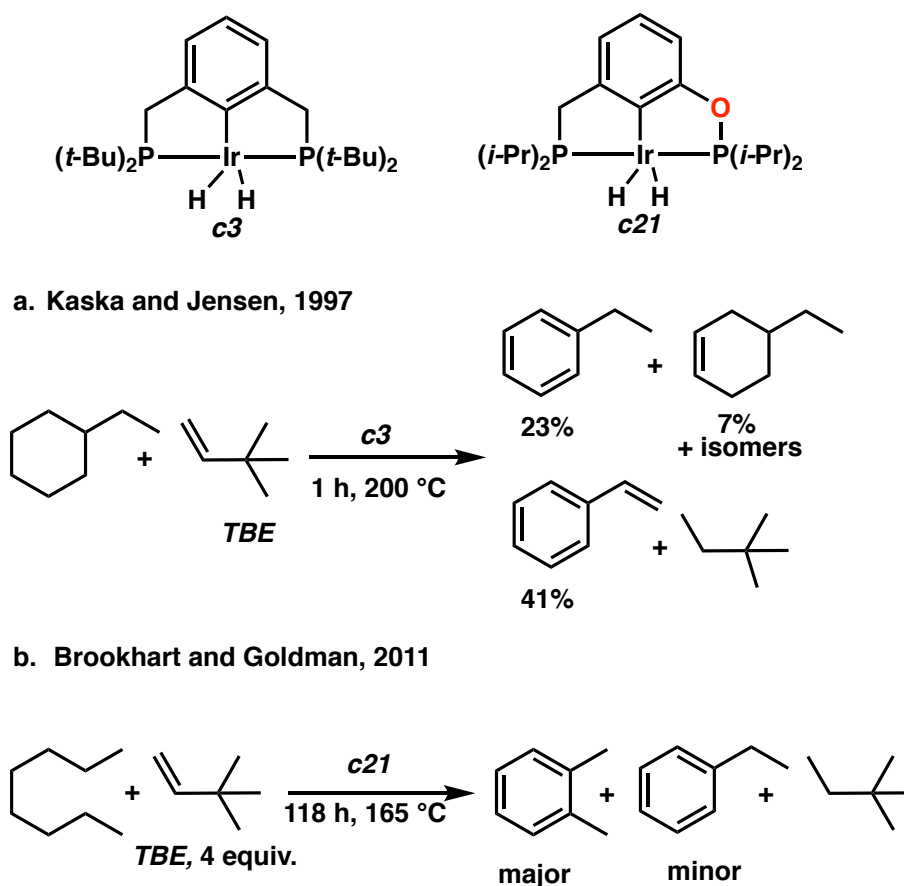
While the previous examples show tremendous achievements in the field,

these methods suffer from requiring several equivalents of **TBE** and harsh reaction

conditions (high temperatures, extended reaction times), making them uneconomical.

In addition, these methods are non-selective toward dehydroaromatization and

generate a complex mixture of side products, imposing separation challenges and thus lack of industrial practicality especially at large scales. There is a need to find and develop alternative methods that are more economical, selective toward dehydroaromatization, industrially scalable, and which operate at milder conditions

Herein, we present a facile method of benzene and ethylbenzene formation *via* the disproportionation of 1-cyclohexene and 4-vinyl-1-cyclohexene and without the need of an exogenous H_2 acceptor, at temperatures as low as 120 °C (Scheme 3.6).

Scheme 3.6 *Our Work in Cyclohexenyl Derivatives Dehydrogenation by Ir Pincer Ligated Complexes*
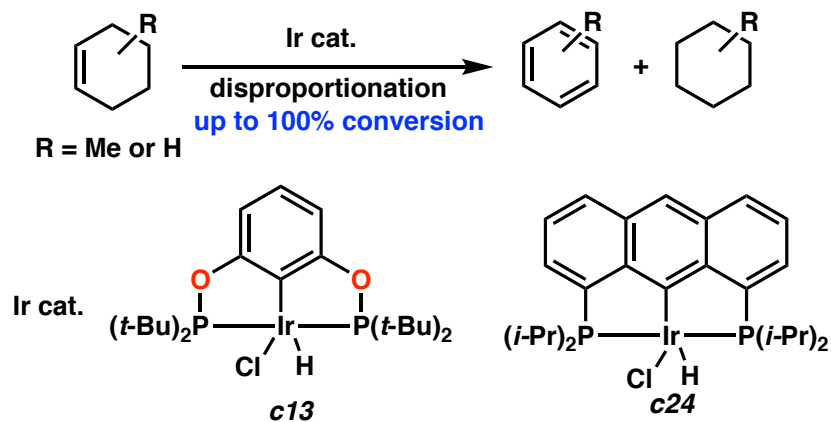
3.3   1-CYCLOHENE DISPROPORTIONATION BY IRIDIUM PINCER LIGATED COMPLEXES

We were interested to explore the reactivities and catalytic activity of complexes ($^{t\text{-}Bu4}$POCOP)–Ir **c13**, ($^{i\text{-}Pr4}$PSCOP)–Ir **c22**, and ($^{i\text{-}Pr4}$anthraphos)–Ir **c24** in

disproportionating 1-cyclohexene (**77**) to benzene (**78**) and cyclohexane (**79**) and

understand how geometry may affect arenes inhibition (Table 3.1).

Table 3.1 *1-Cyclohexene Disproportionation Investigated by Ir Pincer Ligated Complexes*
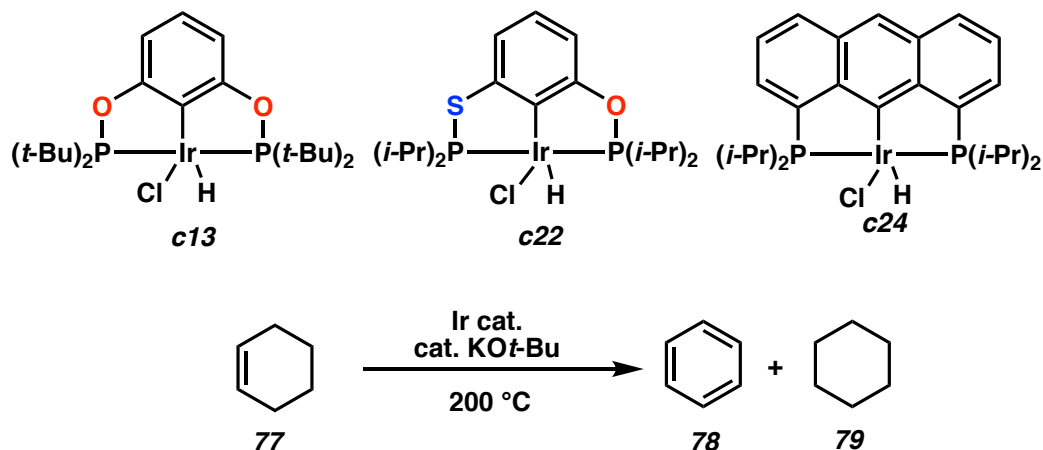
entry	cat.	loading (mol.%)	time (h)	conversion	78 yield[b]	TON[c]
1	c13	0.14	22 h	100.0%	33.0%	714
2	c13	0.13	11 h	100.0%	33.0%	769
3	c22	0.29	22 h	71.3%	23.1%	246
4	c22	0.33	22 h	56.7%	13.4%	180
5	c24	0.27	23 h	100.0%	33.0%	370

[a] Conditions: 3.5 - 5 mmol of **78**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ¹H NMR using hexamethylbenzene as an internal standard. [c] TON per conversion.

We commenced the investigations with complex **c13** and found that it was

catalytically active and achieved 100% conversion of **77** and 33% of **78** and 66% of

79 was generated when the reaction was carried at 200 °C for 22 h (Table 3.1 entry

1). We carried the reaction again with a shorter reaction period , 11 h, and observed

similar results (Table 3.1 entry 2). We then investigated the reactivity of complex

c22 under similar conditions and found that it was not as catalytically active as complex **c13** in disproportionating **77** to **78** and **79**, even when increasing the catalyst loading compared to **c13** from 0.14 mol.% to 0.33 mol.%, and only up to 71.3% conversion was achieved (Table 3.1 entry 3 and 4). We also investigated the catalytic activity of complex **c24** and found that it was very active in disproportionating **77** to **78** and **79** and 100% conversion was achieved and up to 33.0% of benzene (**78**) was generated (Table 3.1 entry 5).

Given complex ($^{t\text{-}Bu4}$POCOP)–Ir **c13** has exhibited superior catalytic activity when dehydrogenating **77** and various substrate systems in Chapter 2, we decided to optimize reaction conditions using it as a catalyst as the next step (Table 3.2). We wanted to investigate the effect of lowering the temperature on complex **c13** catalytic activity. We investigated the disproportionation of **77** to **78** and **79** at 100 °C while extending the reaction time to 28 h, and observed 100.0% conversion of **77** (Table 3.2 entry 1). We also carried the reaction again under similar conditions but for a shorter period of time, 6 h, and observed slightly lower conversion of **77** up to 92.6% (Table 3.2 entry 2). We found optimal conditions were achieved when carrying the reaction at 120 °C for 4 h and adding 0.52 mol.% of complex **c13** (Table 3.2 entry 3). In all cases, we only observed **78** and **78** and we did not observe any cyclohexadiene intermediates even when we did not obtain full conversion of **77**.

Table 3.2 *Optimizing 1-Cyclohexene Disproportionation by Complex* (*t-Bu4POCOP*)–*Ir*

c13
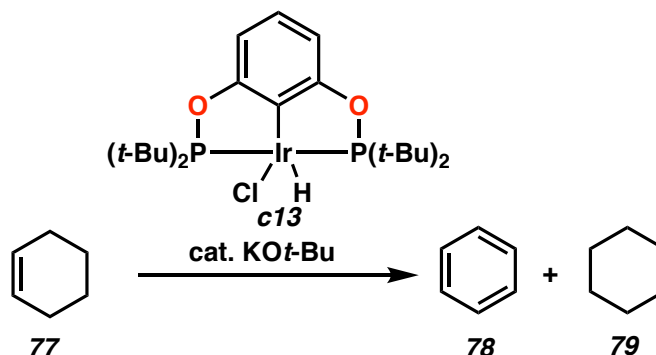
entry	loading (mol.%)	time (h)	temperature (°C)	conversion	*78* yield[b]	TON[c]
1	0.20	28 h	100	100.0%	33.0%	278
2	0.36	6 h	100	92.6%	30.5%	463
3	0.52	4 h	120	100.0%	33.0%	192

[a] Conditions: 3.5 mmol of **78**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ¹H NMR using hexamethylbenzene as an internal standard. [c] TON per conversion.

The inhibition of (*t-Bu4*PCP)–Ir **c3** by benzene and other arenes was noted by Kaska and Jensen, and formation of a C–H addition complex to (PCP)-Ir type catalysts has been described by Goldman.[12, 14, 17] We thus investigated the time course of the reaction and catalytic activity over time to gain an insight of the mechanism of **77** disproportionation by complex **c13**. We looked at the reaction products over a period of 6 hours every 10 minutes for the first 30 minutes and then every 30 minutes for the remaining 5.5 hours (Table 3.3). In all cases, we only observed **78** and **79** and remaining unreacted **77**. It's evident that the second dehydrogenation of **77** is very fast because we did not observe any hexadiene intermediates even within the first 10 minutes of reaction time (Scheme 3.7).

Scheme 3.7 1-Cyclohexene Disproportionation Pathway
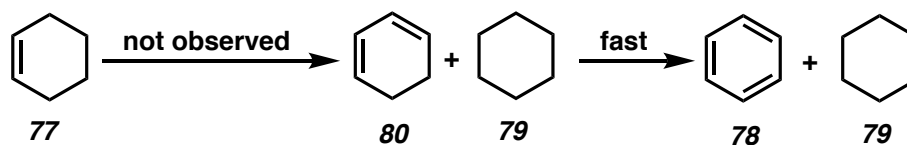
We also observed that around 60% conversion of **77** was achieved within the first hour of reaction time. These data show that the initial dehydrogenation of 1-cyclohexene is faster than the subsequent dehydrogenations which is in agreement with previous reports by Jensen, and was explained by catalyst inhibition by the arene products.[14]

Hence, we then investigated the disproportionation of **77** with spiking the reaction initially with 20 mol.% and 50 mol.% benzene (Table 3.3). Surprisingly, we did not observe significant catalyst inhibition of ($^{t\text{-}Bu4}$POCOP)–Ir **c13** (Figure 3.1) . It appears that the high activity for the disproportionation of 1-cyclohexene (**77**) catalyzed by **c13** may be enabled by its ability to operate in the presence of arene products. These results indicate that a key mechanistic feature of our system is a lack of catalyst inhibition by arenes.

Table 3.3 *Kinetics Investigation of 1-Cyclohexene Disproportionation by Complex*

($^{t\text{-}Bu4}$POCOP)–Ir **c13**
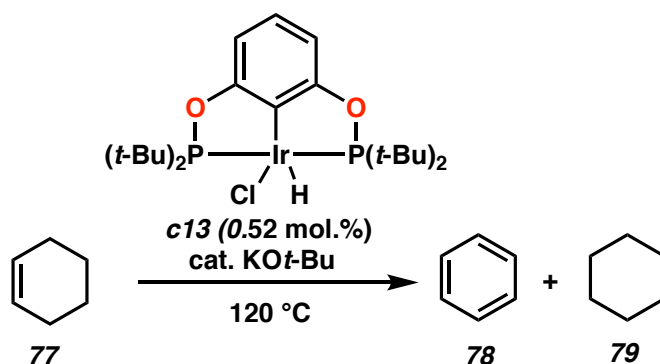
| entry	time	AVG 77 conversion	spiked with 20% benzene	spiked with 50% benzene
1	10 min	18.2%	10.71%	16.67%
2	20 min	31.4%	21.67%	27.53%
3	30 min	41.4%	30.07%	40.83%
4	1.0 h	63.7%	51.06%	64.49%
5	1.5 h	79.1%	65.20%	74.57%
6	2.0 h	88.1%	75.23%	80.70%
7	2.5 h	93.3%	-	85.50%
8	3.0 h	96.5%	86.18%	88.95%
9	3.5 h	98.2%	89.98%	91.85%
10	4.0 h	100.0%	92.44%	94.07%
11	4.5 h	-	94.08%	95.34%
12	5.0 h	-	95.74%	96.28%
13	6.0 h	-	96.85%	97.95%

[a] Conditions: 3.5 mmol of **78**, precatalyst with at least 1.2 equiv. KO*t*-Bu. [b] Yield determined by GC and ¹H NMR using hexamethylbenzene as an internal standard.
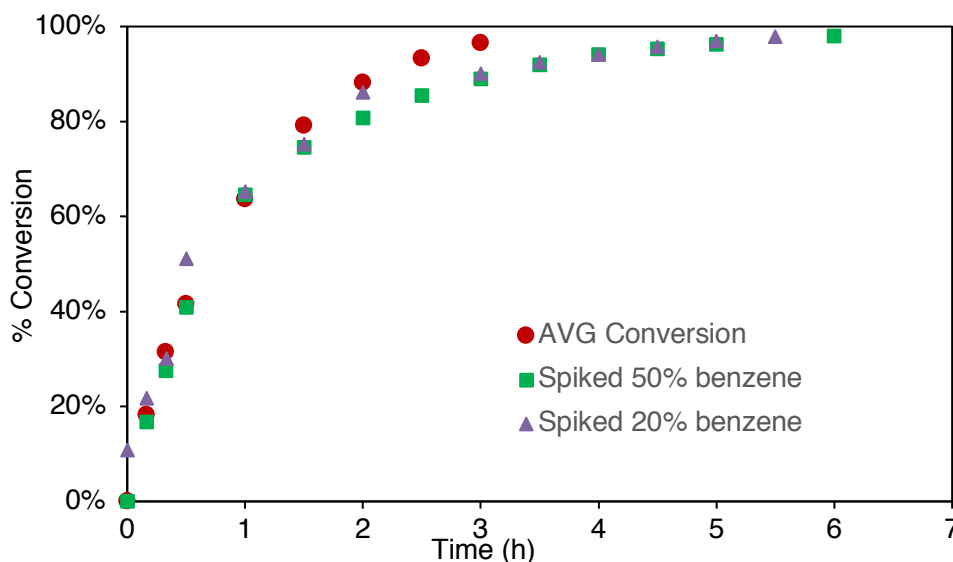
Figure 3.1 *1-Cyclohexene Disproportionation Conversion by Complex (^{t-Bu4}POCOP)–Ir*

c13

3.4   4-VINYL-1-CYCLOHEXENE DISPROPORTIONATION TO BY COMPLEX (*^{t-Bu4}*POCOP)–Ir c13

Following the same approach, we were interested in disproportionating 4-vinyl-1-cyclohexene (**81**). We subjected **81** to the disproportionation conditions using complex (*^{t-Bu4}*POCOP)–Ir **c13** (Table 3.4). We expected that we would make styrene, however after optimizing reaction conditions, we observed 100% conversion and only ethylbenzene (**82**) and ethylcyclohexane (**83**) was observed with a statistical distribution of 2:1 respectively (Table 3.4 entry 3). [18] In all cases, no styrene product was generated.

Table 3.4 *Optimizing 4-Vinyl-1-Cyclohexene Disproportionation by Complex* (t-Bu4POCOP)–Ir **c13**
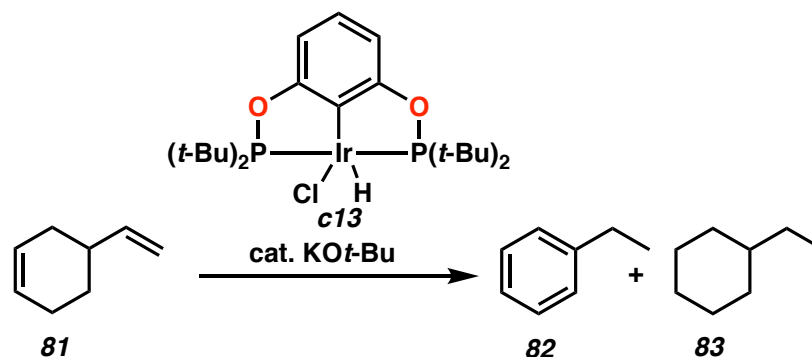
entry	loading (mol.%)	time (h)	temperature (°C)	conversion	78 yield[b]	TON[c]
1	0.47	28 h	200	98.2%	61.8%	209
2	0.52	4 h	120	92.6%	62.7%	178
3	0.52	6 h	120	100.0%	63.8%	192

[a] Conditions: 3.0 mmol of **78**, precatalyst with at least 1.2 equiv. KOt-Bu. [b] Yield determined by GC and ¹H NMR using hexamethylbenzene as an internal standard. [c] TON per conversion.

We investigated ethylbenzene (**82**) transfer dehydrogenation by complex **c13** and using **TBE** as the H₂ acceptor (Scheme 3.8). We did not observe styrene and complex **c13** was not catalytically active in this system; perhaps styrene is not thermodynamically favored.

A plausible reaction pathway for the disproportionation of 4-vinyl-1-cyclohexene (**81**) disproportionation starts with the transfer hydrogenation between 2 equivalents of **81** to provide **85** and **86** (Scheme 3.9). The transfer of one equivalent of H₂ between **85** and **81** generates **86** and **83**. The isomerization of **86** to

82 completes the transformation. This reaction pathway explains the observed 2:1

ratio of **82** to **83**.

Scheme 3.8 *Attempts to Transfer Dehydrogenate Ethylbenzene to Styrene*
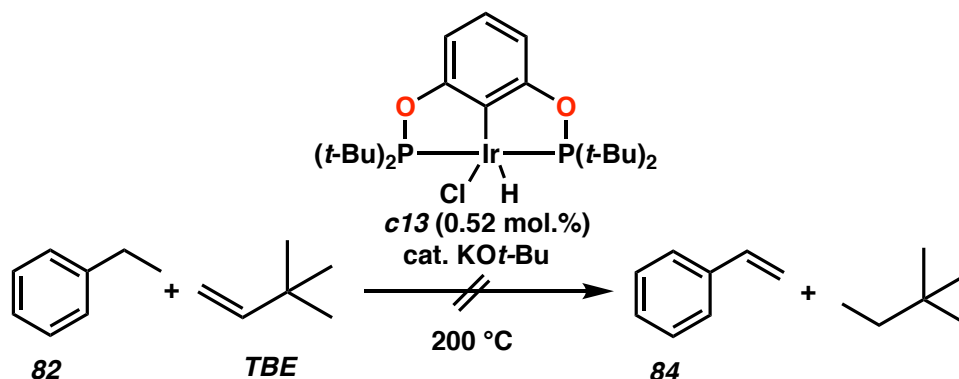
Scheme 3.9 *Plausible Reaction Pathway of 4-Vinyl-1-Cyclohexene Disproportionation*
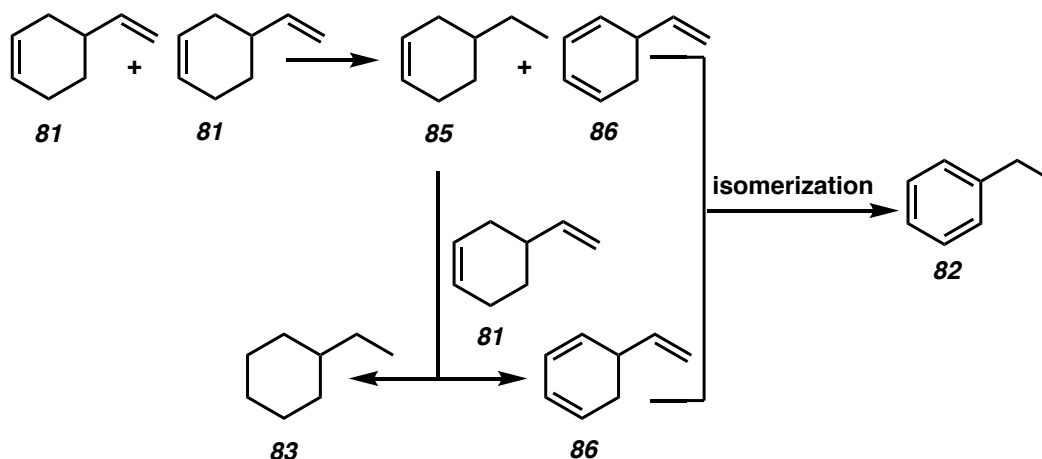
3.5   SUMMARY AND CONCLUSIONS

Benzene and ethylbenzene are among the most important industrial building

blocks. The direct dehydroaromatization of C(sp³)–H alkanes and alkenes to

aromatics may seem conceptually simple but in fact is a challenging transformation.

The current industry practice utilizes energy-intensive processes operating at high

pressures and temperatures due to the requirement of such conditions to overcome the endergonic and unreactive nature of alkanes. Previous reports utilizing Ir pincer ligated complexes in the context of dehydrogenating alkanes to benzene and other aromatics have been limited. Our study provides a novel pathway to access important aromatic building blocks like benzene and ethylbenzene without the need of a sacrificial olefin.

We demonstrated the disproportionation of 1-cyclohexene to benzene and cyclohexane, and the disproportionation of 4-vinyl-1-cyclohexene to ethylbenzene and ethylcyclohexane with complex ($^{t\text{-Bu4}}$POCOP)–Ir **c13** (Scheme 3.10). In both cases we obtained 100.0% conversion at significantly lower temperatures relative to previous reports. We observed lower catalytic activity when complex ($^{i\text{-Pr4}}$PSCOP)–Ir **c22** was employed as a dehydrogenation catalyst when disproportionating 1-cyclohexene. The lower catalytic activity is indicative that steric hinderance around the Ir metal center likely mitigates arene inhibition. We further investigated this hypothesis by spiking the reaction initially with benzene and did not observe significant catalyst inhibition of ($^{t\text{-Bu4}}$POCOP)–Ir **c13**. These results indicate that a key mechanistic feature of our system is a lack of catalyst inhibition by arenes.

Scheme 3.10 *Industrially Relevant Disproportionation via Dehydrogenation Forming*

Benzene and Ethylbenzene by Complex (*t-Bu4POCOP*)–*Ir* **c13**
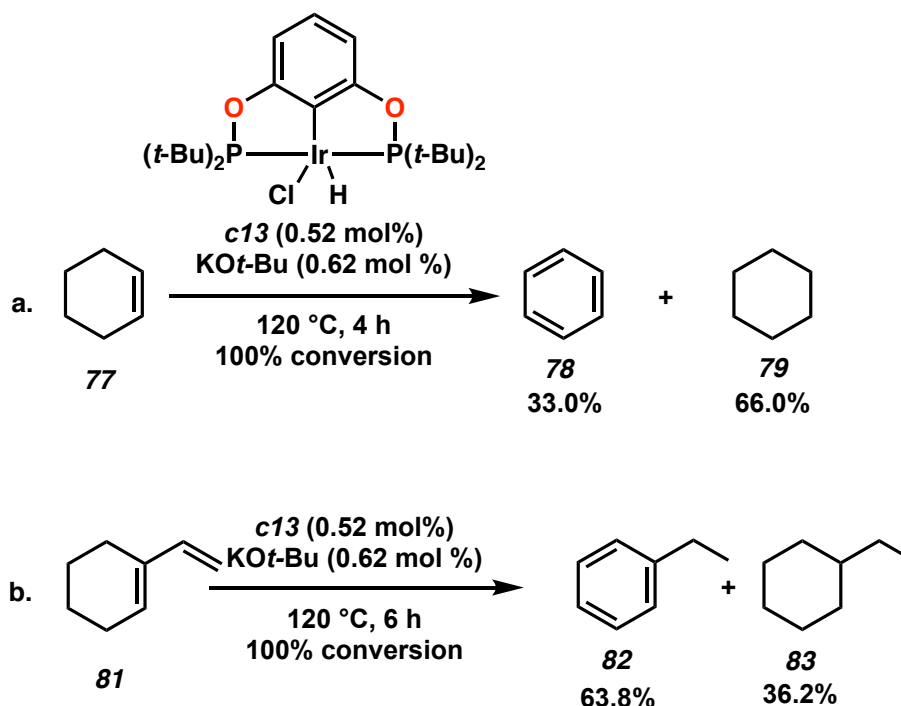
Overall, we provided a new route to access important building blocks like benzene and ethylbenzene. 85% of styrene commercial production comes from the direct dehydrogenation of ethylbenzene, and hence our method has promising commercial applications and could be supported with heterogeneous catalysis as a second step to make styrene, providing a new method to its synthesis.[19]

3.6   NOTES AND REFERENCES

1.   Michael Findlater, J. C., Alan S. Goldman, Maurice Brookhart. In *Alkane C-H Activation Activation By Single-Site Metal Catalysis*, 1 ed.; Perez, P. J., Ed. Springer Netherlands: Dordrecht, 2012; pp 113-141.

2.   Gunnoe, B. T. In *Alkane C-H Activation Activation By Single-Site Metal Catalysis*, 1 ed.; Perez, P. J., Ed. Springer Netherlands: Dordrecht, 2012; pp 1-15.

3.   Schulze, M., *Chem. Ing. Tech.* **2014,** 86 (8), 1304-1304.

4.   Chenier, P. J., *Survey of Industrial Chemistry*. 3 ed.; Springer US: New York, 2002; p XV, 515.

5.   Crabtree, R. H.; Mihelcic, J. M.; Quirk, J. M., *Journal of the American Chemical Society* **1979,** 101 (26), 7738-7740.

6.   Baudry, D.; Ephritikhine, M.; Felkin, H., *J. Chem. Soc., Chem. Commun.* **1980,** (24), 1243-1244.

7.   Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Parnell, C. A.; Quirk, J. M.; Morris, G. E., *Journal of the American Chemical Society* **1982,** 104 (25), 6994-7001.

8.   Crabtree, R. H.; Mellea, M. F.; Mihelcic, J. M.; Quirk, J. M., *Journal of the American Chemical Society* **1982,** 104 (1), 107-113.

9.   Akshai Kumar, A. S. G. In *The Privileged Pincer-Metal Platform: Coordination Chemistry & Applications*, Gerard Van Koten, R. A. G., Ed. Springer, Cham: Cham, 2015; Vol. 54, pp 307-334.

10.   Kumar, A.; Bhatti, T. M.; Goldman, A. S., *Chemical Reviews* **2017,** 117 (19), 12357-12384.

11.   Gupta, M.; Hagen, C.; Flesher, R. J.; Kaska, W. C.; Jensen, C. M., *Chem. Commun.* **1996,** (17), 2083-2084.

12.   Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M., *Journal of the American Chemical Society* **1997,** 119 (4), 840-841.

13.   Gupta, M.; C. Kaska, W.; M. Jensen, C., *Chem. Commun.* **1997,** (5), 461-462.

14.   M. Jensen, C., *Chem. Commun.* **1999,** (24), 2443-2449.

15.   Zhu, K.; Achord, P. D.; Zhang, X.; Krogh-Jespersen, K.; Goldman, A. S., *Journal of the American Chemical Society* **2004,** 126 (40), 13044-13053.

16.   Ahuja, R.; Punji, B.; Findlater, M.; Supplee, C.; Schinski, W.; Brookhart, M.; Goldman, A. S., *Nat. Chem.* **2010,** 3, 167.

17.   Kanzelberger, M.; Singh, B.; Czerw, M.; Krogh-Jespersen, K.; Goldman, A. S., *Journal of the American Chemical Society* **2000,** 122 (44), 11017-11018.

18.   The proton NMR of the reaction was 97% pure and the impurities were mostly in the aliphatic region.

19.   W. M. Castor, D. H. J., *Ullmann's Encyclopedia of Industrial Chemistry.* . 5th ed.; Wiley-VCH: Weinheim, 1994; p 332.

APPENDIX 5

EXPERIMENTAL SECTION AND SPECTRA RELATED TO CHAPTER 3

A5.1   MATERIALS AND METHODS

Unless noted in the specific procedure, reactions were performed in oven-dried glassware. All dehydrogenation reactions were degassed by freeze-pump-thaw x 5 cycles and were carried out under air-free conditions in dry glassware. All liquid reagents were purified by distillation and dried using molecular sieves, NaH, or Na-K alloy. For all the investigated dehydrogenation systems, the substrate was mixed with the H_2 acceptor in a 4 mL sealed Schlenk pressure flask under an argon atmosphere. Then synthesized Ir pincer complexes were added to the reaction mixture with at least 1.2 equivalents of the Ir pincer complexes of KO*t*-Bu when the Ir–HCl version of catalyst is used.

[1]H spectra were recorded on a Varian spectrometer 400 MHz with broadband auto-tune OneProbeor or on a Bruker AV III HD 400 MHz spectrometer equipped

with a Prodigy liquid nitrogen temperature cryoprobe, and are reported in terms of chemical shift relative to residual CHCl$_3$ (δ 7.26).

In addition, the conversions were determined using an Agilent 6850 GC-FID equipped with a Supelco column (SPB^{TM}-1, fused silica capillary column, 30 m x 0.25 μm film thickness) and using methods with temperature programs shown in Tables A5.1 and A5.2 and inlet program showed in Table A1.3. The obtained products were also confirmed by spiking the reaction with a commercial sample of the product.

Table A5.1 *ZAS_Cyclohexene General Method Temperature Ramping Program for 1-Cyclohexdene (**77**) Disproportionation*

Oven Ramp	°C/min	Next °C	Hold min
Initial	-	38	1.50
Ramp 1	5.00	50	5.00
Ramp 2	10.00	100	0.00
Ramp 3	5.00	170	5.00
Ramp 4	20.00	250	0.00

Table A5.2 *ZAS2 General Method Temperature Ramping Program for 4-Vinyl-1-Cyclohexdene (**81**) Disproportionation*

Oven Ramp	°C/min	Next °C	Hold min
Initial	-	38	1.50
Ramp 1	10.00	150	0.00
Ramp 2	20.00	250	5.00

Table A5.3 *Inlet Parameters used in All Methods*

Inlet	Setting
Mode	Split
Gas	He
Heater	250 °C
Pressure	9.52 psi
Total Flow	82.2
Split Ratio	100:1
Split Flow	78.5 mL/min

A5.2 Relevant Spectra
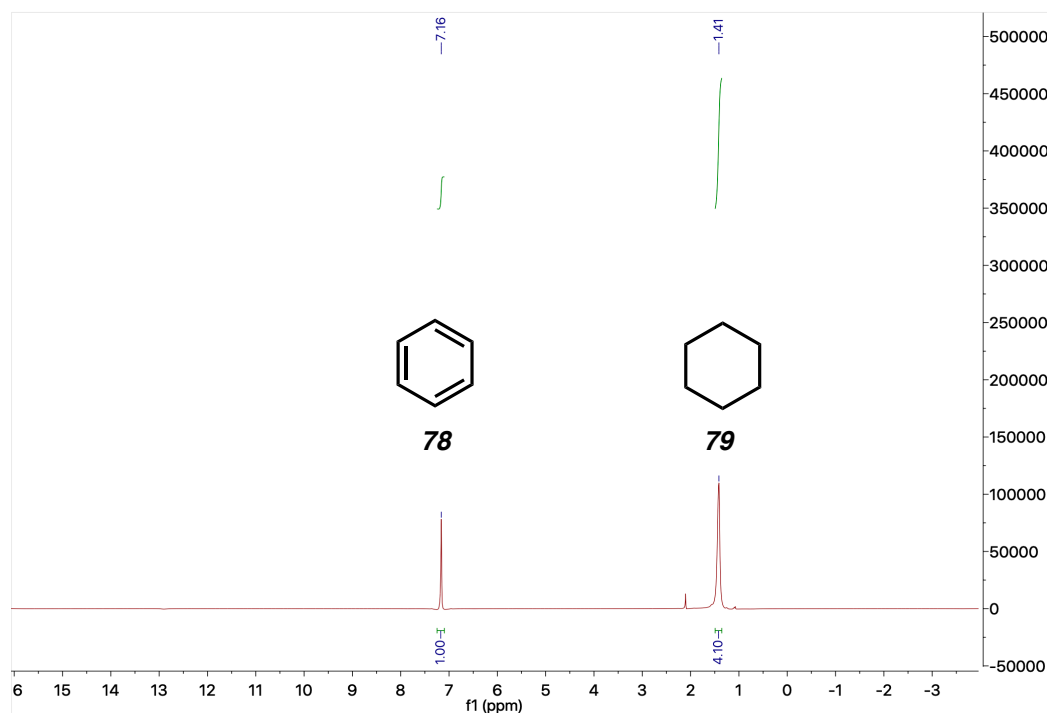
Figure A5.1 *Table 3.2 Entry 3 ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction Showing Full Conversion to Benzene (**78**) and Cyclohexane (**79**), Yield Calculated with Hexamethylbenzene as an Internal Standard*
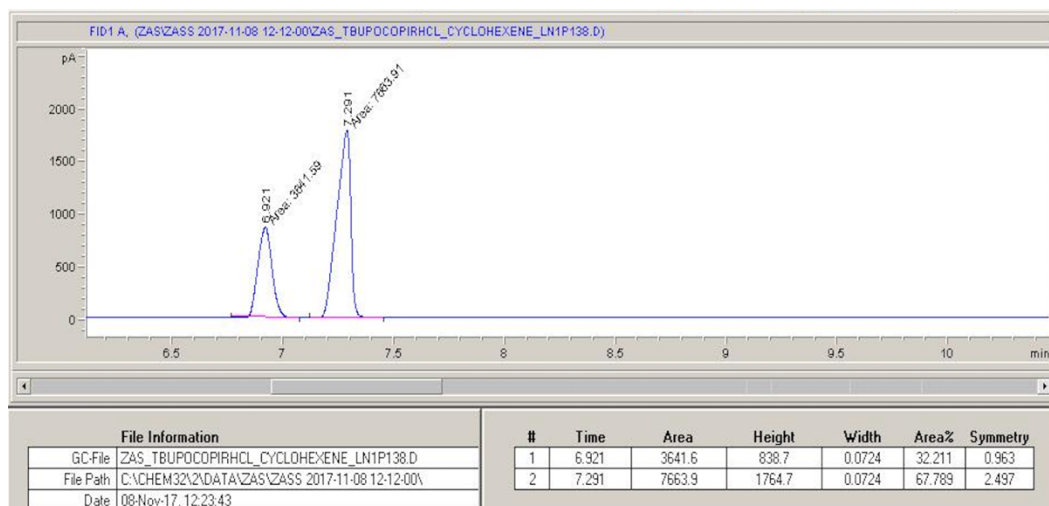
Figure A5.2 *GC Spectra of **77** Crude Reaction: **78**@6.92 and **79**@7.29 Using ZAS_Cyclohexene Method in Table A5.1*
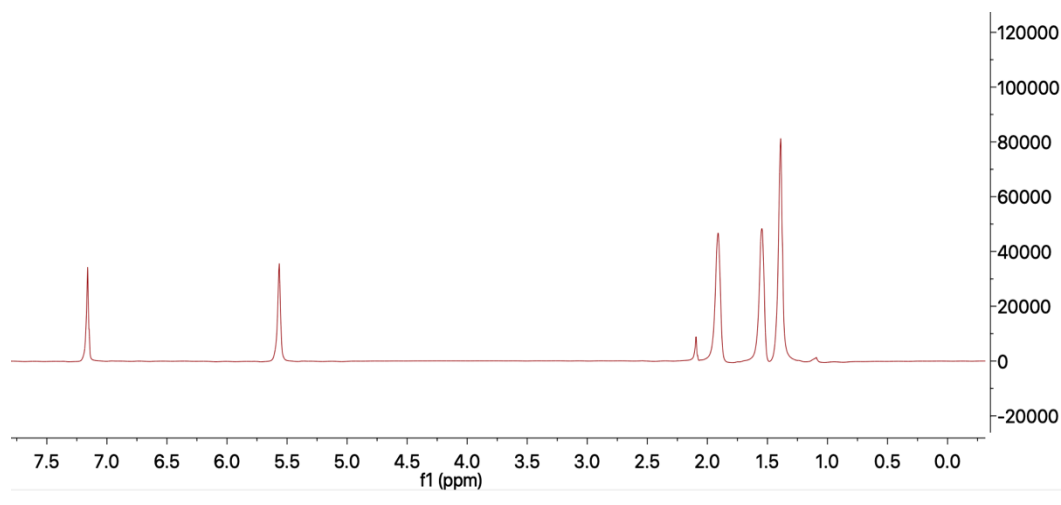
Figure A5.3 *Table 3.3 Entry 1 (AVG 77 Conversion) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*

Figure A5.4 *Table 3.3 Entry 2 (AVG 77 Conversion) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*

Figure A5.5 *Table 3.3 Entry 3 (AVG 77 Conversion) ¹H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*

Figure A5.6 *Table 3.3 Entry 4 (AVG 77 Conversion) ¹H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*

Figure A5.7 *Table 3.3 Entry 5 (AVG 77 Conversion) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*

Figure A5.8 *Table 3.3 Entry 6 (AVG 77 Conversion) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*

Figure A5.9 *Table 3.3 Entry 7 (AVG 77 Conversion) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*

Figure A5.10 *Table 3.3 Entry 8 (AVG 77 Conversion) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*

Figure A5.11 *Table 3.3 Entry 9 (AVG 77 Conversion) ¹H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
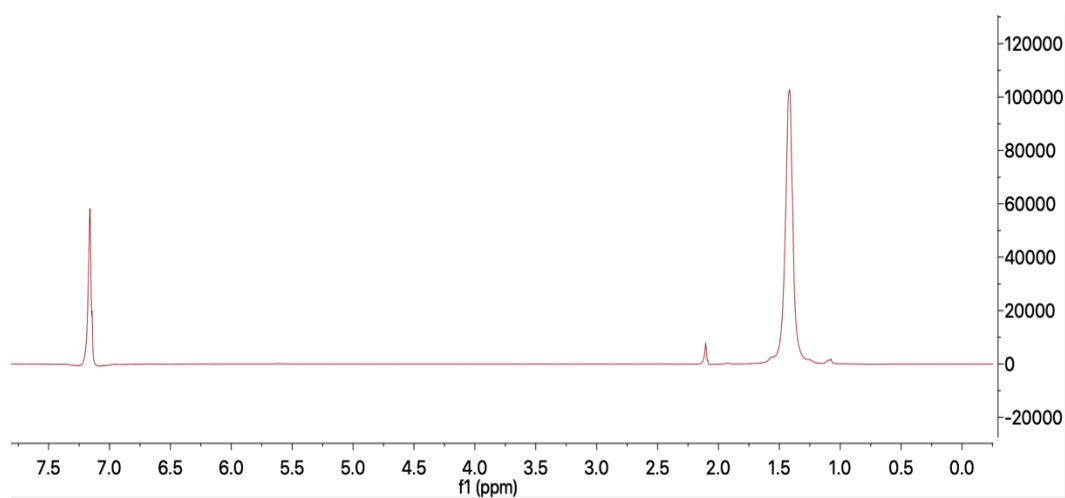
Figure A5.12 *Table 3.3 Entry 10 (AVG 77 Conversion) ¹H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
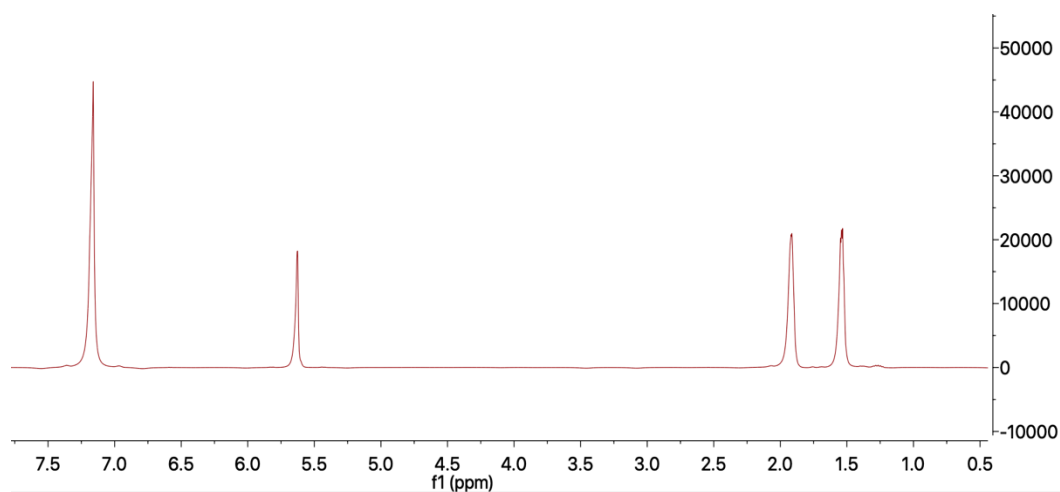
Figure A5.13 *(Spiked With 50% Benzene) @ 0 Min ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
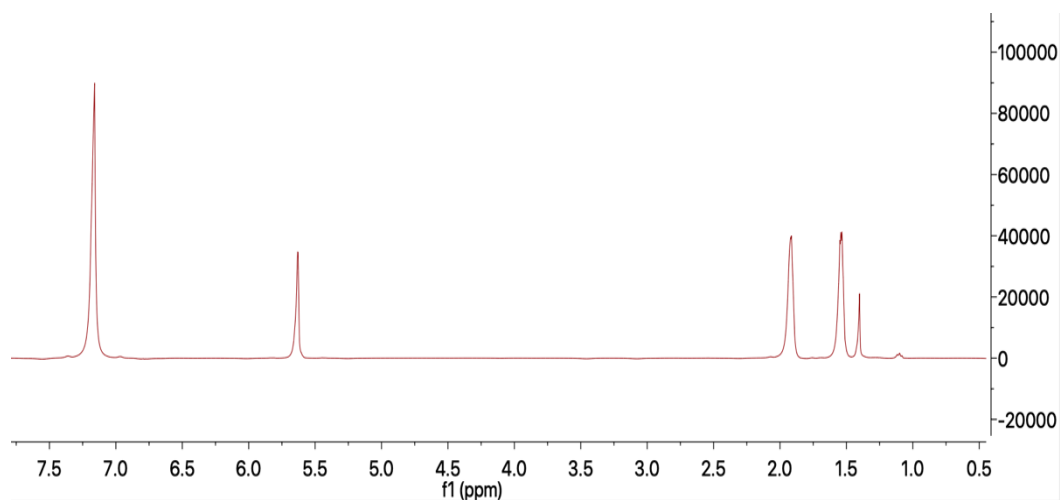
Figure A5.14 *Table 3.3 Entry 1 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
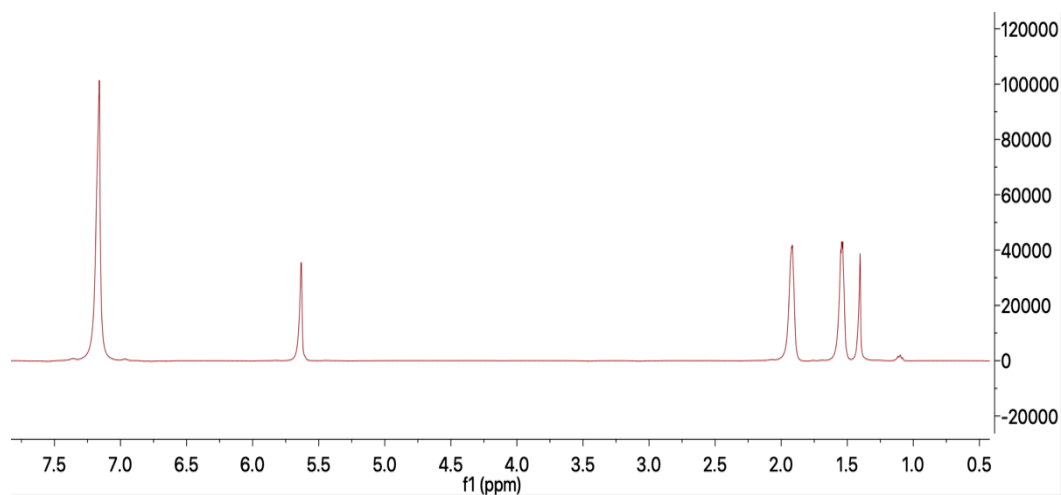
Figure A5.15 *Table 3.3 Entry 2 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
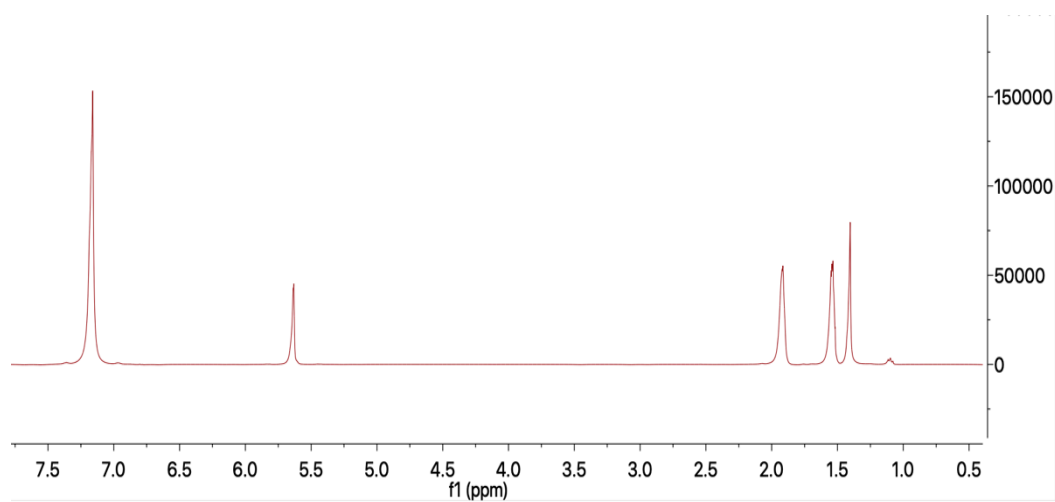
Figure A5.16 *Table 3.3 Entry 3 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
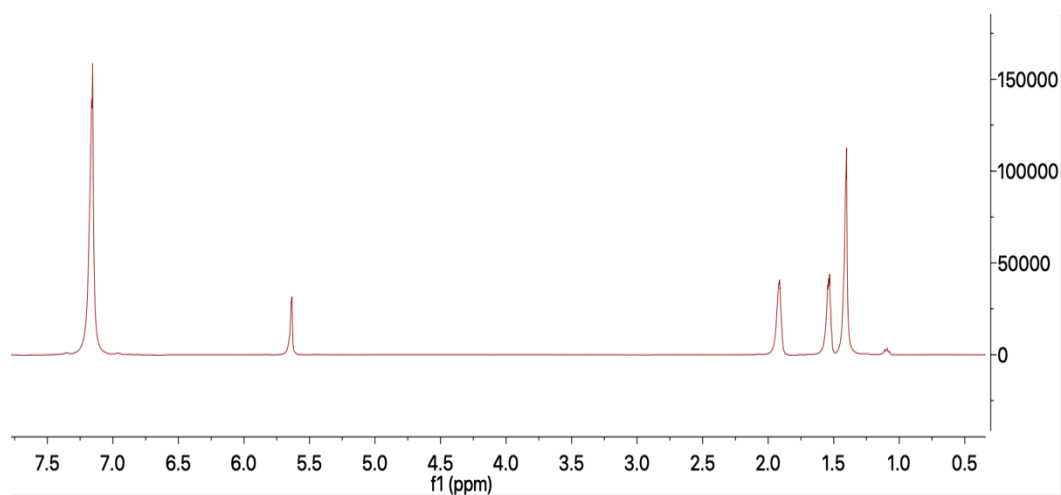
Figure A5.17 *Table 3.3 Entry 4 (Spiked With 50% Benzene) ¹H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
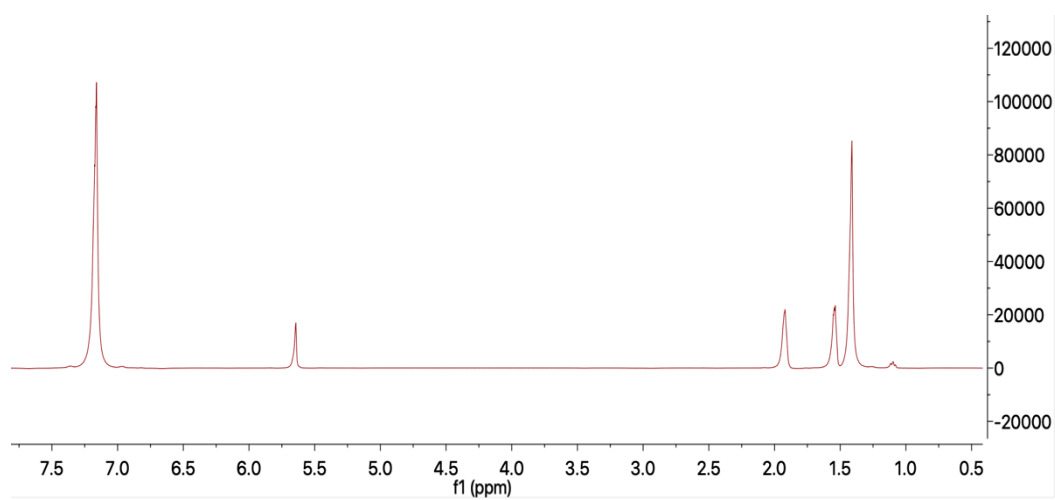
Figure A5.18 *Table 3.3 Entry 5 (Spiked With 50% Benzene) ¹H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
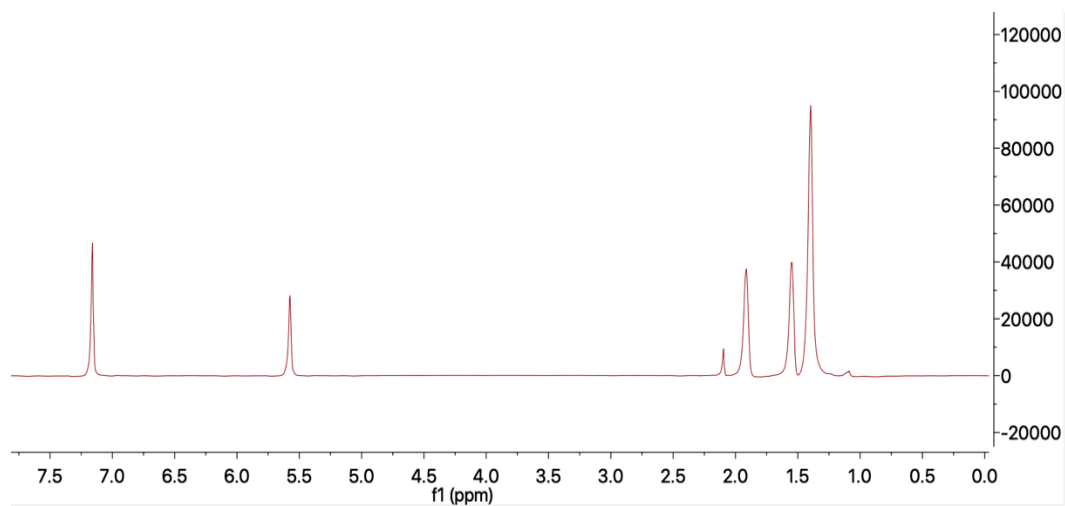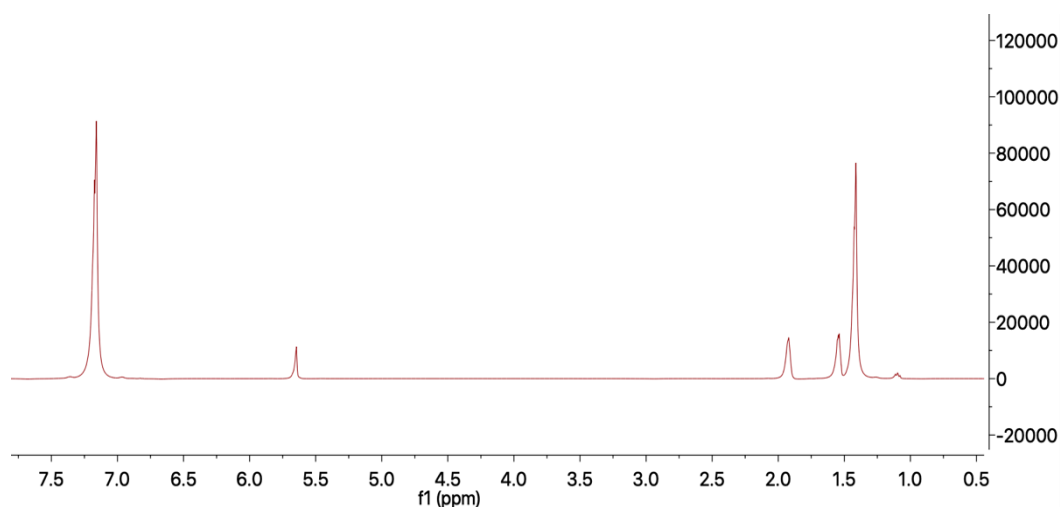
Figure A5.19 *Table 3.3 Entry 6 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
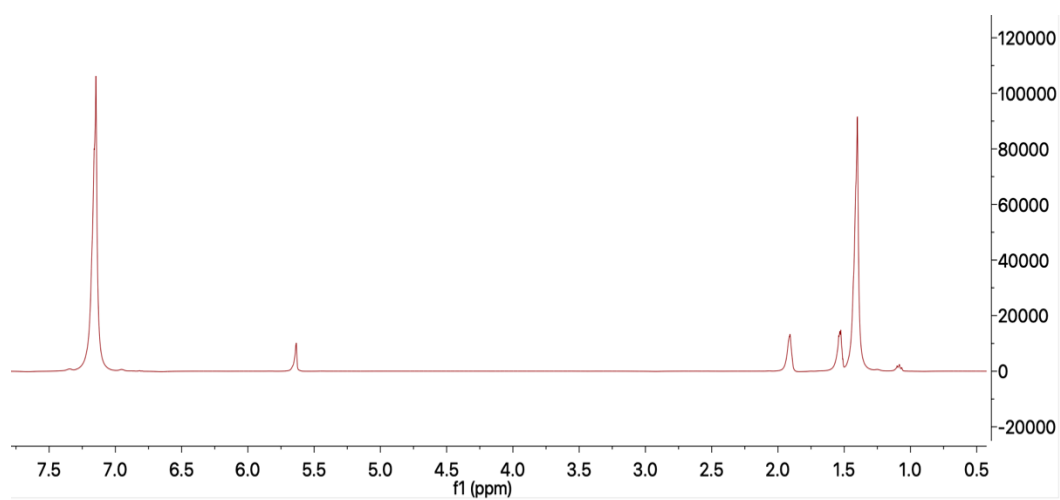
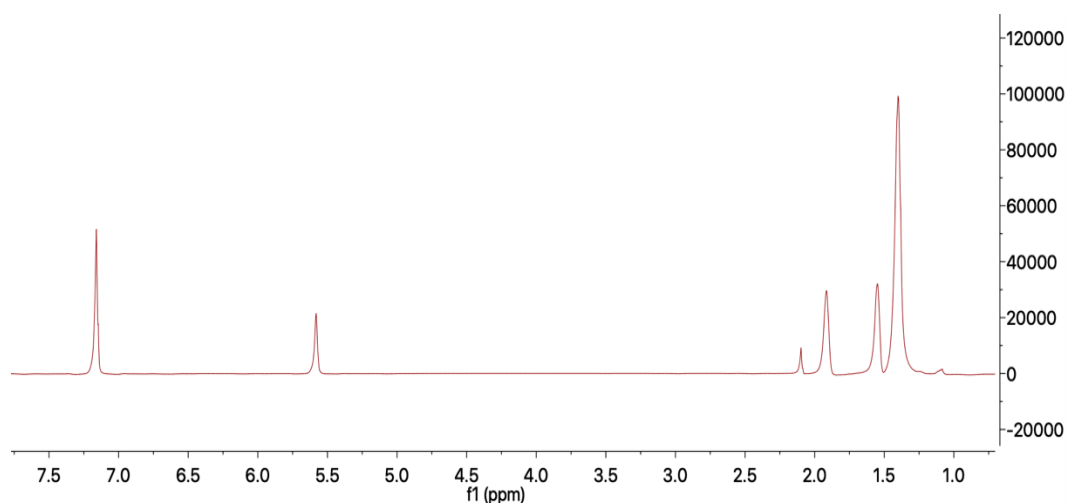**Figure A5.20** *Table 3.3 Entry 7 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
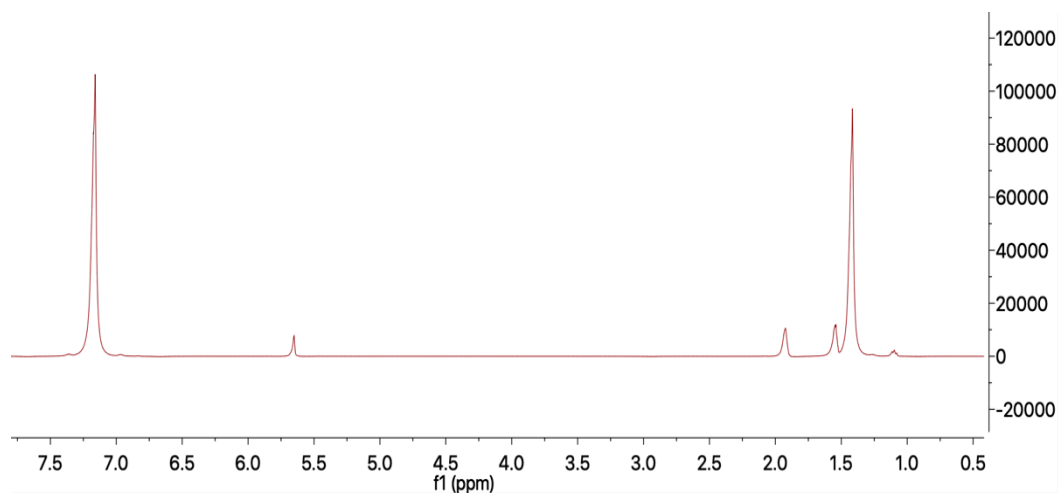
Figure A5.21 *Table 3.3 Entry 8 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
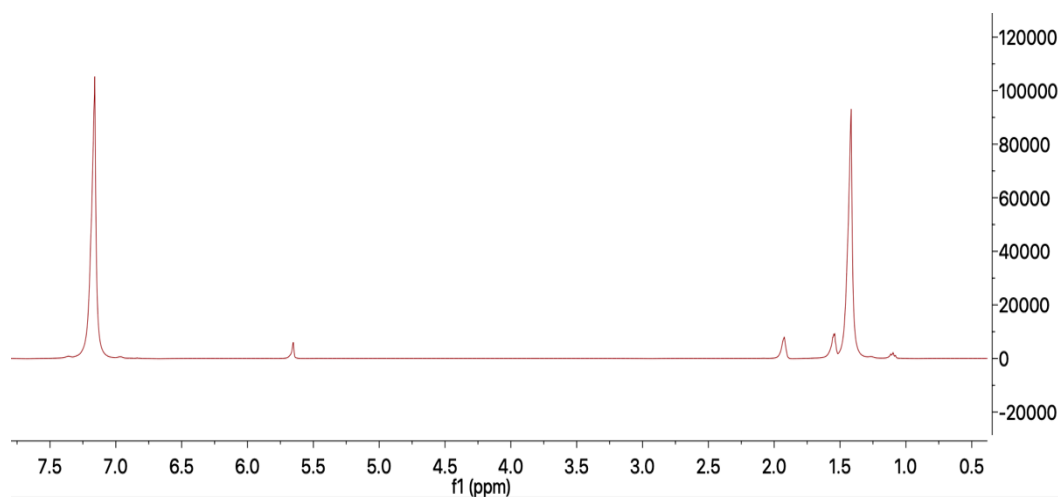
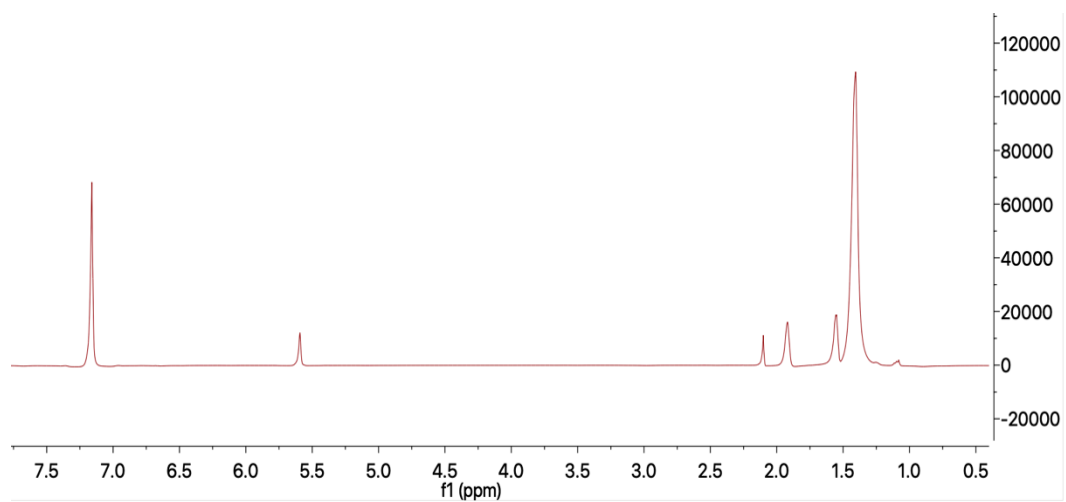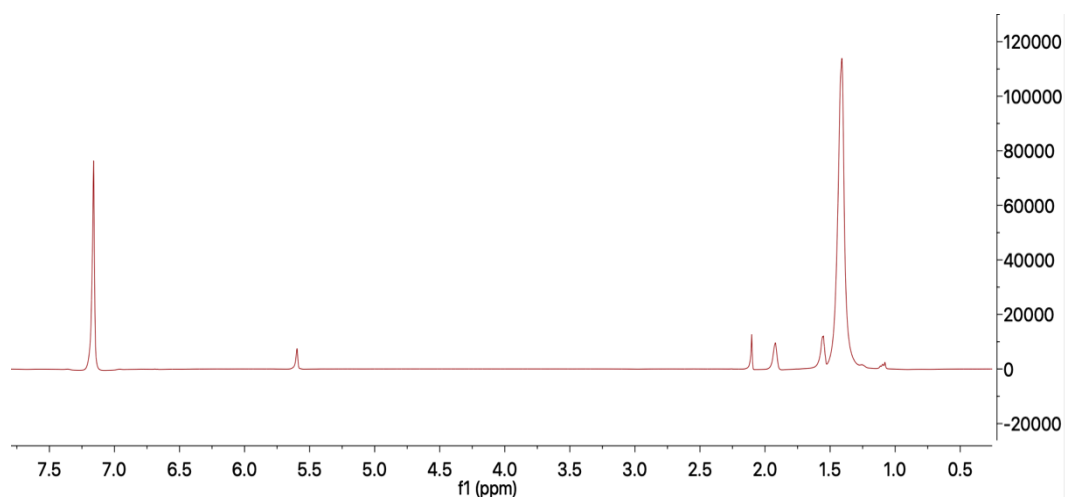**Figure A5.22** *Table 3.3 Entry 9 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
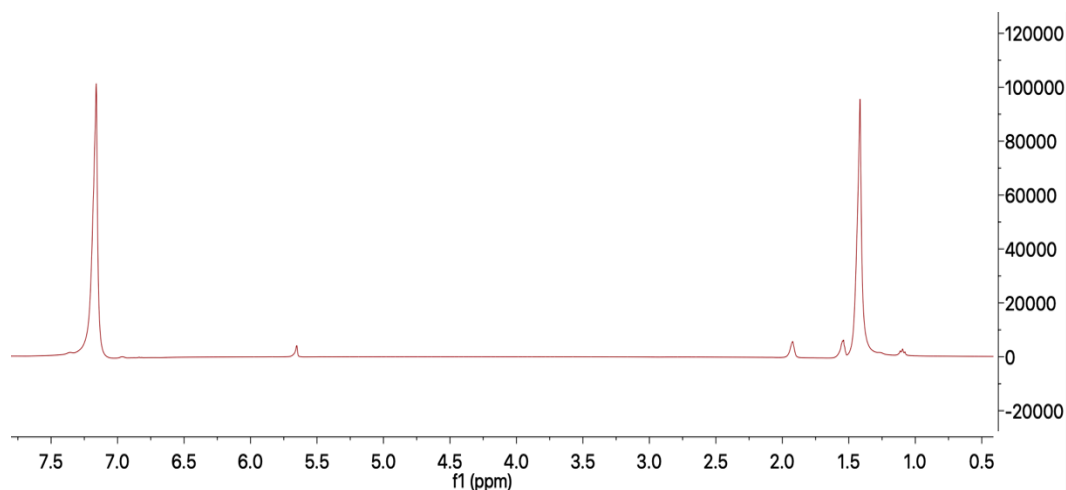
Figure A5.23 *Table 3.3 Entry 10 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
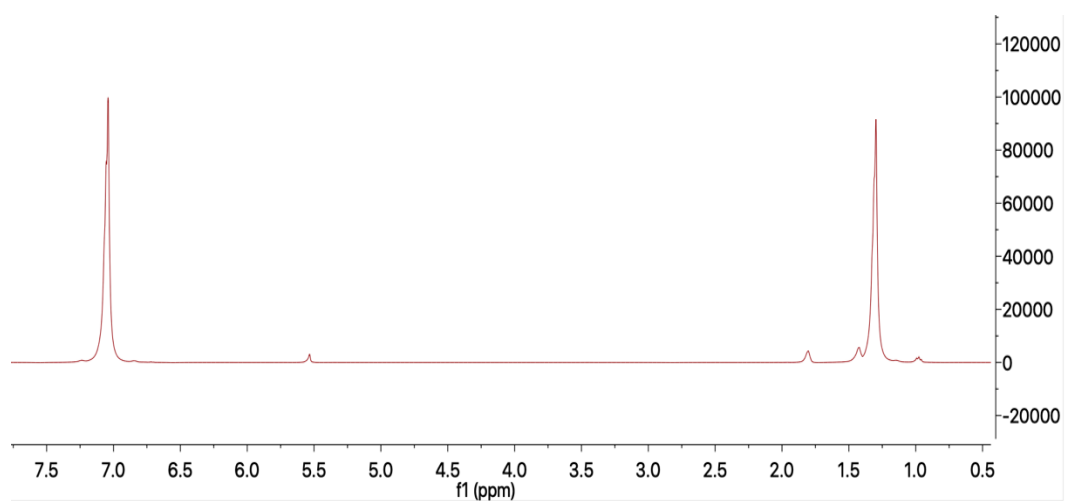
Figure A5.24 *Table 3.3 Entry 11 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard*
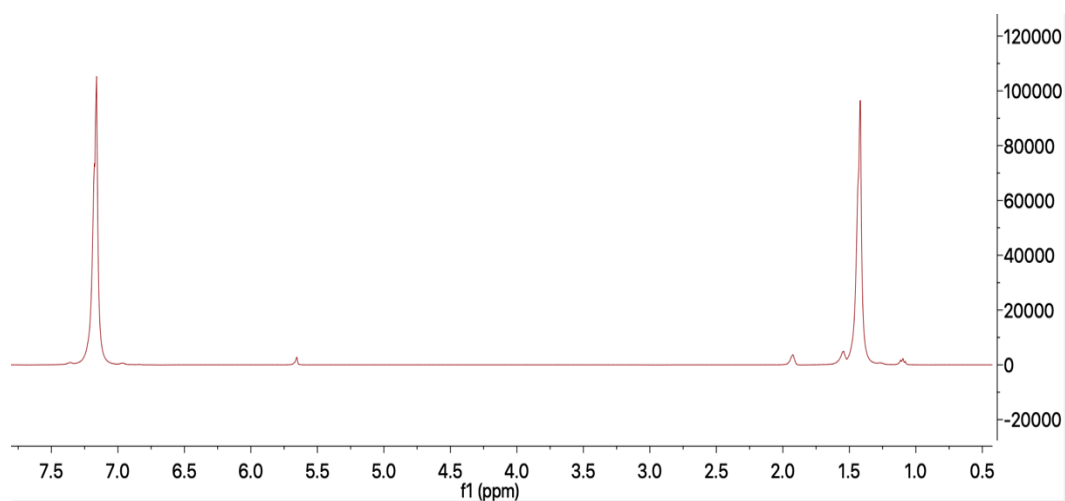
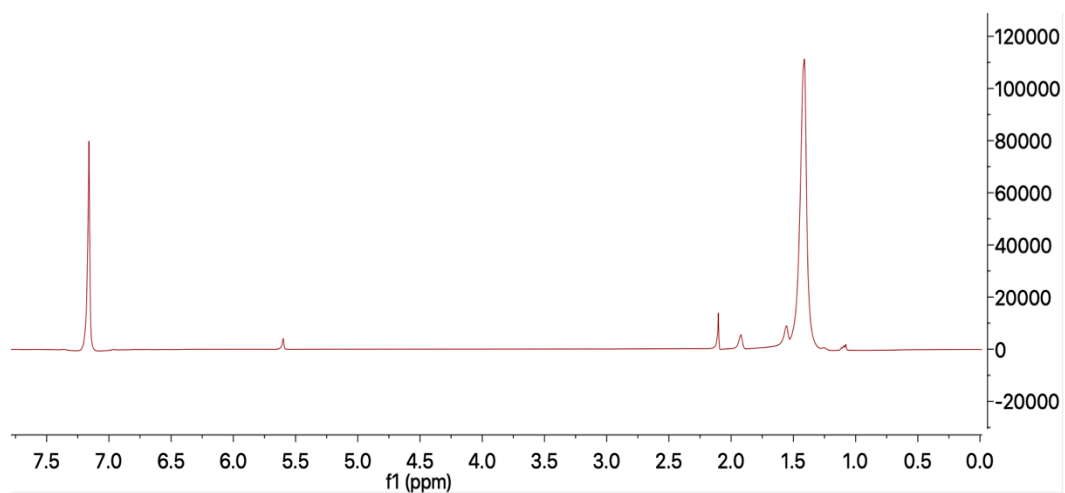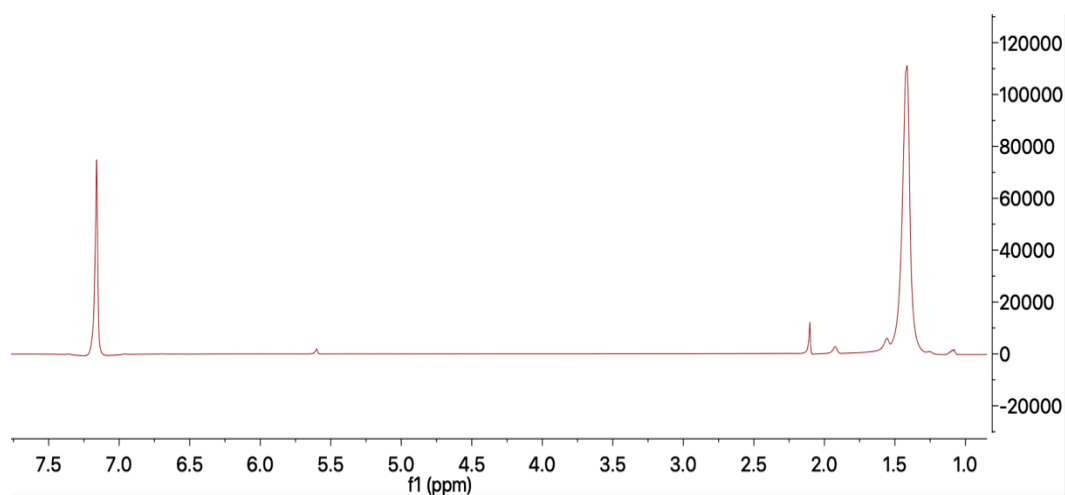**Figure A5.25** Table 3.3 Entry 12 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard
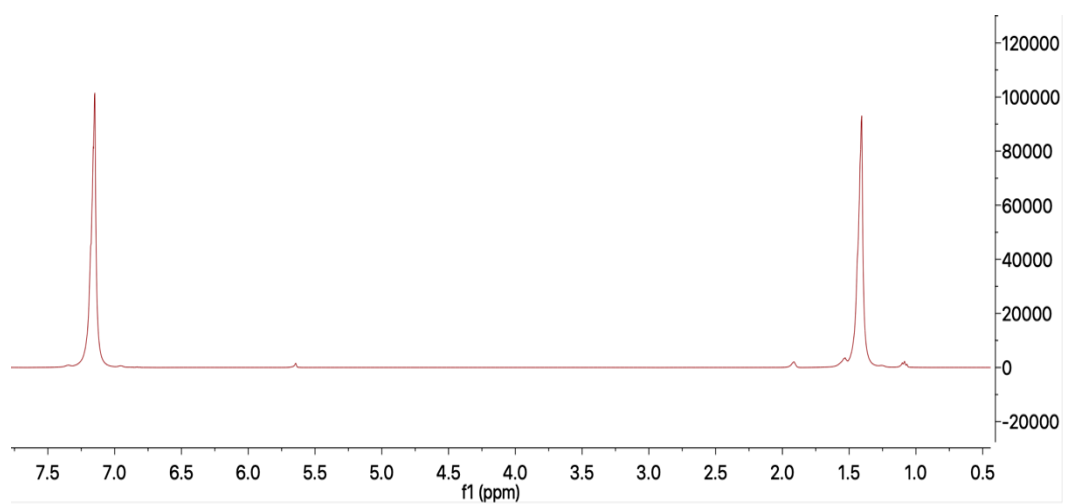
Figure A5.26 Table 3.3 Entry 13 (Spiked With 50% Benzene) ^{1}H NMR (400 MHz, Neat Reaction) of Crude Reaction, Yield Calculated with Hexamethylbenzene as an Internal Standard

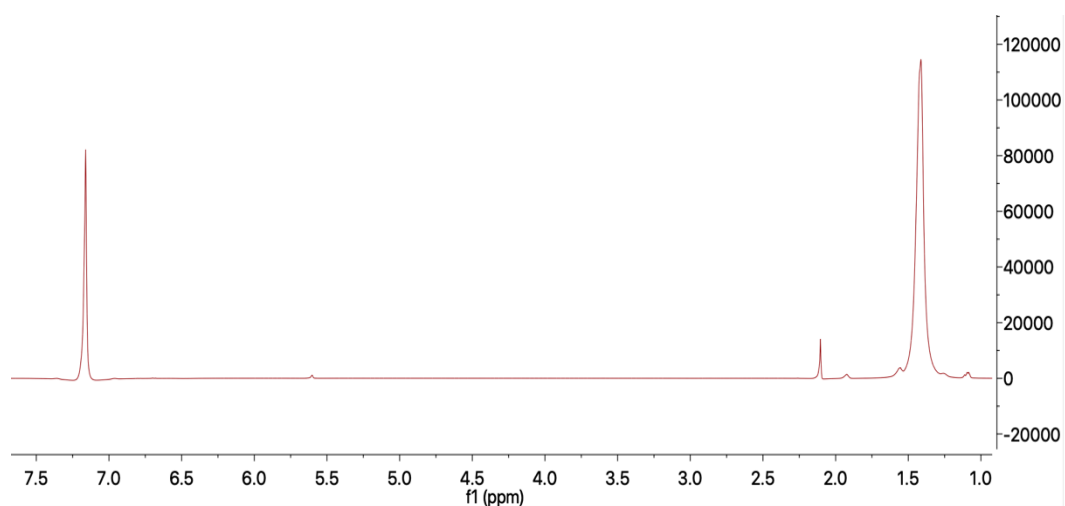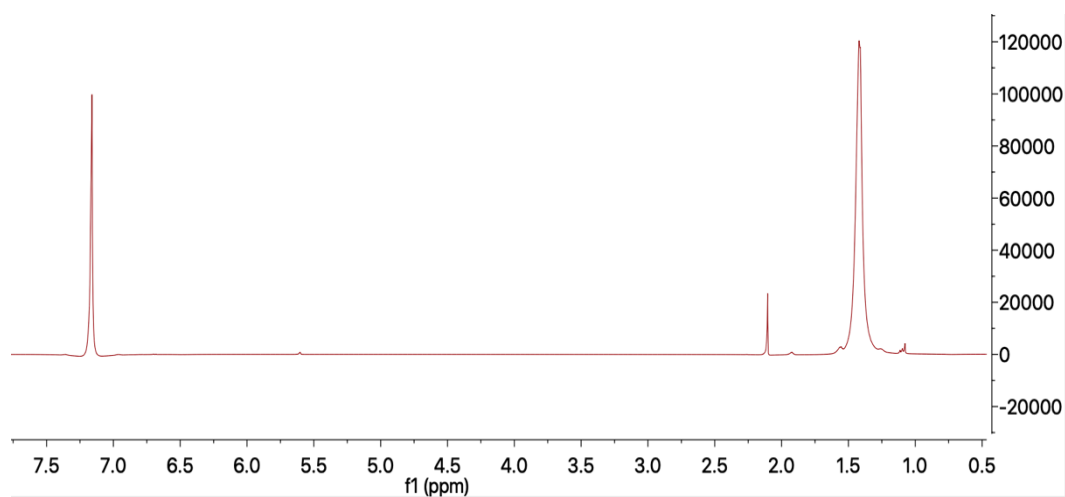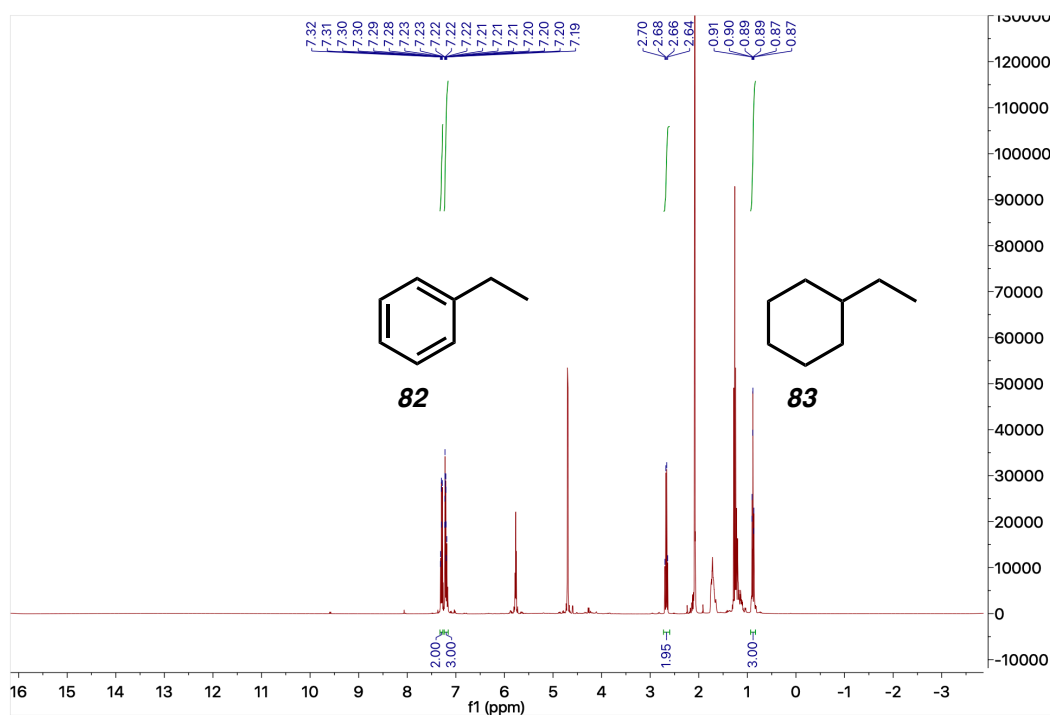**Figure A5.27** *Table 3.4 Entry 3 ¹H NMR (400 MHz, Neat Reaction) of Crude Reaction Showing Full Conversion to Ethylbenzene (**82**) and Ethylcyclohexane (**83**), Yield Calculated with Cis-1,4-Diacetoxy-2-Butene as an Internal Standard – 97% Purity.*
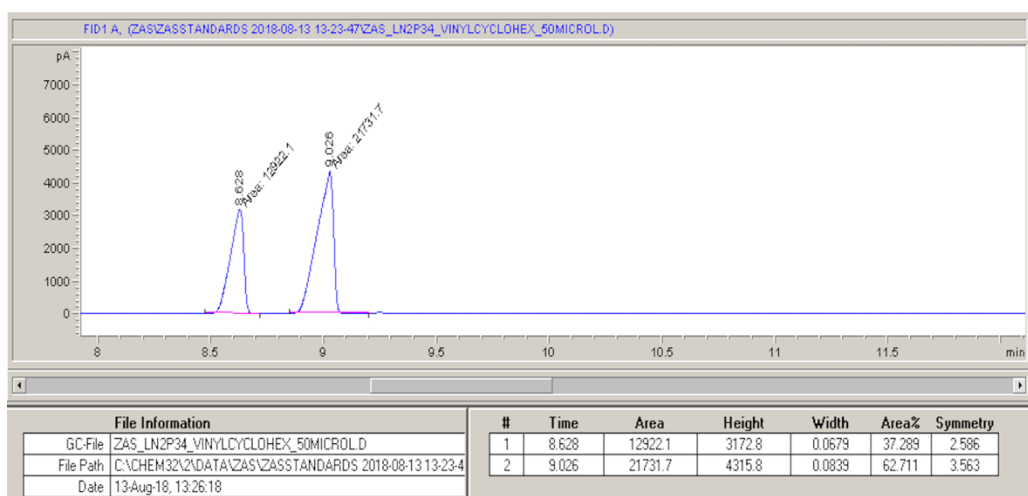
Figure A5.28 *GC Spectra of **81** Crude Reaction: **83** @8.63 and **82**@9.03 Using ZAS2 Method in Table A5.2*
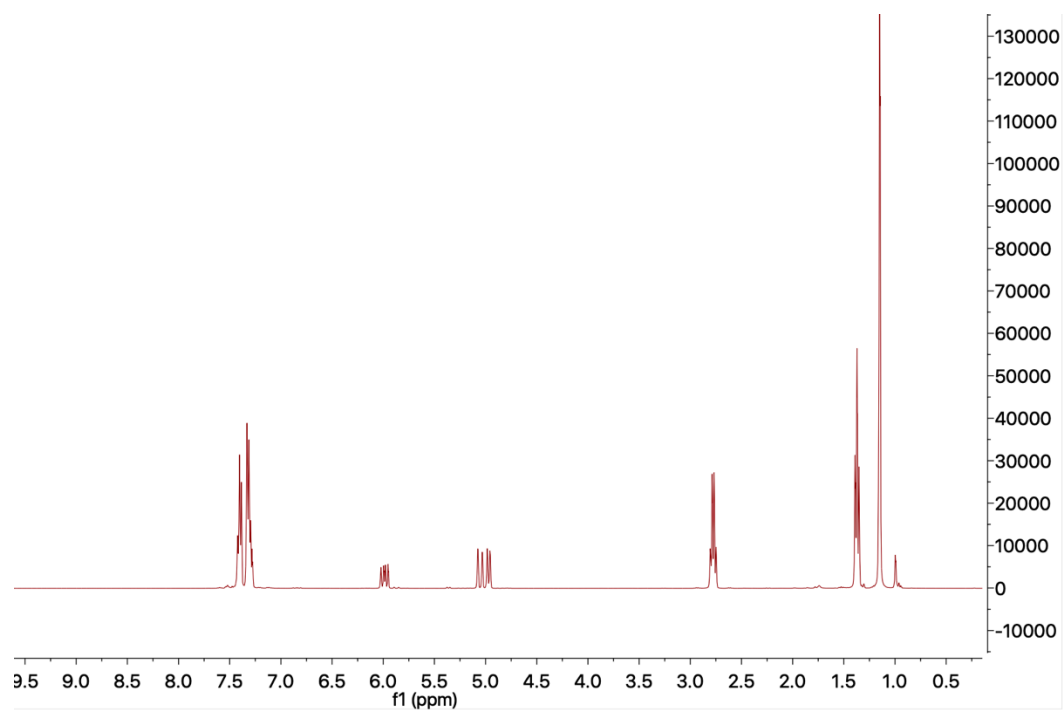
Figure A5.29 *Scheme 3.7 ¹H NMR (400 MHz, Neat Reaction) of Crude Reaction Showing No Conversion*

COMPREHENSIVE BIBLIOGRAPHY

1.   Bischler, A.; Napieralski, B., *Berichte der deutschen chemischen Gesellschaft* **1893,** 26 (2), 1903-1908.

2.   Pictet, A.; Spengler, T., *Berichte der deutschen chemischen Gesellschaft* **1911,** 44 (3), 2030-2036.

3.   Franzen, H.; Kempf, H., *Berichte der deutschen chemischen Gesellschaft* **1917,** 50 (1), 101-104.

4.   Anderson, A. G.; Anderson, R. G., *Journal of the American Chemical Society* **1955,** 77 (24), 6610-6611.

5.   E.W. Schoeffel, D. M. B. Naphthalene. August 28, 1956.

6.   Stevens Donna, G. H. H., Marshall B. Pearlman Phenols From Aromatic Sulfonic, Sulfamic, and Sulfone Compounds. April 22, 1958.

7.   Black, J. W.; Crowther, A. F.; Shanks, R. G.; Smith, L. H.; Dornhorst, A. C., *The Lancet* **1964,** 283 (7342), 1080-1081.

8.   Eisch, J. J. In *Adv. Heterocycl. Chem.*, Katritzky, A. R., Boulton, A. J., Eds. Academic Press: 1967; Vol. 7, pp 1-37.

9.   Cantrell, T. S.; Shechter, H., *The Journal of Organic Chemistry* **1968,** 33 (1), 114-118.

10.   Kaminsky, D.; Meltzer, R. I., *J. Med. Chem.* **1968,** 11 (1), 160-163.

11.   Buechi, G.; Wuest, H., *The Journal of Organic Chemistry* **1971,** 36 (4), 609-610.

12.   Somersall, A. C.; Guillet, J. E., *Macromolecules* **1972,** 5 (4), 410-415.

13.   Kress, T. J.; Costantino, S. M., *J. Heterocycl. Chem.* **1973,** 10 (3), 409-410.

14.   Moulton, C. J.; Shaw, B. L., *J. Chem. Soc., Dalton Trans.* **1976,** (11), 1020-1024.

15.   Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry: Part A: Structure and Mechanisms*, Carey, F. A., Sundberg, R. J., Eds. Springer US: Boston, MA, 1977; pp 325-360.

16.   Crabtree, R. H.; Mihelcic, J. M.; Quirk, J. M., *Journal of the American Chemical Society* **1979,** 101 (26), 7738-7740.

17.   Laguerre, M.; Felix, G.; Dunogues, J.; Calas, R., *The Journal of Organic Chemistry* **1979,** 44 (24), 4275-4278.

18.   Baudry, D.; Ephritikhine, M.; Felkin, H., *J. Chem. Soc., Chem. Commun.* **1980,** (24), 1243-1244.

19.   Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Parnell, C. A.; Quirk, J. M.; Morris, G. E., *Journal of the American Chemical Society* **1982,** 104 (25), 6994-7001.

20.   Crabtree, R. H.; Mellea, M. F.; Mihelcic, J. M.; Quirk, J. M., *Journal of the American Chemical Society* **1982,** 104 (1), 107-113.

21.   Baudry, D.; Ephritikhine, M.; Felkin, H.; Holmes-Smith, R., *J. Chem. Soc., Chem. Commun.* **1983,** (14), 788-789.

22.   Shiraiwa, M.; Sakamoto, T.; Yamanaka, H., *Chem. Pharm. Bull. (Tokyo)* **1983,** 31 (7), 2275-2280.

23.   Wong, D. T.; Robertson, D. W.; Bymaster, F. P.; Krushinski, J. K.; Reid,
       L. R., *Life Sci.* **1988,** 43 (24), 2049-2057.

24.   Przybilla, K. J.; Vögtle, F., *Chem. Ber.* **1989,** 122 (2), 347-355.

25.   Brown, C. E.; Ishikawa, Y.; Hackett, P. A.; Rayner, D. M., *Journal of the
       American Chemical Society* **1990,** 112 (7), 2530-2536.

26.   Fan, Z.; Nakayama, K.; Sawanobori, T.; Hiraoka, M., *Pflügers Archiv*
       1992, 421 (5), 409-415.

27.   W. M. Castor, D. H. J., *Ullmann's Encyclopedia of Industrial Chemistry.*
       . 5th ed.; Wiley-VCH: Weinheim, 1994; p 332.

28.   Gupta, M.; Hagen, C.; Flesher, R. J.; Kaska, W. C.; Jensen, C. M., *Chem.
       Commun.* **1996,** (17), 2083-2084.

29.   Hall, C.; Perutz, R. N., *Chemical Reviews* **1996,** 96 (8), 3125-3146.

30.   Nakayama, J. In *Comprehensive Heterocyclic Chemistry II*, Katritzky, A.
       R., Rees, C. W., Scriven, E. F. V., Eds. Pergamon: Oxford, 1996; pp
       607-677.

31.   Tyman, J. H. P. In *Studies in Organic Chemistry*, Elsevier: New York,
       1996; Vol. 52, pp 558-661.

32.   Gupta, M.; C. Kaska, W.; M. Jensen, C., *Chem. Commun.* **1997,** (5),
       461-462.

33.   Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M.,
       Journal of the American Chemical Society **1997,** 119 (4), 840-841.

34. Sun, X.-Z.; Grills, D. C.; Nikiforov, S. M.; Poliakoff, M.; George, M. W., *Journal of the American Chemical Society* **1997,** 119 (32), 7521-7525.

35. Foley, M.; Tilley, L., *Pharmacol. Ther.* **1998,** 79 (1), 55-87.

36. Liu, F.; S. Goldman, A., *Chem. Commun.* **1999,** (7), 655-656.

37. M. Jensen, C., *Chem. Commun.* **1999,** (24), 2443-2449.

38. Kanzelberger, M.; Singh, B.; Czerw, M.; Krogh-Jespersen, K.; Goldman, A. S., *Journal of the American Chemical Society* **2000,** 122 (44), 11017-11018.

39. Haenel, M. W.; Oevers, S.; Angermund, K.; Kaska, W. C.; Fan, H.-J.; Hall, M. B., *Angewandte Chemie International Edition* **2001,** 40 (19), 3596-3600.

40. Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R., *Journal of the American Chemical Society* **2001,** 123 (14), 3239-3242.

41. Watson, M. D.; Fechtenkötter, A.; Müllen, K., *Chemical Reviews* **2001,** 101 (5), 1267-1300.

42. Bangcuyo, C. G.; Rampey-Vaughn, M. E.; Quan, L. T.; Angel, S. M.; Smith, M. D.; Bunz, U. H. F., *Macromolecules* **2002,** 35 (5), 1563-1568.

43. Chenier, P. J., *Survey of Industrial Chemistry.* 3 ed.; Springer US: New York, 2002; p XV, 515.

44. Klapars, A.; Huang, X.; Buchwald, S. L., *Journal of the American Chemical Society* **2002,** 124 (25), 7421-7428.

45. Bymaster, F. P.; Beedle, E. E.; Findlay, J.; Gallagher, P. T.; Krushinski, J. H.; Mitchell, S.; Robertson, D. W.; Thompson, D. C.; Wallace, L.; Wong, D. T., *Bioorg. Med. Chem. Lett.* **2003,** 13 (24), 4477-4480.

46. de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L., *Tetrahedron* **2003,** 59 (1), 7-36.

47. Denmark, S. E.; Fu, J., *Chemical Reviews* **2003,** 103 (8), 2763-2794.

48. Hayashi, T.; Yamasaki, K., *Chemical Reviews* **2003,** 103 (8), 2829-2844.

49. Luo, Y.-R., Handbook of Bond Dissociation Energies in Organic Compounds. CRC Press: Boca Raton, 2003.

50. Renkema, K. B.; Kissin, Y. V.; Goldman, A. S., *Journal of the American Chemical Society* **2003,** 125 (26), 7770-7771.

51. Zhang, X.; Fried, A.; Knapp, S.; Goldman, A. S., *Chem. Commun.* **2003,** (16), 2060-2061.

52. Göttker-Schnetmann, I.; Brookhart, M., *Journal of the American Chemical Society* **2004,** 126 (30), 9330-9338.

53. Göttker-Schnetmann, I.; White, P.; Brookhart, M., *Journal of the American Chemical Society* **2004,** 126 (6), 1804-1811.

54. Göttker-Schnetmann, I.; White, P. S.; Brookhart, M., *Organometallics* **2004,** 23 (8), 1766-1776.

55. Morales-Morales, D.; Redón, R. o.; Yung, C.; Jensen, C. M., *Inorg. Chim. Acta* **2004,** 357 (10), 2953-2956.

56. Omae, I., *Coord. Chem. Rev.* **2004,** 248 (11), 995-1023.

57.   Ozerov, O. V.; Guo, C.; Papkov, V. A.; Foxman, B. M., *Journal of the American Chemical Society* **2004,** 126 (15), 4792-4793.

58.   Zhu, K.; Achord, P. D.; Zhang, X.; Krogh-Jespersen, K.; Goldman, A. S., *Journal of the American Chemical Society* **2004,** 126 (40), 13044-13053.

59.   Fraser, H. L.; Floyd, M. B.; Barrios Sosa, A. C. In *Prog. Heterocycl. Chem.*, Gribble, G. W., Joule, J. A., Eds. Elsevier: 2005; Vol. 17, pp 261-303.

60.   Kim, J. I.; Shin, I.-S.; Kim, H.; Lee, J.-K., *Journal of the American Chemical Society* **2005,** 127 (6), 1614-1615.

61.   Rossiter, S.; Péron, J.-M.; Whitfield, P. J.; Jones, K., *Bioorg. Med. Chem. Lett.* **2005,** 15 (21), 4806-4808.

62.   Zhan, Z.-P.; Yang, R.-F.; Lang, K., *Tetrahedron Letters* **2005,** 46 (22), 3859-3862.

63.   Bentley, K. W., *Nat. Prod. Rep.* **2006,** 23 (3), 444-463.

64.   Kuklin, S. A.; Sheloumov, A. M.; Dolgushin, F. M.; Ezernitskaya, M. G.; Peregudov, A. S.; Petrovskii, P. V.; Koridze, A. A., *Organometallics* **2006,** 25 (22), 5466-5476.

65.   Ranu, B. C.; Jana, R., *Eur. J. Org. Chem.* **2006,** 2006 (16), 3767-3770.

66.   Anthony, J. E., *Angewandte Chemie International Edition* **2008,** 47 (3), 452-483.

67.   Binder, J. B.; Raines, R. T., *Curr. Opin. Chem. Biol.* **2008,** 12 (6), 767-773.

68. Humljan, J.; Kotnik, M.; Contreras-Martel, C.; Blanot, D.; Urleb, U.; Dessen, A.; Šolmajer, T.; Gobec, S., *J. Med. Chem.* **2008,** 51 (23), 7486-7494.

69. Krohn, K.; Kouam, S. F.; Cludius-Brandt, S.; Draeger, S.; Schulz, B., *Eur. J. Org. Chem.* **2008,** 2008 (21), 3615-3618.

70. Lowell, A. N.; Fennie, M. W.; Kozlowski, M. C., *The Journal of Organic Chemistry* **2008,** 73 (5), 1911-1918.

71. Romero, P. E.; Whited, M. T.; Grubbs, R. H., *Organometallics* **2008,** 27 (14), 3422-3429.

72. Azerraf, C.; Gelman, D., *Organometallics* **2009,** 28 (22), 6578-6584.

73. Huang, Z.; Brookhart, M.; Goldman, A. S.; Kundu, S.; Ray, A.; Scott, S. L.; Vicente, B. C., *Adv. Synth. Catal.* **2009,** 351 (1-2), 188-206.

74. Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L., *Coord. Chem. Rev.* **2009,** 253 (5), 687-703.

75. Kundu, S.; Choliy, Y.; Zhuo, G.; Ahuja, R.; Emge, T. J.; Warmuth, R.; Brookhart, M.; Krogh-Jespersen, K.; Goldman, A. S., *Organometallics* **2009,** 28 (18), 5432-5444.

76. Ahuja, R.; Punji, B.; Findlater, M.; Supplee, C.; Schinski, W.; Brookhart, M.; Goldman, A. S., *Nat. Chem.* **2010,** 3, 167.

77. Brunetti, F. G.; Gong, X.; Tong, M.; Heeger, A. J.; Wudl, F., *Angewandte Chemie International Edition* **2010,** 49 (3), 532-536.

78. Crabtree, R. H., *Chemical Reviews* **2010,** 110 (2), 575-575.

79.   Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G., *Chemical Society Reviews* **2010,** 39 (6), 2093-2105.

80.   Hebden, T. J.; Goldberg, K. I.; Heinekey, D. M.; Zhang, X.; Emge, T. J.; Goldman, A. S.; Krogh-Jespersen, K., *Inorg. Chem.* **2010,** 49 (4), 1733-1742.

81.   Huang, Z.; Rolfe, E.; Carson, E. C.; Brookhart, M.; Goldman, A. S.; El-Khalafy, S. H.; MacArthur, A. H. R., *Adv. Synth. Catal.* **2010,** 352 (1), 125-135.

82.   Punji, B.; Emge, T. J.; Goldman, A. S., *Organometallics* **2010,** 29 (12), 2702-2709.

83.   Stabile, P.; Lamonica, A.; Ribecai, A.; Castoldi, D.; Guercio, G.; Curcuruto, O., *Tetrahedron Letters* **2010,** 51 (24), 3232-3235.

84.   Chien, R.-H.; Lai, C.-T.; Hong, J.-L., *The Journal of Physical Chemistry C* **2011,** 115 (13), 5958-5965.

85.   Izawa, Y.; Pun, D.; Stahl, S. S., *Science* **2011,** 333 (6039), 209.

86.   Pan, M.; Lin, X.-M.; Li, G.-B.; Su, C.-Y., *Coord. Chem. Rev.* **2011,** 255 (15), 1921-1936.

87.   Schultz, K. M.; Goldberg, K. I.; Gusev, D. G.; Heinekey, D. M., *Organometallics* **2011,** 30 (6), 1429-1437.

88.   Zhang, X.; Wang, D. Y.; Emge, T. J.; Goldman, A. S., *Inorg. Chim. Acta* **2011,** 369 (1), 253-259.

89.   Abe, M.; Eto, M.; Yamaguchi, K.; Yamasaki, M.; Misaka, J.; Yoshitake, Y.; Otsuka, M.; Harano, K., *Tetrahedron* **2012,** 68 (18), 3566-3576.

90.   Biswas, S.; Huang, Z.; Choliy, Y.; Wang, D. Y.; Brookhart, M.; Krogh-
        Jespersen, K.; Goldman, A. S., *Journal of the American Chemical
        Society* **2012,** 134 (32), 13276-13295.

91.   Gunnoe, B. T. In *Alkane C-H Activation Activation By Single-Site Metal
        Catalysis*, 1 ed.; Perez, P. J., Ed. Springer Netherlands: Dordrecht, 2012;
        pp 1-15.

92.   Lyons, T. W.; Guironnet, D.; Findlater, M.; Brookhart, M., *Journal of
        the American Chemical Society* **2012,** 134 (38), 15708-15711.

93.   Matano, Y.; Saito, A.; Suzuki, Y.; Miyajima, T.; Akiyama, S.; Otsubo,
        S.; Nakamoto, E.; Aramaki, S.; Imahori, H., *Chemistry – An Asian
        Journal* **2012,** 7 (10), 2305-2312.

94.   Michael Findlater, J. C., Alan S. Goldman, Maurice Brookhart. In *Alkane
        C-H Activation Activation By Single-Site Metal Catalysis*, 1 ed.; Perez, P.
        J., Ed. Springer Netherlands: Dordrecht, 2012; pp 113-141.

95.   Nishida, J.-i.; Tsukaguchi, S.; Yamashita, Y., *Chemistry – A European
        Journal* **2012,** 18 (29), 8964-8970.

96.   Spadaro, A.; Frotscher, M.; Hartmann, R. W., *J. Med. Chem.* **2012,** 55
        (5), 2469-2473.

97.   Wang, Y.; Zhang, X.; Zhao, J.; Xie, S.; Wang, C., *J. Med. Chem.* **2012,**
        55 (7), 3502-3512.

98.   Wood, J. D.; Jellison, J. L.; Finke, A. D.; Wang, L.; Plunkett, K. N.,
        Journal of the American Chemical Society **2012,** 134 (38), 15783-15789.

99.   Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A., *Adv. Synth. Catal.* **2013,** 355 (11-12), 2203-2207.

100.   Deria, P.; Von Bargen, C. D.; Olivier, J.-H.; Kumbhar, A. S.; Saven, J. G.; Therien, M. J., *Journal of the American Chemical Society* **2013,** 135 (43), 16220-16234.

101.   Dobereiner, G. E.; Yuan, J.; Schrock, R. R.; Goldman, A. S.; Hackenberg, J. D., *Journal of the American Chemical Society* **2013,** 135 (34), 12572-12575.

102.   Kundu, S.; Lyons, T. W.; Brookhart, M., *ACS Catalysis* **2013,** 3 (8), 1768-1773.

103.   Liu, X.; Braunstein, P., *Inorg. Chem.* **2013,** 52 (13), 7367-7379.

104.   Musa, S.; Ackermann, L.; Gelman, D., *Adv. Synth. Catal.* **2013,** 355 (14-15), 3077-3080.

105.   Nawara-Hultzsch, A. J.; Hackenberg, J. D.; Punji, B.; Supplee, C.; Emge, T. J.; Bailey, B. C.; Schrock, R. R.; Brookhart, M.; Goldman, A. S., *ACS Catalysis* **2013,** 3 (11), 2505-2514.

106.   Pho, T. V.; Toma, F. M.; Chabinyc, M. L.; Wudl, F., *Angewandte Chemie International Edition* **2013,** 52 (5), 1446-1451.

107.   Romm, D. G. a. R. In *Organometallic Pincer Chemistry*, Gerard Van Koten, D. M., Ed. Springer-Verlag Berlin Heidelberg: Heidelberg, 2013; pp 289-317.

108.   Shi, Y.; Suguri, T.; Dohi, C.; Yamada, H.; Kojima, S.; Yamamoto, Y., *Chemistry – A European Journal* **2013,** 19 (32), 10672-10689.

109. Zhang, H.-P.; Li, H.-Y.; Xiao, H.-F., *Journal of Chemical Research* **2013,** 37 (9), 556-558.

110. Bézier, D.; Brookhart, M., *ACS Catalysis* **2014,** 4 (10), 3411-3420.

111. Brayton, D. F.; Beaumont, P. R.; Fukushima, E. Y.; Sartain, H. T.; Morales-Morales, D.; Jensen, C. M., *Organometallics* **2014,** 33 (19), 5198-5202.

112. Dang, J.-S.; Wang, W.-W.; Zhao, X.; Nagase, S., *Org. Lett.* **2014,** 16 (1), 170-173.

113. Despiau, C. F.; Dominey, A. P.; Harrowven, D. C.; Linclau, B., *Eur. J. Org. Chem.* **2014,** 2014 (20), 4335-4341.

114. El-Sheshtawy, H. S.; Abou Baker, A. M., *J. Mol. Struct.* **2014,** 1067, 225-232.

115. Fancelli, D.; Abate, A.; Amici, R.; Bernardi, P.; Ballarini, M.; Cappa, A.; Carenzi, G.; Colombo, A.; Contursi, C.; Di Lisa, F.; Dondio, G.; Gagliardi, S.; Milanesi, E.; Minucci, S.; Pain, G.; Pelicci, P. G.; Saccani, A.; Storto, M.; Thaler, F.; Varasi, M.; Villa, M.; Plyte, S., *J. Med. Chem.* **2014,** 57 (12), 5333-5347.

116. Jia, X.; Zhang, L.; Qin, C.; Leng, X.; Huang, Z., *Chem. Commun.* **2014,** 50 (75), 11056-11059.

117. Liu, X.; Jiang, L.; Li, J.; Wang, L.; Yu, Y.; Zhou, Q.; Lv, X.; Gong, W.; Lu, Y.; Wang, J., *Journal of the American Chemical Society* **2014,** 136 (38), 13094-13097.

118. Ouros, A.; Oberson de Souza, M.; Pastore, H., *Journal of the Brazilian Chemical Society* **2014,** 25.

119. Schmidt, R.; Griesbaum, K.; Behr, A.; Biedenkapp, D.; Voges, H.-W.; Garbe, D.; Paetz, C.; Collin, G.; Mayer, D.; Höke, H., *Ullmann's Encyclopedia of Industrial Chemistry* **2014**, 1-74.

120. Schulze, M., *Chem. Ing. Tech.* **2014,** 86 (8), 1304-1304.

121. Yao, W.; Zhang, Y.; Jia, X.; Huang, Z., *Angewandte Chemie International Edition* **2014,** 53 (5), 1390-1394.

122. Zhang, X.; Xie, T.; Cui, M.; Yang, L.; Sun, X.; Jiang, J.; Zhang, G., *ACS Appl. Mater. Interfaces* **2014,** 6 (4), 2279-2284.

123. Akshai Kumar, A. S. G. In *The Privileged Pincer-Metal Platform: Coordination Chemistry & Applications*, Gerard Van Koten, R. A. G., Ed. Springer, Cham: Cham, 2015; Vol. 54, pp 307-334.

124. Banothu, J.; Basavoju, S.; Bavantula, R., *J. Heterocycl. Chem.* **2015,** 52 (3), 853-860.

125. Chang, J.; Song, X.; Huang, W.; Zhu, D.; Wang, M., *Chem. Commun.* **2015,** 51 (84), 15362-15365.

126. DeBono, A.; Capuano, B.; Scammells, P. J., *J. Med. Chem.* **2015,** 58 (15), 5699-5727.

127. Ding, L.; Yang, C.; Su, Z.; Pei, J., *Science China Chemistry* **2015,** 58 (2), 364-369.

128. Girard, S. A.; Huang, H.; Zhou, F.; Deng, G.-J.; Li, C.-J., *Organic Chemistry Frontiers* **2015,** 2 (3), 279-287.

129. Lyons, T. W.; Bézier, D.; Brookhart, M., *Organometallics* **2015,** 34 (16), 4058-4062.

130. Ponra, S.; Vitale, M.; Michelet, V.; Ratovelomanana-Vidal, V., *Arkivoc* **2015,** 2016.

131. Zhang, Z.-H.; Zhang, H.-J.; Deng, A.-J.; Wang, B.; Li, Z.-H.; Liu, Y.; Wu, L.-Q.; Wang, W.-J.; Qin, H.-L., *J. Med. Chem.* **2015,** 58 (18), 7557-7571.

132. Costa, E. V.; Pinheiro, M. L. B.; Maia, B. H. L. N. S.; Marques, F. A.; Ruiz, A. L. T. G.; Marchetti, G. M.; Carvalho, J. E. d.; Soares, M. B. P.; Costa, C. O. S.; Galvão, A. F. C.; Lopes, N. P.; Koolen, H. H. F.; Bezerra, D. P.; Barison, A., *J. Nat. Prod.* **2016,** 79 (6), 1524-1531.

133. Ke, Z.; Tsui, G. C.; Peng, X.-S.; Yeung, Y.-Y. In *Prog. Heterocycl. Chem.*, Gribble, G. W., Joule, J. A., Eds. Elsevier: 2016; Vol. 28, pp 219-274.

134. Kwan, E. H.; Kawai, Y. J.; Kamakura, S.; Yamashita, M., *Dalton Trans.* **2016,** 45 (40), 15931-15941.

135. Li, Y.; Clevenger, R. G.; Jin, L.; Kilway, K. V.; Peng, Z., *The Journal of Physical Chemistry C* **2016,** 120 (2), 841-852.

136. Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B., *Journal of the American Chemical Society* **2016,** 138 (10), 3294-3297.

137. Rossi, R.; Lessi, M.; Manzini, C.; Marianetti, G.; Bellina, F., *Synthesis* **2016,** 48 (22), 3821-3862.

138. Yuan, B.; Zhuang, J.; Kirmess, K. M.; Bridgmohan, C. N.; Whalley, A. C.; Wang, L.; Plunkett, K. N., *The Journal of Organic Chemistry* **2016,** 81 (18), 8312-8318.

139. Ando, H.; Kusumoto, S.; Wu, W.; Nozaki, K., *Organometallics* **2017,** 36 (12), 2317-2322.

140. Enoki, T.; Matsuo, K.; Ohshita, J.; Ooyama, Y., *Phys. Chem. Chem. Phys.* **2017,** 19 (5), 3565-3574.

141. Jana, A.; Misztal, K.; Żak, A.; Grela, K., *The Journal of Organic Chemistry* **2017,** 82 (8), 4226-4234.

142. Jayaram, V.; Sridhar, T.; Sharma, G. V. M.; Berrée, F.; Carboni, B., *The Journal of Organic Chemistry* **2017,** 82 (3), 1803-1811.

143. Kumar, A.; Bhatti, T. M.; Goldman, A. S., *Chemical Reviews* **2017,** 117 (19), 12357-12384.

144. Vardanyan, R. In *Piperidine-Based Drug Discovery*, Vardanyan, R., Ed. Elsevier: 2017; pp 299-332.

145. Wen, L.-R.; Dou, Q.; Wang, Y.-C.; Zhang, J.-W.; Guo, W.-S.; Li, M., *The Journal of Organic Chemistry* **2017,** 82 (3), 1428-1436.

146. Bizzarri, C.; Spuling, E.; Knoll, D. M.; Volz, D.; Bräse, S., *Coord. Chem. Rev.* **2018,** 373, 49-82.

147. Jayaram, V.; Sridhar, T.; Sharma, G. V. M.; Berrée, F.; Carboni, B., *The Journal of Organic Chemistry* **2018,** 83 (2), 843-853.

148. Kidonakis, M.; Mullaj, A.; Stratakis, M., *The Journal of Organic Chemistry* **2018,** 83 (24), 15553-15557.

149. Yavari, I.; Khajeh-Khezri, A., *Synthesis* **2018,** 50 (20), 3947-3973.

150. Balewski, Ł.; Sączewski, F.; Gdaniec, M.; Kornicka, A.; Cicha, K.; Jalińska, A., *Molecules (Basel, Switzerland)* **2019,** 24 (22), 4070.

151. He, X.; Zheng, Y.-W.; Lei, T.; Liu, W.-Q.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z., *Catalysis Science & Technology* **2019,** 9 (13), 3337-3341.

152. Mahato, S.; Mukherjee, A.; Santra, S.; Zyryanov, G. V.; Majee, A., *Org. Biomol. Chem.* **2019,** 17 (34), 7907-7917.

153. Matsuura, K.; Nishida, J.-i.; Ito, T.; Yokota, R.; Kitamura, C.; Kawase, T., *Tetrahedron* **2019,** 75 (2), 278-285.

154. Pahlavan, F.; Hosseinnezhad, S.; Samieadel, A.; Hung, A.; Fini, E., *Industrial & Engineering Chemistry Research* **2019,** 58 (27), 11939-11953.

155. Varejão, J. O. S.; Varejão, E. V. V.; Fernandes, S. A., *Eur. J. Org. Chem.* **2019,** 2019 (27), 4273-4310.

156. Cortegiani, A.; Ingoglia, G.; Ippolito, M.; Giarratano, A.; Einav, S., *J. Crit. Care* **2020.**

157. Holshue, M. L.; DeBolt, C.; Lindquist, S.; Lofy, K. H.; Wiesman, J.; Bruce, H.; Spitters, C.; Ericson, K.; Wilkerson, S.; Tural, A.; Diaz, G.; Cohn, A.; Fox, L.; Patel, A.; Gerber, S. I.; Kim, L.; Tong, S.; Lu, X.; Lindstrom, S.; Pallansch, M. A.; Weldon, W. C.; Biggs, H. M.; Uyeki, T. M.; Pillai, S. K., *N. Engl. J. Med.* **2020,** 382 (10), 929-936.

158. Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G., *Cell Res.* **2020,** 30 (3), 269-271.

ABOUT THE AUTHOR

Zainab Ahmed Al-Saihati was born in Saudi Arabia on August 24th, 1989 to Huda and Ahmed Al-Saihati. She grew up in a small city called Saihat in the Eastern Province. Since a young age, she was always passionate and curious to understand the phenomena unfolding in the world at large. At this time, women in the Middle East do not have the same liberties as men. As a Saudi woman, Zainab has been inspired to defy the limiting beliefs and societal norms in regards to being a Middle Eastern woman. Fortunately, Saudi Aramco, a world-renowned chemical and energy company, opened an elite international scholarship program for aspiring young Saudi citizens including women for the first time a year before Zainab's high school graduation.

At the age of 18, Zainab was awarded a scholarship from Saudi Aramco and moved abroad on her own to attend the University of Texas at Austin. During her undergraduate studies, Zainab became interested in research and participated in several research projects. She joined Professor Katherine Willet's lab and investigated the design and synthesis of silver nanocubes, including the characterization of their shape by Scanning Electron Microscope technology. While visiting her family in Saudi Arabia during the summer, she worked as a summer intern researcher at Saudi Aramco, conducting research to find separation methods of contaminants in diesel fuels. Additionally, she studied the effect of aromatics contamination on its properties.

Zainab enjoys the outdoors, traveling, exploring diverse cultures, and building friendships with people from different backgrounds. She also enjoys participating in outreach programs and has taught science classes to elementary school kids. Although being thousands of miles away from her home and family, has not been easy, Zainab has found her journey navigating the USA on her own to be an empowering experience. Zainab believes this experience has enriched her personality, molding her into an independent, strongly motivated woman.

Upon completion of her BSc degree, she joined Saudi Aramco's R&D Department in 2012, and worked for three years as a fuels scientist. She led a variety of projects encompassing crude oil and refined products characterizations, fuels additives testing, and understanding structure-activity relationships. Zainab presented her work-related research at the 9th International Conference & Exhibition on Chemistry in Industry (ChemIndex) in 2013, where she met her future co-advisor for the first time, Professor Robert H. Grubbs. In 2015, Zainab was awarded another scholarship from her employer Saudi Aramco to continue her education and follow her dream to pursue a PhD. She chose to attend California Institute of Technology in Pasadena, California where she pursued doctoral studies under the supervision of Professors Robert H. Grubbs and Brian M. Stoltz. Zainab's PhD research has focused on developing relatively environmentally benign methods toward the synthesis of substituted and unsubstituted aromatics *via* dehydrogenation by single-site iridium pincer ligated complexes.

Upon completion of her doctoral research in May 2020, Zainab will be the first Saudi woman to obtain a PhD from Caltech. She will return to Saudi Arabia and continue her professional career at Saudi Aramco. She is interested in green chemistry and will continue to conduct research toward finding and developing methods toward the synthesis of important industrial building blocks.

One of Zainab's favorite quotes by Albert Einstein, who was a visiting professor at Caltech, is "education is not the learning of facts, but the training of the mind to think." With her PhD, she aspires to shape and change science in Saudi Arabia and create new fields of research. Her ultimate dream is to inspire and mentor women in Saudi Arabia and the Middle East, and encourage and aid those who are interested to join STEM fields.