COMPUTATIONAL STUDIES OF C–H/C–C MANIPULATION UTILIZING TRANSITION METAL COMPLEXES

Daniel B. Pardue, B. S.

Dissertation Prepared for the Degree of

DOCTOR OF PHILOSOPHY

UNIVERSITY OF NORTH TEXAS

May 2015

APPROVED:

Thomas R. Cundari, Major Professor
Mohammad A. Omary, Committee Member
Angela K. Wilson, Committee Member
Michael G. Richmond, Committee Member
William E. Acree, Jr., Chair of the Department of Chemistry
Mark Wardell, Dean of the Toulouse Graduate School
Density Functional Theory (DFT) is an effective tool for studying diverse metal systems. Presented herein are studies of a variety of metal systems, which can be applied to accomplish transformations that are currently difficult/impossible to achieve. The specific topics studied utilizing DFT include: 1) C–H bond activation via an Earth-abundant transition metal complex, 2) C–H bond deprotonation via an alkali metal superbase, 3) and amination/aziridination reactions utilizing a Cu¹ reagent.

Using DFT, the transformation to methanol (CH₃OH) from methane (CH₄) was examined. The transition metal systems studied for this transformation included a model FeⅡ complex. This first-row transition metal is an economical, Earth-abundant metal. The ligand set for this transformation includes a carbonyl ligand in one set of complexes as well as a phosphite ligand in another. The 3d Fe metal shows the ability to convert alkyls/aryls to their oxidized counterpart in an energetically favorable manner.

Also, “superbasic” alkali metal amides were investigated to perform C—H bond cleavage. Toluene was the substrate of interest with Cs chosen to be the metal of interest because of the highly electropositive nature of this alkali metal. These highly electrophilic Cs metal systems allow for very favorable C—H bond scission with a toluene substrate.

Finally, the amination and aziridination of C–H and C=C bonds, respectively, by a Cu¹ reagent was studied. The mechanism was investigated using DFT calculations. Presently, these mechanisms involving the use of coinage metals are debated. Our DFT simulations shed some insight into how these transformations occur and ultimately how they can be manipulated.
Copyright 2015

by

Daniel B. Pardue
ACKNOWLEDGEMENTS

I would like to thank my advisor Dr. Cundari for giving me the opportunity to be a mentee within his group. The dedication and passion for the success of the students within his group was truly valuable to have witnessed. His love, dedication, and knowledge of the field is matched by none. His patience, guidance, and assistance will not be forgotten or ever unappreciated.

I would like to acknowledge my coworkers/friends that I have met while in graduate school. Your assistance and motivation is greatly cherished. The members of the Cundari group in particular, both past and present, have had a tremendous influence on my success.

I would like to thank my family for their love and support while attending graduate school. In particular, I would like to acknowledge my parents. It was your unconditional love and support that made me realize this was possible. The work ethic and dedication to your jobs that you both displayed allowed me to have confidence that I can be successful no matter what field I choose. Lastly, I would like to acknowledge my wife, Ashley. Thank you for your patience, motivation, and encouragement while at UNT. This achievement is not one that I have completed alone but rather one that we have completed together.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF ILLUSTRATIONS</td>
<td>xi</td>
</tr>
<tr>
<td>ABBREVIATION AND SYMBOLS</td>
<td>xii</td>
</tr>
<tr>
<td>CHAPTER 1. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1 C–H Activation Employing Organometallic Complexes</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Theory</td>
<td>4</td>
</tr>
<tr>
<td>1.3 References</td>
<td>6</td>
</tr>
<tr>
<td>CHAPTER 2. DENSITY FUNCTIONAL THEORY STUDY OF OXYGEN-ATOM INSERTION</td>
<td>10</td>
</tr>
<tr>
<td>INTO METAL–METHYL BONDS OF IRON(II) COMPLEXES: STUDY OF METAL-MEDIATED</td>
<td></td>
</tr>
<tr>
<td>C–O BONDS FORMATION</td>
<td></td>
</tr>
<tr>
<td>2.1 Introduction</td>
<td>10</td>
</tr>
<tr>
<td>2.2 Computational Methods</td>
<td>12</td>
</tr>
<tr>
<td>2.3 Results and Discussion</td>
<td>13</td>
</tr>
<tr>
<td>2.4 Baeyer-Villiger Mechanism for Oxy-Insertion: Cp*Fe(Ph)(OPy)(CO)</td>
<td>13</td>
</tr>
<tr>
<td>2.5 Oxo Pathway: Impact of Metal</td>
<td>14</td>
</tr>
<tr>
<td>2.6 Impact of Migrating Group: Replacement of Phenyl with Methyl</td>
<td>19</td>
</tr>
<tr>
<td>2.7 Hammett Studies</td>
<td>21</td>
</tr>
<tr>
<td>2.8 Effect of Ligand L for Cp*Fe(L)(OPy)Ph Complexes</td>
<td>26</td>
</tr>
<tr>
<td>2.9 CO Ligand Oxidation</td>
<td>28</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>2.10</td>
<td>Electronic Structure of Fe-Oxo Intermediate</td>
</tr>
<tr>
<td>2.11</td>
<td>Comparison of M06 and B3LYP</td>
</tr>
<tr>
<td>2.12</td>
<td>Redox (Oxo) Pathway for Oxy-Insertion</td>
</tr>
<tr>
<td>2.13</td>
<td>Impact of a Bigger Basis Set</td>
</tr>
<tr>
<td>2.14</td>
<td>Impact of Solvent</td>
</tr>
<tr>
<td>2.15</td>
<td>Combination of Differing Ligands</td>
</tr>
<tr>
<td>2.16</td>
<td>Summary, Conclusions and Prospectus</td>
</tr>
<tr>
<td>2.17</td>
<td>References</td>
</tr>
</tbody>
</table>

CHAPTER 3. OXYGEN ATOM INSERTION INTO IRON(II) PHENYL AND METHYL BONDS VIA PHOSPHITE FeII COMPLEX ..................................................................................................................44

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Introduction</td>
<td>44</td>
</tr>
<tr>
<td>3.2</td>
<td>Computational Methods</td>
<td>45</td>
</tr>
<tr>
<td>3.3</td>
<td>Oxy-Insertion into an Fe-Ph bond via an oxo pathway</td>
<td>47</td>
</tr>
<tr>
<td>3.4</td>
<td>Oxy-insertion into an Fe-P bond via an oxo pathway</td>
<td>50</td>
</tr>
<tr>
<td>3.5</td>
<td>Summary, Conclusions and Prospectus</td>
<td>51</td>
</tr>
<tr>
<td>3.6</td>
<td>References</td>
<td>52</td>
</tr>
</tbody>
</table>

CHAPTER 4. COMPUTATIONAL STUDY OF CARBON-HYDROGEN BOND DEPROTONATION BY ALKALI METAL SUPERBASES ..................................................................................................................54

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>Computational Methods</td>
<td>56</td>
</tr>
<tr>
<td>4.3</td>
<td>Cleavage of Methane CH bonds</td>
<td>57</td>
</tr>
<tr>
<td>4.4</td>
<td>Method Sensitivity</td>
<td>60</td>
</tr>
<tr>
<td>4.5</td>
<td>Benzylic C—H Cleavage of Toluene</td>
<td>61</td>
</tr>
<tr>
<td>4.6</td>
<td>Electronic Impact of Substrate Modification</td>
<td>63</td>
</tr>
</tbody>
</table>
4.7 Impact of Alkali Metal ................................................................. 66
4.8 Solvent Effects ............................................................................ 68
4.9 Summary, Conclusions and Prospectus ....................................... 70
4.10 References ................................................................................ 75

CHAPTER 5. A MECHANISTIC STUDY ON C-H AMINATION AND OLEFIN AZIRIDINATIONS VIA TRIPODAL CU(I) REAGENT ............................................................... 78

5.1 Introduction .................................................................................. 78
5.2 Computational Details ................................................................. 79
5.3 Computed Nitrene Intermediate .................................................... 80
5.4 Catalytic Aziridination Calculations .............................................. 91
5.5 Calculated EWG/EDG Substituted Aziridinations ....................... 94
5.6 Conclusions .................................................................................. 95
5.7 References ................................................................................... 97

CHAPTER 6. SUMMARY AND FUTURE DIRECTIONS ............................ 100

6.1 C–H Activation Employing Organometallic Complexes ............... 100

6.2 Density Functional Theory Study of Oxygen-Atom Insertion into Metal–Methyl Bonds of Iron(II), Ruthenium(II), and Osmium(II) Complexes: Study of Metal-Mediated C–O Bond Formation ................................................................. 102

6.3 Oxygen Atom Insertion Phenyl and Methyl Bonds via FeII Phosphite Complex ........................................................................................................... 102

6.4 Computational Study of Carbon-Hydrogen Bond Deprotonation by Alkali Metal Superbases ................................................................................................... 102

6.5 A Mechanistic Study on C-H Amination and Olefin Aziridinations via A Tripodal Cu(I) Reagent ...................................................................................... 103
6.6 Future Research Directions.................................................................104
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>Comparison of M=O bond lengths, bond angles, spin densities, M-C bond lengths (Ph), M=O bond strengths for Cp*M(CO)(O)Ph, M = Fe, Ru, Os.</td>
<td>18</td>
</tr>
<tr>
<td>2-2</td>
<td>Comparison of calculated bond dissociation free energies to free energies of activation for hydrocarbyl migration to oxo ligands.</td>
<td>22</td>
</tr>
<tr>
<td>2-3</td>
<td>Free energies of activation and migration for all complexes studied.</td>
<td>33</td>
</tr>
<tr>
<td>2-4</td>
<td>Relative free energy (kcal/mol) relative to MCI for ΔG_{oxo} and ΔG_{oxo}‡, and oxo intermediate</td>
<td>35</td>
</tr>
<tr>
<td>2-5</td>
<td>Absolute free energy (kcal/mol) relative to MCI (versus Cp*Fe(OPy)(Ph)(CO)) in gas phase and with continuum THF solvent model. The B3LYP functional was used for these simulations</td>
<td>36</td>
</tr>
<tr>
<td>4-1</td>
<td>Comparing barriers (kcal/mol) and thermodynamics (kcal/mol) of CH cleavage of methane by CsNH₂ using differing computational methods.</td>
<td>60</td>
</tr>
<tr>
<td>4-2</td>
<td>Comparing bond lengths (Å) of methane CH cleavage by CsNH₂ systems using differing computational methods. LANL2DZ used for Cs basis set in all calculations.</td>
<td>61</td>
</tr>
<tr>
<td>4-3</td>
<td>Slopes ($\rho_p$ and $\rho_m$) of Hammett graphs for deprotonation of benzylic C—H bond of toluene by Li and Cs cyclohexyl amide for solvated (SMD butylamine) and gas-phase) systems.</td>
<td>71</td>
</tr>
<tr>
<td>5-1</td>
<td>B3LYP/6-31G(d) Computed $\Delta G$’s and $\Delta G^{‡}$’s (kcal/mol) for the Steps shown in Scheme 5-1.</td>
<td>90</td>
</tr>
<tr>
<td>5-2</td>
<td>B3LYP/6-31G(d) calculated bond lengths (Å) and Cu–N–S $\angle$ (°) of $^{3}$[Cu]NTs comparing the BP86 and B3LYP functionals.</td>
<td>90</td>
</tr>
<tr>
<td>5-3</td>
<td>Aziridination Transition State (triplets) N–C (olefin) and C–C (Olefin) Bond Lengths.</td>
<td>96</td>
</tr>
</tbody>
</table>
LIST OF ILLUSTRATIONS

Figure 2-1. B3LYP/CEP-31G(d) calculated bond lengths (Å) and bond angles (°) of the transition state active sites for different Group 8 metals for the transition state for formation of oxo complexes and the transition state for phenyl-to-oxo migration.................................................................17

Figure 2-2. B3LYP/CEP-31G(d) spin density plot of oxo intermediate, Cp*Fe(CO)(=O)(Ph). ........................................................................................................................................31

Figure 2-3. B3LYP/CEP-31G(d) calculated bond lengths (in Å) of the singlet Baeyer-Villiger transition state for Cp*Fe(Pt--O--Py)(CO). .................................................................33

Figure 4-1. DFT calculated bond lengths (Å) and bond angles (°) for methane adduct reactant, Cs(CH₄)NH₂ and the product, Cs(CH₃)NH₃. .................................................................57

Figure 4-2. DFT calculated bond lengths (Å) and bond angles (°) of the TS for cleavage of the CH bond of methane for the conversion of Cs(CH₄)NH₂ to Cs(CH₃)NH₃. ......................58

Figure 4-3. Calculated Cs to ring centroid distance (Å) for toluene substituted structures. ....62

Figure 4-4. Substitutions made at the meta or para positions of toluene along with calculated benzylic C—H cleavage barriers.........................................................64

Figure 4-5. Hammett plot of inductive (σᵳ) and resonance (σᵲ) effects (x-axis) versus relative rate (y-axis) for benzylic C—H cleavage of p-X-C₆H₄CH₃ by cesium cyclohexylamide. ...............65

Figure 4-6. Calculated M—Centroid distance (pm) versus crystal ionic radii (pm) for alkali metals.................................................................67

Figure 4-7. Calculated Li (left) and Cs (Right) bond distances (Å) for TS of toluene CH cleavage.................................................................67

Figure 4-8. Alkali metals and their influence on the calculated barriers and thermodynamics of toluene benzylic C—H cleavage. .................................................................68

Figure 4-9. Explicitly solvated structure with either NH₃ or CyNH₂ as the explicit solvent model and computed free energies of cleavage of toluene benzylic C—H bond. .........................71

Figure 4-10. Calculated toluene C—H cleavage barrier (kcal/mol) versus Mulliken electronegativity. .................................................................72
Figure 5-1. Compound 1 with X denoting the location in which variations were modeled. Bond lengths, and difference of lengths, of singlet and triplet nitrene $^3$[Cu]NTs. ..........................80

Figure 5-2. Important frontier alpha SOMOs for triplet [Cu]=N-Ts. Note the delocalization from the copper-nitrene active site to the sulfonyl, para-tolyl and TMGtrphen moieties. ...............81

Figure 5-3. Plot of the total spin density for triplet [Cu]=NTs at the B3LYP/6-31G(d) level of theory. ................................................................................................................................................84

Figure 5-4. Frontier Kohn-Sham orbitals with significant density on the copper-nitrene active site of triplet [Cu]=N-Ts. ........................................................................................................87

Figure 5-5. The alpha and beta occupied orbitals (eV) at the B3LYP/6-31G(d) level of theory are given and occupancy indicated. ........................................................................................88

Figure 5-6. Frontier Kohn-Sham orbital energies. ..................................................................................89

Figure 5-7. B3LYP/6-31G(d) computed $^3${[Cu]–NHTs--CH2Ph} caged adduct. Singlet radical rebound TS (Constrained) for the amination of toluene by 1. Radical rebound product. Dissociated product. ...............................................................................................................................93

Figure 5-8. B3LYP/6-31G(d) computed triplet TS for the aziridination of styrene by 1. “Open” triplet intermediate. Radical rebound TS. Singlet aziridine complex. .................................96

Figure 5-9. B3LYP/6-31G(d) calculated $C_\alpha$N$_{Ts}$, $C_\beta$N$_{Ts}$, and $C_\alpha$C$_\beta$ bond lengths (Å) in isolated aziridine product. .......................................................................................................................96
ABBREVIATIONS AND SYMBOLS

DFT  Density Functional Theory
HOMO  Highest occupied molecular orbital
LUMO  Lowest unoccupied molecular orbital
SOMO  Singly occupied molecular orbital
MTM  Methane to methanol
Ψ  The wavefunction
BDE  Bond dissociation energy
BDFE  Bond dissociation free energy
PES  Potential Energy Surface
η  Eta coordination
κ  Kappa coordination
OMBV  Organometallic Baeyer-Villiger
Cp*  Pentamethylcyclopentadienyl
ΔG  Free Energy Change
ΔH  Enthalpy change
MCI  Metallo-criegee intermediate
Cy  Cyclohexyl
ρ  Slope of the Hammett line
e−  Electron
RR  Radical rebound
Ts  Tosylate
Bz  Benzene
Chapter 1

Introduction

The C–H bond is the most abundant bond within petrochemically-derived molecules. This bond possesses very interesting characteristics. Alkanes are poor electron donors and also poor electron acceptors. The $\sigma_{\text{CH}}$ HOMO (highest occupied molecular orbital) is very low-lying in energy and not conducive for electron donation, while the $\sigma_{\text{CH}}^{*}$ LUMO (lowest unoccupied molecular orbital) is high in energy and is not suitable for accepting electron density. The C–H bond of an alkane is thermodynamically strong and also nonpolar and thus kinetically inert. The selective activation of the C–H bond has been sought after for many years. However, activation is not the only obstacle that must be overcome in the conversion of C–H to C–X functionalities. The substrate must also not be overoxidized, which is not an easy task. One specific example that forms a foundation of the chemical industry is the conversion of hydrocarbons to oxygenated products. However, many existing processes for oxygenation of hydrocarbons occur at high temperatures and pressures.$^{1-3}$ For example, methanol is more desirable than methane as it can be more easily stored and transported, can be used as a fuel or blended with gasoline and can serve as a precursor to ethylene and propylene.$^{4}$ Currently, there is an estimated 2,500 trillion ft$^3$ of natural gas in U.S. reserves.$^{5}$ However, in part because of the expense of transportation and distribution of natural gas, disposal by burning (flaring) remains common.$^{4,6}$ An efficient method to directly convert methane to methanol (MTM) at relatively low temperatures ($\sim$200 °C) and pressures ($<$ 500 psi) using dioxygen as the oxidant (either directly or indirectly) remains one of the most desirable
chemical transformations; the selective direct partial oxidation of other hydrocarbons at near ambient conditions also would be beneficial\(^2,3,7-9\). 

Prior to scientists considering organometallic systems for C–H activation/functionalization, Nature has been effectively accomplishing partial oxidation catalysis\(^10\). Examples include cytochrome P-450 and methane monooxygenase (MMO).\(^11\) Monooxygenases reduce using NADH or NADPH, which is hard to duplicate synthetically. Cytochrome P-450 uses an iron-porphyrin active site with a thiolate axial ligand. These thiolate ligands are prone to oxidization when they are replicated within model systems. Typically, ligands such as pyridine are used in the place of the thiolates when synthetically attempting to mimic P-450.

The current industrial method for conversion of natural gas (of which methane is the primary component) to methanol involves initial production of syngas (CO/H\(_2\)) with a high temperature (~800 °C) and pressure (500 psi) steam reforming catalyst; syngas is then transformed into methanol or other products.\(^12\) The high temperatures and pressures of the two-step process result in prohibitively high capital costs for plants that utilize such chemistry, which thus limit the scaled up conversion of natural gas to liquids, particularly at remote locations. Efficient low temperature (< 250 °C) and low pressure direct partial oxidation of methane (and other light alkanes) would provide a less expensive alternative to the two-step process.\(^2,3,13-15\)

Given the strict requirements for selectivity for a viable commercial process for MTM,\(^3,16\) a substantial challenge for partial oxidation of hydrocarbons is the functionalization of strong hydrocarbon C–H bonds in the presence of the weaker C–H bonds of the products. For example, the bond dissociation energy (BDE) of methane C–H bonds is 105 kcal/mol while the C–H BDE
of methanol is 96 kcal/mol.\textsuperscript{17} Examples of transition metal mediated activation of C–H bonds that are selective (kinetic and thermodynamic) for strong C–H bonds over weaker C–H bonds have been reported.\textsuperscript{18-23} Thus, the use of transition metal catalysts for MTM (and other hydrocarbon oxidations) has been heavily pursued. Electrophilic catalysts based on late transition metals have been among the most successful.\textsuperscript{14,24-30} For these catalysts, the carbon-heteroatom bond-forming step is generally proposed to occur by addition of a nucleophile to an electrophilic alkyl ligand (methyl if the substrate is methane). Thus, the electronegative character of the metal is a key feature of these catalysts. Success of this class of catalysts has been limited by product inhibition, slow rates and the required use of strongly acidic solvents (e.g., concentrated sulfuric acid).

More electron rich metals [e.g., Ir(I), Ir(III), Rh(I), Re(I), Ru(II), Fe(II)] are known to initiate C–H activation;\textsuperscript{31-38} however, these metals are less likely to have M–R bonds polarized toward electrophilic hydrocarbyl ligands. One method that has received interest involves the development of a catalyst that mediates oxygen atom insertion into a M–R bond after C–H activation (Scheme 1-1).\textsuperscript{39-53}

![Scheme 1-1. Proposed catalytic cycle for alkane to alcohol catalysis. RH = alkane, YO = oxidant, Y = leaving group, LₙM = catalyst.](image)

Chapter 2 investigates the activation of C–H utilizing an organometallic Fe\textsuperscript{II} complex ligated with carbonyl ligands. Chapter 3 looks into addressing overoxidation issues seen within chapter 2
by employing a phosphite ligand. Chapter 4 addresses the manipulation of C–H bond not through an organometallic complex but rather utilizing alkali metal superbases. Chapter 5 slightly deviates from the topic of small alkane C–H bond manipulation and considers a regio-, sterio-, and chemoselective introduction of a C–N bond into a less active C–H or more active C=C bond. Specifically, amination and aziridination reactions are investigated utilizing a Cu\(^1\) catalyst.

1.2 Theory

\[ \hat{H} \Psi = E \Psi \]  

(1.1)

\[ \hat{H} = -\frac{\hbar^2}{2m} \sum_{\alpha} \Delta_{\alpha}^2 - \frac{\hbar^2}{2me} \sum_{l} \Delta_{l}^2 + \sum_{\alpha} \sum_{l>l} Z_{\alpha}Z_{\beta} e^{l^2} - \sum_{\alpha} \sum_{l} \frac{Z_{\alpha} e^{l^2}}{r_{\alpha l}} - \sum_{i>j} \frac{e^{i^2}}{r_{ij}} \]  

(1.2)

Utilizing mathematical equations and approximations allows one to use quantum mechanics to compute properties of molecular systems. A few of these properties include: vibrational frequencies, charge distributions, NMR spectra, transition state energies, and ground state energies. These properties are calculated from the Time Independent Schrödinger Equation, Equation 1.1.\(^{54}\)

The Schrödinger equation consists of three variables: (1) E, the total energy of the molecular system, (2) \(\Psi\), the wavefunction describing the position and momentum of all the particles, and (3) \(\hat{H}\), the Hamiltonian operator, which specifies the kinetic and potential energies of all the particles in the system of interest. Exact analytical solutions to this equation are only available for the simplest of quantum mechanical systems. The terms in equation 1.2 correspond to: the kinetic energy of the nuclei, the kinetic energy of the electrons, nuclear-nuclear repulsion, nuclear-electron attraction, and electron-electron repulsion, respectively.
The main reason solving the Time Independent Schrödinger Equation is such a challenging task is the electron-electron repulsion term (last term in Equation 1.2). Therefore, approximations must be made. The most well-known of these approximations is the Born-Oppenheimer approximation, which fixes the position of the nuclei. Upon applying these approximations, the Schrödinger equation can be solved to obtain the energy \( E \), which can then be used to derive the Potential Energy Surface (PES). It is from the important chemical states on this PES in which local minima are used to identify ground states, and local maxima are used to find transition states, from which one can model chemical reactions and catalytic mechanisms. Methods developed to solve eq. 1.1 without utilizing empirical parameters are known as \textit{ab initio} methods. The most notable and earliest scheme being that of Hartree and Fock. However, Hartree-Fock methods scale as roughly \( N^{3-4} \), with \( N \) being the number of basis functions employed. The HF method entails solution to equation 1.1 based upon wavefunctions. The cost of this method is prohibitively expensive when it comes to complexes that are larger in size such as the transition metal systems modeled in this dissertation, plus it neglects the effects of electron correlation.

Based on the work of Hohenberg and Kohn, Density Functional Theory (DFT) was developed. DFT is a method that is more suitable for transition metal systems in comparison to \textit{ab initio} methods. The biggest advantage of DFT is that it is not wavefunction based but rather is based upon the electron density of a system. Because of this, the computational cost of DFT is often as or more affordable than HF methods, scaling as \( N^3 \). Also, DFT methods allow facile incorporation of electron correlation effects into the Hamiltonian, which is particularly important for chemical reactions involving transition metals, and for accurate reaction energies. DFT is thus
a suitable method choice in balancing computational cost against expected accuracy. DFT has been repeatedly shown to afford reliable energies and geometries for transition metal systems.

1.3 References


Chapter 2

Density Functional Theory Study of Oxygen-Atom Insertion into Metal–Methyl Bonds of Iron(II), Ruthenium(II), and Osmium(II) Complexes: Study of Metal-Mediated C–O Bond Formation

2.1 Introduction

There are two key steps in the catalytic cycle for hydrocarbon oxidation shown in Scheme 1-1: C–H activation via net 1,2-addition across M–OR bond and C–O (or C–X, where –X can be converted to –OH) bond formation. Although C–H activation is generally regarded as the most challenging step, well defined oxy-insertion into M–R bonds has less precedent. The selective conversion of the Re–R bond of methyltrioxorhenium (MTO) and ArReO₃ (Ar = Ph) to methanol or a phenol, respectively, that proceeds by oxy-insertion into the Re–R bond using a variety of external oxidants (YO) has been reported. Experimental and computational studies suggested that the reaction proceeds via a pathway that is similar to a (non-redox) organic Baeyer-Villiger reaction as opposed to hydrocarbyl migration to an oxo ligand. Our groups have reported that the reaction of Cp*W(O)₂(CH₂SiMe₃) with a variety of O atom donors results in oxy-insertion to ultimately form Me₃SiCH₂OH. Mechanistic studies allowed the elucidation of two pathways: one pathway involves a direct O atom insertion into the W–CH₂SiMe₃ bond while the second pathway occurs via an η²-peroxide intermediate. Bercaw and coworkers reported a study of Cp*₂Ta(η²-O₂)CH₃ that showed acceleration of oxy-insertion by Lewis and Brønsted acids. Hillhouse and co-workers reported examples of Ni d⁸ systems undergoing net oxy-insertion into

---

1*"This chapter was reprinted with permission from (Density Functional Theory Study of Oxygen-Atom Insertion into Metal-Methyl Bonds of Iron(II), Ruthenium (II), and Osmium(II) Complexes: Study of Metal-Mediated C-O Bond Formation). Copyright (2014) American Chemical Society."
Ni–C bonds using N\textsubscript{2}O as the oxidant.\textsuperscript{12,22} Very few examples of using a 3d metal to mediate oxy-insertion into a metal-carbon bonds are known, but calculations suggest that such transformations could occur with low activation barriers.\textsuperscript{15} Figg et al. studied the mechanism of the Hillhouse system.\textsuperscript{10} Our current research aims to extend the aforementioned studies to (a) different transition metal systems (particularly those incorporating Earth abundant 3d metals), (b) complexes with metals in non-d\textsuperscript{0} electronic configurations (since these are most likely to combine oxy-insertion with C–H activation), (c) a variety of oxidants, particularly mild oxidants, and most importantly, (d) organometallic motifs demonstrated to effect C–H activation to expand the knowledge base for oxy-insertion (M–R \rightarrow M–OR) and to identify viable catalysts for hydrocarbon partial oxidation.\textsuperscript{13}

Recently, a joint experimental and computational analysis of aromatic C–H activation by Cp*Fe(CO)(NCMe)Ph (Cp* = pentamethylcyclopentadienyl) under ambient conditions has been reported.\textsuperscript{23} This work set the foundation for efforts to uncover inexpensive catalysts for partial hydrocarbon oxidation. Theory indicates a preferred C–H activation pathway for Cp*Fe(CO)Ph involving σ-bond metathesis, which maintains iron in the Fe\textsuperscript{II} oxidation state. Hence, subsequent oxy-insertion steps may still access reasonably available Fe\textsuperscript{III/IV} states even if a non-redox, Baeyer-Villiger pathway presents a high activation barrier. Also, the analyses suggested that formally spin-forbidden processes, long a concern in 3d metal catalysis, did not hinder the C–H activation transformations.\textsuperscript{24,25} In another important experimental precedent, Ni and Power\textsuperscript{26} have reported oxy-functionalization of coordinatively unsaturated Fe\textsuperscript{II}-aryls utilizing O\textsubscript{2} as the oxidant.

Given recent reports of C–H activation/functionalization and C–O bond formation using Fe\textsuperscript{II} complexes, it was sought to undertake a modeling study of oxy-insertion reactions relevant to the
Fe$^{II}$ complex Cp*$\text{Fe(CO)(NCMe)Ph}$ and heavier Group 8 congeners. In the present chapter, the results of a computational study are reported for redox (i.e., formation of metal-oxo intermediates) versus organometallic Baeyer-Villiger (OMBV, no change in metal formal oxidation state) pathways for oxy-insertion by CpM$^{II}$ (CO)R (M = Fe, Ru or Os). The primary goals of this research are to (1) compare redox vs. non-redox pathways for oxy-insertion, (2) identify the key electronic features of Fe$^{II}$ complexes that define the potential energy surfaces for oxy-insertion.

2.2 Computational Methods

Density functional theory (DFT) within the Gaussian 09 package$^{27}$ was used for geometry optimization and vibrational frequency calculations. A standard level of theory was employed – B3LYP or M06 with a double zeta basis set with pseudopotentials and added d functions for group elements (e.g., CEP-31G(d)).$^{28}$ This level of theory has been used in previous modeling of oxygen atom transfer and oxy-insertion reactions and was shown to correspond well with experimental trends whilst maintaining reasonable computational cost.$^{14,15,29}$ Tests with larger basis sets were also performed and shown to negligibly impact the potential energy surfaces of interest. The reader should assume a B3LYP/CEP-31G(d) level of theory, unless otherwise stated. The energies quoted are free energies that were calculated at 298.15 K and 1 atm. The stationary points were defined as minima or transition states (TSs) by the presence of 0 or 1 imaginary frequencies, respectively, as obtained from the calculated energy Hessians. Different spin states were studied for the 3d metals; the 4d and 5d systems were all calculated to be singlets in their lowest energy states with the exception of the Ru$^{IV}$-oxo intermediate structure, which was predicted to be a triplet.

2.3 Results and Discussion
Modeling of the O atom insertion reactions begins with \( \text{Cp}^* \text{Fe}(\text{CO})(\text{OPy})\text{Ph} \) (1) where \( \text{Py} = \) pyridine and \( \text{Cp}^* = \eta^5\text{C}_5\text{Me}_5 \). The metallo-Criegee intermediate (MCI), \( \text{Cp}^* \text{Fe}(\text{CO})(\text{OPy})\text{Ph} \), named using the language of the organic Baeyer-Villiger (BV) reaction,\(^{30}\) is the adduct formed upon coordination of the oxidant (\( e.g., \) pyridine-\( \text{N-oxide} \)) to the 16-electron complex \( \text{Cp}^* \text{Fe}(\text{L})\text{Ph} \).

We have calculated the energetics for oxygen atom insertion into the Fe–Ph bond of 1 by the OMBV pathway and via formation of an Fe-oxo complex. To understand the role that the metal identity, ancillary ligands and oxidant play, substitutions were made at various positions in the MCI \( \text{Cp}^* \text{M}(\text{R})(\text{OY})(\text{L}) \): \( \text{M} = \text{Fe}, \text{Ru}, \text{Os}; \ \text{YO} = \text{OPy}, 4\text{-NO}_2\text{-OPy}, 4\text{-NMe}_2\text{-OPy}; \ \text{L} = \text{CO}, \text{NO}^+, \text{Cl}^-, \text{NMe}_2^-, \text{NH}_3; \ \text{R} = \text{C}_6\text{H}_5, \text{m-} \text{and } \text{p-NO}_2\text{-C}_6\text{H}_5, \text{m-} \text{and } \text{p-NMe}_2\text{-C}_6\text{H}_5 \) and the energetics for oxygen atom insertion were calculated (Chart 2-1).

![Chart 2-1](image)

**Chart 2-1.** Series of complexes studied.

### 2.4 Baeyer-Villiger Mechanism for Oxy-Insertion: \( \text{Cp}^* \text{Fe}(\text{Ph})(\text{OPy})(\text{CO}) \)

The OMBV pathway for oxy-insertion into the Fe–Ph bond of 1 is shown in Scheme 1. Pyridine is released from the PyO oxidant in concert with insertion of the oxygen atom into the Fe–Ph bond.\(^{13,15,29}\) The B3LYP/CEP-31G(d) optimized geometry of the singlet BV transition state is given in Scheme 2-1 and is similar to OMBV transition states reported previously.\(^{13-15,18,20,29}\) At the B3LYP/CEP-31G(d) level of theory, formation of the phenoxide product is highly exergonic.
by -63.2 kcal/mol, but the OMBV conversion of Cp*Fe(Ph)(OPy)(CO) to Cp*Fe(OPh)(Py)(CO) has a prohibitively large calculated free energy barrier of $\Delta G_{\text{BV}}^\dagger = 74.0$ kcal/mol (Scheme 2-2). The OMBV transition states for triplet and quintet multiplicity could not be found, despite numerous starting geometries and transition state searches. In each case, the high spin transition states converged to previously identified stationary points. This is perhaps not surprising since the strongly $\pi$-acidic CO ligand will stabilize low spin complexes.

### 2.5 Oxo Pathway: Impact of Metal

Periodic trends for the oxy-insertion pathway were probed for Cp*M(CO)(OPy)Ph (M = Fe, Ru or Os; Scheme 2-3). The overall oxy-insertions from Cp*M(CO)(OY)Ph to make the phenoxide complexes Cp*M(CO)OPh ($\Delta G_{\text{tot}}$) were calculated to become less exergonic for the heavier metals: $-66.5$ (Fe), $-50.4$ (Ru) and $-49.3$ (Os) kcal/mol. All Ru and Os ground states were calculated to be singlets with the exception of the Ru$^{IV}$-oxo intermediate Cp*Ru(CO)(O)Ph, which is predicted to be a triplet. In all three cases, formation of the oxo was exergonic relative to the MCI: $\Delta G_{\text{oxo}}$ (kcal/mol) = $-21.8$ (Fe); $-9.6$ (Ru); $-20.2$ kcal/mol (Os) (Scheme 2-3). The free energy barrier for formation of the oxo complex Cp*M(CO)(O)Ph ($\Delta G_{\text{oxo}}^\dagger$) is calculated to be substantially lower for the Fe complex (22.9 kcal/mol) than for Ru (48.8 kcal/mol) or Os (39.6 kcal/mol). The overall $\Delta \Delta G_{\text{oxo}}^\dagger$ (> 25.9 kcal/mol) indicates that the first row metal Fe has a tremendous kinetic advantage for oxidation to the metal oxo intermediate.
Scheme 2-1. B3LYP/CEP-31G(d) calculated reaction pathway for the organometallic Baeyer-Villiger transformation of Cp*Fe(CO)(OPy)Ph to Cp*Fe(CO)(Py)OPh. The lowest energy spin state is denoted by a prefix numeral. Free energies (standard temperature and pressure) are given in kcal/mol relative to the MCI. Calculated BV TS structure in top right.

The $\Delta G_{\text{oxo}}^\dagger$ does not appear to be dictated by the thermodynamics of metal oxo formation since the $\Delta G_{\text{oxo}}$ is most favorable for Fe and Os (both exergonic by $> 20$ kcal/mol) than Ru ($\Delta G_{\text{oxo}} = -9.6$ kcal/mol). The lower activation barrier for Fe seems surprising since more facile oxidation of Ru and Os compared to Fe might be anticipated. The different geometries of the Group 8 triad can be seen in Figure 2-1. In general, the calculated TSs are similar. For example, the M–O bond length in Cp*M(CO)(OPy)Ph is ~0.1 Å shorter for M = Fe than that of M = Ru, Os. Constrained geometry calculations on PyO suggest that this perturbation has a free energy cost of ~4 kcal/mol, which provides partial reasoning why the barrier concerning M = Fe is lower than that of M = Ru, Os.
Although hydrocarbyl migration to an oxo ligand has been considered a challenging reaction\textsuperscript{31-33} for all three Cp*M(CO)(O)Ph complexes the calculated free energy of activation for phenyl migration to the oxo ligand is lower than the corresponding activation energy for formation of the oxo complex (Δ\(G_{\text{oxo}}\). Thus, the rate limiting step is predicted to be formation of the metal oxo intermediate. For the phenyl migration to oxo ligand form phenoxide complexes, the Fe complex is predicted to hold a kinetic advantage over Ru and Os complexes, but ΔΔ\(G_{\text{mig}}\) (5.4 kcal/mol) is less than the ΔΔ\(G_{\text{oxo}}\) (25.9 kcal/mol). Since the geometric differences for the metal oxo complexes and the transition states for phenyl migration are small (see below and Figure 2-1), it is likely that the larger Δ\(G_{\text{mig}}\)'s for Ru and Os result from the stronger metal-oxo π-bonds for the heavier metals. Thus, weaker metal-oxo bonding is expected to facilitate hydrocarbyl migration to the oxo π-ligand. Perhaps important is that this rationale differs from that proposed by Mayer and Brown for their study of phenyl-to-oxo migration for [TpRe(O)\(\text{Ph}^+\).\textsuperscript{31} Suggested therein is that strong π-donation, which should increase metal-oxo bond strength, is vital to impart electrophilicity at the oxo ligand and in turn a low barrier for phenyl-to-oxo migration (see Summary and Conclusions).

Table 2-1 lists M–O bond distance as well as spin multiplicity for the oxo intermediates of M = Fe, Ru and Os. Also, the spin densities for M = Fe and Ru (the Os-oxo intermediate is computed to be a ground state singlet) as well as the oxygen are listed.
Scheme 2-3. B3LYP/CEP-31G(d) calculated formation of oxo intermediate and phenyl migration steps in redox pathway for oxy-insertion comparing energetics for Group 8 metals. Calculated relative and absolute free energies (kcal/mol), Cp*M(OPy)(CO)(Ph), for Fe (blue), Ru (red) and Os (orange).

Figure 2-1. B3LYP/CEP-31G(d) calculated bond lengths (Å) and bond angles (°) of the transition state active sites for different Group 8 metals for the transition state for formation of oxo complexes (left) and the transition state for phenyl-to-oxo migration (right). Table 2-1 shows M = Fe to have the shortest M–C<sub>Ph</sub> bond distance at 0.12 Å and 0.11 Å longer for the M = Ru and Os, respectively.

The computed M–OPy bond dissociation free energy (BDFE) of Cp*M(CO)(OPy)Ph complexes is exergonic (-5.5 kcal/mol; ΔH = 4.6 kcal/mol) for M = Fe and endergonic, 7.4
kcal/mol ($\Delta H = 19.8$ kcal/mol) and 4.2 kcal/mol ($\Delta H = 16.7$ kcal/mol), for $M = \text{Ru}$ and Os, respectively.

<table>
<thead>
<tr>
<th></th>
<th>Fe</th>
<th>Ru</th>
<th>Os</th>
</tr>
</thead>
<tbody>
<tr>
<td>M=O Bond Distance (Å)$^a$</td>
<td>1.673</td>
<td>1.842</td>
<td>1.799</td>
</tr>
<tr>
<td>Multiplicity$^a$</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>M Spin Density ($e^-$)$^a$</td>
<td>1.262</td>
<td>0.784</td>
<td>-</td>
</tr>
<tr>
<td>O Spin Density ($e^-$)$^a$</td>
<td>0.923</td>
<td>1.105</td>
<td>-</td>
</tr>
<tr>
<td>M–C$_\text{Ph}$ (Å)$^a$</td>
<td>1.998</td>
<td>2.119</td>
<td>2.106</td>
</tr>
<tr>
<td>M=O BDFE$^{a,b}$</td>
<td>60.1</td>
<td>60.8</td>
<td>68.2</td>
</tr>
<tr>
<td>$\angle M$–O–N ($^\circ$)$^c$</td>
<td>121.2</td>
<td>128.9</td>
<td>128.7</td>
</tr>
<tr>
<td>M–OPy BDFE$^{b,c}$</td>
<td>-5.5 (4.6)</td>
<td>7.4 (19.8)</td>
<td>4.2 (16.7)</td>
</tr>
</tbody>
</table>

Table 2-1. Comparison of M=O bond lengths, bond angles, spin densities, M-C bond lengths (Ph), M=O bond strengths for Cp*M(CO)(O)Ph, $M = \text{Fe, Ru, Os}$. M–OPy bond strength (kcal/mol), [DH’s in parenthesis] for Cp*M(CO)(OPy)Ph ($M = \text{Fe, Ru, Os}$). Structures calculated at the B3LYP/CEP-31G(d) level of theory. $^a$ For Cp*M(CO)(O)Ph. $^b$ kcal/mol. $^c$ For Cp*M(CO)(OPy)Ph.

Given the similar ground and transition state structures (Figure 2-1), we propose that binding of OPy to the larger metal is facilitated by more favorable steric factors especially given the bent coordination of ligated pyridine-N-oxide (see $\angle M$–O–N in Table 2-1). The BDFEs for oxidant binding suggest that a major contribution to the differences in $\Delta G_{\text{oxo}}$ between Fe and its heavier congeners could be the stabilization of the ground state energies upon coordination of OPy for the Ru and Os complexes relative to Fe.
2.6 Impact of Migrating Group: Replacement of Phenyl with Methyl

Since conversion of alkanes is a primary target for catalytic oxidation reactions, the impact of replacing the phenyl ligand of Cp*Fe(CO)(OPy)Ph with methyl to give Cp*Fe(CO)(OPy)Me was studied. The free energy barrier to oxo formation ($\Delta G_{\text{oxo}}^\dagger$) was lowered by 1.3 kcal/mol for the methyl complex compared to the phenyl complex (Scheme 2-4), and formation of the oxo ($\Delta G_{\text{oxo}}$) is calculated to be more exergonic by 2.0 kcal/mol. The modest changes in $\Delta G_{\text{oxo}}$ and $\Delta G_{\text{oxo}}^\dagger$ are reasonable as the hydrocarbyl group is a spectator ligand in the formation of the oxo intermediate.

For the second step of the overall oxy-insertion reaction, the free energy barrier for methyl migration ($\Delta G_{\text{mig}}^\dagger$) was calculated to be 21.8 kcal/mol for the methyl derivative (Scheme 2-4), versus 20.5 kcal/mol for the corresponding phenyl complex. The higher barrier for methyl versus phenyl migration is consistent with previous calculations on PtII complexes.29

![Scheme 2-4. Reaction pathway comparing R (phenyl vs. methyl); free energies are listed (kcal/mol) relative to the MCI. Calculated at the B3LYP/CEP-31G(d) level of theory.](image)

For organic oxy-insertion transformations, phenyl migration is more facile than methyl migration,29,34 so the calculated larger activation barrier for methyl migration to the oxo ligand is
not surprising; however, the relatively modest $\Delta \Delta G_{\text{mig}}^{\ddagger}$ of 1.3 kcal/mol is smaller than anticipated\textsuperscript{30} (see below) and bodes well for development of catalysts for methane functionalization. Moreover, unlike previous studies of organometallic Baeyer-Villiger insertion of second- and third-row transition metals,\textsuperscript{15,29,35} the calculated free energy barriers for methyl migration from Cp*Fe(CO)(O)Me are reasonable for incorporation into catalytic cycles. In the present case, the methyl migration transition state lies below the free energy of the initial oxo formation transition state, so that the latter is still calculated to be the rate limiting step in the overall oxy insertion process.

Given the small $\Delta \Delta G_{\text{mig}}^{\ddagger}$ of 1.3 kcal/mol for phenyl and methyl migration, we sought to probe if radical processes might compete with concerted hydrocarbyl migration. The data in Table 2-2 provide a comparison of the calculated bond dissociation free energies (BDFEs) for Fe–Me and Fe–Ph of Cp*Fe(CO)(O)(R) (R = Me or Ph) to the free energy barriers for phenyl and methyl migration ($\Delta G_{\text{mig}}^{\ddagger}$). The computed BDFE for the Fe–Me bond is substantially lower (by 12 kcal/mol) than the calculated barrier for migration of the methyl, and the Fe–Ph BDFE is calculated to be more similar to the free energy barrier for phenyl migration and within the limits of uncertainty of the computational methods. Based on these data, it is reasonable to assume that homolytic cleavage of the Fe–Me ligand to form a methyl radical might compete with the even-electron concerted migration. Of course, formation of a radical methyl could be followed by rapid rebound to the oxo ligand to form a C–O bond.\textsuperscript{36-38} In contrast to the Fe–Me intermediate, the calculated energetics for the Fe–Ph complex suggest that a migration route to form the phenoxide ligand is likely to be competitive with a radical pathway. Such considerations are important for catalyst design since competition between even- and odd-electron pathways is a well-known
challenge in utilizing Earth abundant 3d metals in catalysis. To achieve selective catalysts, avoiding radical transformations may be desirable.

2.7 Hammett Studies

Calculations were carried out to probe for Hammett correlations using substituents on the aryl ligand \( (i.e., \) modification of the phenyl ligand) and the pyridine-\( N \)-oxide \( (\) modification of the pyridyl ring).\)

\[
\begin{array}{ccc}
\text{BDFE} & \Delta G_{\text{mig}}^\ddagger \\
\text{Fe--Me} & 9.8 & < 21.8 \\
\text{Fe--Ph} & 19.6 & \approx 20.5 \\
\end{array}
\]

**Table 2-2.** Comparison of calculated bond dissociation free energies (BDFEs, kcal/mol) to free energies of activation for hydrocarbyl migration to oxo ligands \( (\Delta G_{\text{mig}}^\ddagger, \) kcal/mol).\)

We probed the Hammett impact upon the energetics for the oxo formation as well as the aryl migration to the oxo ligand, Scheme 2-5. An electron-donating (EDG; NMe\(_2\); \( \sigma_p = -0.83 \)) and an electron-withdrawing group (EWG; NO\(_2\); \( \sigma_p = +0.78 \))\(^{39} \) were modeled at: (i) the para and meta positions of the phenyl ligand, and (ii) the 4-position of the pyridine leaving group of the OPy oxidant.

Substitution of the 4-position of the migrating phenyl group has only small impact on the calculated \( \Delta G_{\text{o xo}} \) and \( \Delta G_{\text{o xo}}^\ddagger \)'s for oxo formation (Scheme 2-5). There is no clear trend for changes in ground state energy since the most favorable \( \Delta G_{\text{o xo}} \) is the parent phenyl complex and substitution with either NO\(_2\) or NMe\(_2\) render the transformation slightly less exergonic. The calculated \( \Delta \Delta G_{\text{o xo}}^\ddagger \) for the three complexes is only 0.3 kcal/mol. Therefore, the 4-substituted
phenyl complexes reveal no difference in activation barrier within the expected uncertainty of the calculations. The aryl migration step also was calculated to show little difference in free energy barriers for the \textit{para} substituted phenyl groups.

\begin{center}
\textbf{Scheme 2-5.} Calculated energetics (kcal/mol) for formation of Fe oxo complex and aryl migration for series of \textit{para} substituted phenyl ligands. Calculated at the B3LYP/CEP-31G(d) level of theory.
\end{center}

The computed $\Delta G_{\text{mig}}^\ddagger$ for aryl migration all lie within a narrow range (19 - 20 kcal/mol; Scheme 2-5). Thus, introducing $p$-$\text{NO}_2$ or $p$-$\text{NMe}_2$ functionality into the phenyl ring yields a negligible change in aryl migration free energy barriers.

The same EWG/EDG substituents were placed in the \textit{meta} position of the phenyl ligand (Scheme 2-6). The \textit{meta} substituted systems allowed for calculation of the activation barriers for aryl migration of 21.5 and 20.0 kcal/mol for NO$_2$ and NMe$_2$ functional groups, respectively. Thus, the calculated $\Delta \Delta G_{\text{mig}}^\ddagger$ for the three complexes is 1.6 kcal/mol for the \textit{para} substituted complexes.
and 1.5 kcal/mol for the meta substituted complexes. The small $\Delta \Delta G_{\text{mig}}$'s for both para and meta substituted phenyl rings indicates a very minor influence of aryl charge on hydrocarbyl migration for these Fe complexes.

Scheme 2-6. Calculated free energy of activation (kcal/mol) for aryl migration to oxo ligand of Cp*Fe(CO)(O)Ar complexes. Calculated at the B3LYP/CEP-31G(d) level of theory.

The same substituents (NO$_2$ and NMe$_2$) were modeled at the 4- position of pyridine-N-oxide oxidant. The energetics were calculated for the ground and transition states for oxo formation, and the barriers were compared against those for the parent complex Cp*Fe(R)(OPy)(Ph). Since the pyridine is assumed to play no direct role in the aryl migration step of the oxo pathway (it leaves during the oxo formation step), and the initial oxo formation is the computed rate-determining step, only the first step of the overall two-step transformation was modeled here (Scheme 2-7). Substitution of the 4-position of pyridine-N-oxide with NMe$_2$ raises the calculated $\Delta G_{\text{oxo}}$ for oxo formation by 4.8 kcal/mol. Calculations indicate that substitution of a nitro group in the 4-position lowers the free energy barrier for oxo formation ($\Delta G_{\text{oxo}}$) from 22.9 to 15.9 kcal/mol. Thus, an
EWG at the 4-position of pyridine kinetically enhances the ability of Cp*Fe(CO)(OPy)Ph to form an Fe-oxo intermediate. Thus, the calculated $\Delta G_{\text{oxo}}^\ddagger$'s are consistent with expect oxidizing power of the three pyridine-$N$-oxides.

Our groups have previously reported calculations focused on concerted oxy-insertion (i.e., without formation of an intermediate Pt-oxo complex) into Pt$^{\text{II}}$-phenyl bonds using pyridine-$N$-oxide compounds as the O atom delivery reagent. As part of that research, calculation of relative $N$–$O$ bond energies for 4-X-OPy ($X = H, \text{NO}_2$ or $\text{NMe}_2$) revealed that 4-NO$_2$-OPy had the weakest $N$–$O$ bond and, thus, is the most potent oxidant thermodynamically among the three studied here. Using the same range of substituents on pyridine-$N$-oxide (i.e., H, NO$_2$ and Me$_2$N), our previous results on Pt$^{\text{II}}$ complexes yielded a calculated $\Delta \Delta G^\ddagger$ of only 4.0 kcal/mol for the concerted single-step (i.e., Baeyer-Villiger) migration of a phenyl ligand to the O atom with simultaneous $N$–$O$ bond cleavage. The range of calculated $\Delta G^\ddagger$'s was commensurate with the calculated difference in $N$–$O$ bond dissociation energies of 4-X-OPy (-3.5 kcal/mol for $X = \text{NO}_2$ versus $X = \text{NMe}_2$). The calculated $\Delta \Delta G_{\text{oxo}}^\ddagger$ (NO$_2$-NMe$_2$) of -11.8 kcal/mol for Fe-oxo formation is approximately triple the magnitude for the Pt$^{\text{II}}$ case. The Fe$^{\text{II}}$ transition states involve $N$–$O$ cleavage and Fe–O multiple bond formation. The transition states for the Pt$^{\text{II}}$ complexes involve $N$–$O$ bond cleavage and C–O bond formation. The $N$–$O$ distances in the Fe-mediated oxo formation transition states are considerably shorter (~1.7 Å, Figure 2-1) than those calculated for the Pt transition states (~1.9 Å), implying earlier transition states for the Fe reactions. With an earlier transition state, it is anticipated that the influence upon O atom transfer of different substituents on the pyridyl will be more pronounced. The predicted greater sensitivity of the Fe complexes to oxidant modification, a relatively easy synthetic parameter to modify, is encouraging.
2.8 Effect of Ligand L for Cp*Fe(L)(OPy)Ph Complexes

The role of the ancillary ligand L of Cp*Fe(L)(OPy)Ph complexes was studied. The CO in Cp*Fe(CO)(OPy)Ph was replaced with four different ligands: NO\(^+\), Cl\(^-\), NMe\(_2\)\(^-\) and NH\(_3\) (Scheme 2-8). The overall charge of the complex was adjusted to maintain a formal Fe\(^{II}\) oxidation state for the starting complex. As shown in Scheme 2-8, when CO is replaced with NO\(^+\) the free energy barrier for formation of the Fe-oxo complex is calculated to increase by 14.7 kcal/mol. Likewise, the presence of the nitrosyl ligand results in a large change in the thermodynamics rendering the formation of the oxo complex endergonic by nearly 21 kcal/mol, which is a ΔΔG\(_{\text{oxo}}\) of > 40 kcal/mol compared to the CO complex.

**Scheme 2-7.** Effect of substituting the 4-position of coordinated pyridine-N-oxide on the energetics of formation of Fe-oxo complexes (kcal/mol). Free energies (kcal/mol) are calculated at the B3LYP/CEP-31G(d) level of theory.

Given the similar properties of isoelectronic CO and NO\(^+\) (*i.e.*, both are strong \(\pi\)-acids), the large increases in ΔG\(_{\text{oxo}}\)\(^+\) and ΔG\(_{\text{oxo}}\) are likely a result of the positive charge imbued by the nitrosyl
ligand. The formation of a high oxidation state Fe–oxo intermediate likely is disfavored by the overall positive charge. For the chloride and amide ligands the computed activation barriers for oxo formation are similar to the CO complex with a slight increase of ~3 kcal/mol for chloride and a decrease of ~2 kcal/mol for the amide ligand. Thus, overall anionic complexes do not exhibit a general positive benefit. The decrease in activation barrier for the amide ligand could indicate a positive role for π-donating ligands. Replacing the strong π-acid CO with NH₃, a charge neutral ligand and σ-donor, results in a very modest change of 0.7 kcal/mol for the activation barrier for Fe-oxo formation. Taken together, the data suggest that the overall charge of the complex is likely to be more important than the relative σ/π-donor/acceptor profile of the ancillary ligand for the formation of Fe-oxo complexes from Cp*Fe(L)(OPy)R complexes. Whether this is a general trend for other FeII and d⁶ metal complexes is unclear.

Scheme 2-8. B3LYP/CEP-31G(d) calculated energetics (kcal/mol) for Fe-oxo formation and phenyl-to-oxo migration for Cp*Fe(L)(OPy)Ph complexes.
The free energy barriers for phenyl migration ($\Delta G_{\text{mig}}$) for the Cp*Fe(L)(OPy)Ph complexes were found to vary substantially (Scheme 2-8); however, in all cases the predicted rate limiting step remains the formation of the Fe-oxo intermediate. The calculated $\Delta G_{\text{mig}}$'s for $L = \text{CO}, \text{NO}^+, \text{Cl}^-$, $\text{NMe}_2^-$ and $\text{NH}_3$ are 20.5, 6.5, 9.4, 11.2 and 15.5 kcal/mol, respectively. The $\Delta G_{\text{mig}}$ was thus lowered for all of the variants in which CO was substituted.

2.9 CO Ligand Oxidation

Given the oxidizing conditions for a catalytic process, competing ligand oxidation is an important factor in co-ligand selection. For example, oxidation of the CO ligand to CO$_2$ is an obvious concern for the complexes Cp*M(CO)(OPy)R. From the classic review by Holm and Donahue,$^{40}$ Cl$^-$ $\rightarrow$ ClO$^-$ has a much less favorable oxygen atom transfer potential ($\Delta G_{(aq)} = +22.6$ kcal/mol) than CO $\rightarrow$ CO$_2$ ($\Delta G_{(g)} = -61.5$ kcal/mol). In this regard, anionic co-ligands like chloride and dimethylamide seem promising targets for experimental study.

To probe the energetics of O atom transfer to ancillary ligands, three complexes were modeled ($L = \text{CO}, \text{NO}^+$ and Cl$^-$) since these complexes exhibited low calculated $\Delta G_{\text{oxo}}$'s (Scheme 2-9). The thermodynamics for O atom transfer to CO and NO$^+$ ligands are calculated to be exergonic while oxidation of chloride is thermoneutral. The calculated energetics indicated that the $L \rightarrow$ LO side reaction can be very favorable, as expected, and therefore needs to be considered for catalyst design. The calculations indicate that hard, electronegative co-ligands like chloride are good synthetic targets.

2.10 Electronic Structure of Fe-Oxo Intermediate
Iron oxo complexes are well known in the biological catalysis milieu.41-46 Also, a recent theory-experiment study by Wiese et al. implicates the importance of spin density on the isovalent imidyl ligand (NR*) for the capture of hydrocarbyl radical to form functionalized amine product.10,47,48 In light of previous work by Figg and Cundari10 and the potential competition between radical and concerted hydrocarbyl migration pathways, we sought to investigate more fully the nature of the Fe-oxo intermediates Cp*Fe(CO)(O)Ph. For the lowest energy triplet spin state of Cp*Fe(CO)(O)Ph, the Fe center has a calculated spin density of 1.3 e⁻ while the oxo has a computed 0.9 e⁻ spin density (from a Mulliken population analysis). The spin density of Cp*Fe(CO)(O)Ph is plotted in Figure 2-2 showing the alpha spin density (orange) being located primarily on the oxo ligand and Fe metal with a small amount of beta spin density (purple) on the phenyl and carbonyl ligands. Thus, these computed metrics suggest that the oxo intermediate possesses oxyl (O*) character, and this Fe intermediate is best described as an Fe^{III}–oxyl.

2.11 Comparison of M06 and B3LYP

The BV pathway was also studied using the M06 functional to assess the impact of this theoretical variable.49 The BV transformation was calculated to be exergonic by -69.5 kcal/mol and possess a barrier, ΔGbV‡, of 73.0 kcal/mol at the M06/CEP-31G(d) level of theory. Thus, for B3LYP versus M06, ΔΔGbV‡ ~ 1 kcal/mol while ΔΔG_{rxn} ~ 6 kcal/mol using the same basis set/pseudopotential combination. The calculated BV transition state structures are also similar for both functionals. For example, the distance in the TS between the Fe^{II} and the oxygen involved in the oxidation of the phenyl group was calculated to be 1.94 Å with M06 compared to 1.92 Å from B3LYP (Figure 2-3). The difference in the Fe-N_{py} bond distances in BV‡ is likewise small, (Δr ~
0.05 Å), as well as NpyO (Δr ~ 0.01 Å). Finally, both functionals suggest that Cp*FeII-mediated oxy-insertion via a BV pathway has very unfavorable energetics. For these reasons, subsequent modeling efforts focus on the B3LYP hybrid functional.

Scheme 2-9. B3LYP/CEP-31G(d) calculated energetics (kcal/mol) for O atom transfer from the oxo ligand of Cp*Fe(L)(O)Ph to the ligands L. For comparison, the O to Ph migration barriers (see Scheme 2-8) are also noted.

Figure 2-2. B3LYP/CEP-31G(d) spin density plot of oxo intermediate, Cp*Fe(CO)(=O)(Ph), [scale: 0.2, contour value: 0.0055].
<table>
<thead>
<tr>
<th>Complex</th>
<th>$\Delta G_{\text{OXO}}$</th>
<th>$\Delta G_{\text{MIG}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cp*Fe(Ph)(OPy)(CO)</td>
<td>22.9</td>
<td>20.5</td>
</tr>
<tr>
<td>Cp*Ru(Ph)(OPy)(CO)</td>
<td>48.8</td>
<td>24.5</td>
</tr>
<tr>
<td>Cp*Os(Ph)(OPy)(CO)</td>
<td>39.6</td>
<td>25.9</td>
</tr>
<tr>
<td>Cp*Fe(Me)(OPy)(CO)</td>
<td>21.6</td>
<td>21.8</td>
</tr>
<tr>
<td>Cp*Fe(4-NO$_2$-Ph)(OPy)(CO)</td>
<td>23.0</td>
<td>18.9</td>
</tr>
<tr>
<td>Cp*Fe(4-NMe$_2$-Ph)(OPy)(CO)</td>
<td>23.2</td>
<td>19.1</td>
</tr>
<tr>
<td>Cp*Fe(3-NO$_2$-Ph)(OPy)(CO)</td>
<td>21.5</td>
<td>-</td>
</tr>
<tr>
<td>Cp*Fe(3-NMe$_2$-Ph)(OPy)(CO)</td>
<td>20.0</td>
<td>-</td>
</tr>
<tr>
<td>Cp*Fe(Ph)(4-NO$_2$-OPy)(CO)</td>
<td>15.9</td>
<td>-</td>
</tr>
<tr>
<td>Cp*Fe(Ph)(4-NMe$_2$-OPy)(CO)</td>
<td>27.7</td>
<td>-</td>
</tr>
<tr>
<td>Cp*Fe(Ph)(OPy)(NO)</td>
<td>37.6</td>
<td>6.5</td>
</tr>
<tr>
<td>Cp*Fe(Ph)(OPy)(Cl)</td>
<td>25.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Cp*Fe(Ph)(OPy)(NMe$_2$)</td>
<td>20.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Cp*Fe(Ph)(OPy)(NH$_3$)</td>
<td>22.2</td>
<td>15.5</td>
</tr>
<tr>
<td>$\Delta G_{\text{BV}}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cp*Fe(Ph)(OPy)(CO)</td>
<td>74.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$\Delta G_{\text{MIG}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cp<em>Fe(L)(O)Ph $\rightarrow$ Cp</em>Fe(L)(O)Ph</td>
<td>$\Delta G_{\text{MIG}}$</td>
</tr>
<tr>
<td>Cp*Fe(CO)(O)Ph</td>
<td>7.4</td>
</tr>
<tr>
<td>Cp*Fe(N)(O)Ph</td>
<td>2.6</td>
</tr>
<tr>
<td>Cp*Fe(Cl)(O)Ph</td>
<td>68.8</td>
</tr>
</tbody>
</table>

**Table 2-3.** Free energies of activation and migration for all complexes studied; $\Delta G_{\text{OXO}}$, $\Delta G_{\text{MIG}}$, and $\Delta G_{\text{BV}}$. 
Figure 2-3. B3LYP/CEP-31G(d) calculated bond lengths (in Å) of the singlet Baeyer-Villiger transition state for Cp*Fe(Ph--O--Py)(CO). Cp* ligand is omitted from the figure for clarity.

2.12 Redox (Oxo) Pathway for Oxy-Insertion

An alternative pathway has the Fe$^{II}$ complex Cp*Fe(Ph)(OPy)(CO) undergo oxy-insertion via a two-step mechanism with an Fe$^{IV}$-oxo intermediate, Scheme 2-10. Note that the metal must undergo a formal two-electron oxidation to form the oxo, followed by a two-electron reduction (alkyl/aryl migration to the oxo ligand to form an alkoxide/aryloxide). Both thermodynamics and kinetics were calculated relative to the MCI, Cp*Fe(Ph)(OPy)(CO). The $\Delta G_{\text{oxo}}$ for the initial formation of Cp*Fe(Ph)(O)(CO) + Py was -21.8 kcal/mol while the barrier ($\Delta G_{\text{oxo}}^\ddagger$) was calculated to be 22.9 kcal/mol, a reasonable value for a low temperature MTM catalytic process.

The second step within this pathway is phenyl migration. During the migration the Fe$^{II}$ center transforms from six- to five-coordinate, opening up a coordination site at the Fe center. In a reaction mixture, solvent or the pyridine leaving group of the PyO oxidant could presumably occupy the open coordination site to reform an 18-electron complex. The product of oxy-insertion, Cp*Fe(OPh)(CO), is calculated to be -66.5 kcal/mol ($\Delta G_{\text{oxo}}$) relative to the MCI, yielding $\Delta G_{\text{mig}}^\ddagger$ = -44.7 kcal/mol for Cp*Fe(Ph)(O)(CO) $\rightarrow$ Cp*Fe(OPh)(CO). The alkyl migration TS is 20.5 kcal/mol relative to the oxo formation intermediate and hence $\Delta G_{\text{mig}}^\ddagger$ = 20.5 kcal/mol (Scheme 2-
10). Note that the formation of the Fe\textsuperscript{IV}-oxo intermediate within this two-step pathway is rate-determining, Scheme 2-10.

2.13 Impact of a Bigger Basis Set

Higher levels of theory were examined and then compared those results with the standard B3LYP/CEP-31G(d) approach for the redox pathway to oxy-insertion.

Scheme 2-10. Formation of oxo intermediate and alkyl migration steps in redox pathway for oxy-insertion comparing energetics for Group 8 metals. Calculated relative and absolute free energies, \( \Delta G_{\text{oxo}} \) and \( \Delta G_{\text{oxo}}^\ddagger \), and oxo intermediate \( \text{Cp}^*\text{M(OPy)(CO)(Ph)} \), are given in kcal/mol for Fe (blue), Ru (red) and Os (green).

<table>
<thead>
<tr>
<th>Basis Set</th>
<th>( \Delta G_{\text{oxo}}^\ddagger )</th>
<th>( \Delta G_{\text{MIG}}^\ddagger )</th>
<th>( \Delta G_{\text{oxo}} )</th>
<th>( \Delta G_{\text{MIG}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEP-31G(d)</td>
<td>22.9</td>
<td>20.5</td>
<td>-21.8</td>
<td>-44.7</td>
</tr>
<tr>
<td>“Bigger Basis Set”</td>
<td>27.7</td>
<td>19.1</td>
<td>-17.8</td>
<td>-51.1</td>
</tr>
</tbody>
</table>

Table 2-4. Relative free energy (kcal/mol) relative to MCI for \( \Delta G_{\text{oxo}} \) and \( \Delta G_{\text{oxo}}^\ddagger \), and oxo intermediate \( \text{Cp}^*\text{Fe(Ph)(O)(CO)} \) for B3LYP functional in conjunction with small (CEP-31G(d)) and “Bigger Basis Set”. See text for description of the latter.

Given the results in section 2.4, a bigger basis set was used in conjunction only with the B3LYP for the study of the two-step, oxy-insertion pathway. An all-electron 6-311++G(d,p) basis set was used for all of the atoms in the complex with the exception of Fe for which the triple-zeta CEP-
121G pseudopotential/valence basis set was employed to facilitate eventual comparison of iron with ruthenium and osmium complexes. The difference in the relative free energies of the oxo formation TSs, $\Delta \Delta G_{\text{oxo}}^\dagger$, between the two basis sets was relatively small, with the bigger basis 4.8 kcal/mol higher in free energy, Table 2-4. The relative free energy difference for the phenyl/oxo $\rightarrow$ phenoxide migration TS ($\Delta \Delta G_{\text{mig}}^\dagger$) was smaller by 1.4 kcal/mol. Ground state energy differences were $\Delta \Delta G_{\text{oxo}} = 4.0$ kcal/mol and $\Delta \Delta G_{\text{mig}} = 6.4$ kcal/mol. Despite these changes, the most important conclusions are not changed by the use of a larger, augmented basis set, i.e., the preferred pathway is oxo-mediated, oxy-insertion and initial oxo formation is the rate determining step. Hence, we utilized the more compact B3LYP/CEP-31G(d) level of theory in subsequent simulations unless noted otherwise.

2.14 Impact of Solvent

Using the bigger basis sets (section 2.13) and the B3LYP functional, Cp*Fe(Ph)(OPy)(CO) and its oxy-insertion pathways were modeled with THF (CPCM continuum model) as the solvent. THF was chosen as it is a common solvent in organometallic catalysis.\textsuperscript{50} There is little difference in relative free energies (i.e., relative to $[\text{Cp*Fe(OPy)(Ph)(CO)}]$), between the complex modeled in THF and the complex in the absence of a continuum solvent, Table 2-5. The oxo insertion TS ($\Delta G_{\text{oxo}}^\dagger$) had a free energy difference of 0.9 kcal/mol while $\Delta G_{\text{mig}}^\dagger$ had a free energy difference of -0.7 kcal/mol. $\Delta G_{\text{oxo}}$ and $\Delta G_{\text{mig}}$ yielded calculated differences of 3.2 and 0.3 kcal/mol, respectively, when incorporating continuum, solvent effects. Hence, the use of the THF solvent had little impact on the oxy-insertion pathway, and thus subsequent calculations were modeled in the gas phase. Therefore, the B3LYP/CEP-31G(d) level of theory is used for the remainder of this research given its use in previous studies of oxy-insertion.\textsuperscript{50,51}
<table>
<thead>
<tr>
<th></th>
<th>$\Delta G_{oxo}^\dagger$</th>
<th>$\Delta G_{mig}^\dagger$</th>
<th>$\Delta G_{oxo}$</th>
<th>$\Delta G_{mig}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bigger Basis Set/Gas</td>
<td>27.7</td>
<td>19.1</td>
<td>-17.8</td>
<td>-51.1</td>
</tr>
<tr>
<td>Bigger Basis Set/THF</td>
<td>28.6</td>
<td>18.4</td>
<td>-21.0</td>
<td>-51.4</td>
</tr>
</tbody>
</table>

Table 2.5. Absolute free energy (kcal/mol) relative to MCI (versus Cp*Fe(OPy)(Ph)(CO)) in gas phase and with continuum THF solvent model. The B3LYP functional was used for these simulations.

2.15 Combination of Differing Ligands

It was concluded that the substitution of Cl$^-$ in the place of CO as well as 4-NO$_2$-pyridine in place of pyridine had positive effects on the reaction energetics. These two modifications were both introduced to the original Fe$^{II}$ complex to yield the $[\text{Cp*Fe(Cl)(Ph)(4-NO}_2\text{-Py)}]\text{]^\dagger}$ as a model MCI. The thermodynamics were determined to be -12.1 and -68.8 kcal/mol for the oxo-formation ($\Delta G_{oxo}$) and alkyl migration ($\Delta G_{tot}$) steps, respectively. Most importantly, $\Delta G_{oxo}^\dagger$, which defines the rate determining step, was lowered from 25.8 kcal/mol for $[\text{Cp*Fe(CO)(Cl)(Ph)(OPy)}]\text{]^\dagger}$ to 21.0 kcal/mol for $[\text{Cp*Fe(CO)(Cl)(Ph)(4-NO}_2\text{-OPy)}]\text{]$. Interestingly, this double modification also lowered the phenyl migration barrier to 9.4 kcal/mol.

2.16 Summary, Conclusions and Prospectus

Recent conceptual and synthetic achievements have significantly advanced the goal of achieving oxy-insertion into M–C bonds including the use of Earth abundant metals.$^{10,14,23}$ When combined with the recent experimental demonstration of C–H activation by Fe$^{II}$ and Ni$^{II}$ complexes,$^{10,23}$ the goal of selective hydrocarbon functionalizations via traditional metal-mediated C–H activation and subsequent M–R functionalization seems viable. The present computational
results reveal that the functionalization M–R to M–OR is plausible through the use of FeII starting complexes and provide some guidance on experimentally plausible research directions.

A baseline Cp*Fe(CO)(OPy)Ph complex was modified to gain insight into the impact of modification of the chemical components on the thermodynamics and kinetics of oxy-insertion into the Fe–Ph bond. The modifications modeled include: adding electron withdrawing/donating groups on the migrating group (Ph) and oxidant (PyO), changing the metal to heavier Group 8 metals, and substituting various co-ligands for CO. The main points are outlined below.

(1) Calculations support a two-step (or redox) oxo-mediated pathway as more energetically favorable in comparison to a one-step (or non-redox) organometallic Baeyer-Villiger pathway. Moreover, for the systems modeled here, the initial barrier to oxo formation ($\Delta G_{\text{oxo}}^{\ddagger} = 22.9$ kcal/mol) marked the highest point on the reaction coordinate while the transition state for phenyl migration is predicted to occur with a lower free energy of activation ($\Delta G_{\text{mig}}^{\ddagger} = 20.5$ kcal/mol).

The oxo intermediate formed by the initial oxygen atom transfer from OPy to the metal is most accurately described as an oxyl (FeIII$O^\cdot$) as opposed to an oxide (FeIV$O^2$) or oxene (FeII$O^\cdot\cdot$) intermediate. This echoes a recent computational study of oxy-insertion into a NiII hydrocarbyl bond. Modification of the supporting ligands to enhance oxyl identity and the correlation this may have with oxy-insertion activation barriers would be of interest from both an experimental and computational perspective, not only for the current models but also for other systems. One may reasonably hypothesize that the reduced nucleophilicity of an oxyl versus an oxide may enhance hydrocarbyl migration aptitude.
(2) The iron of Cp*Fe(CO)(OPy)Ph was replaced by Ru and Os. The barriers for the oxo formation step showed the 3d and 4d metals to be more similar with Os having the most divergence. The strength of bonding of the oxidant OPy to Cp*M(CO)Ph was identified as an important discriminant among the Group 8 metals. The barriers for alkyl migration trended as Fe > Ru > Os, which contrasted the calculated trend for the metal oxo formation step. Thus, as in a previous study of the organometallic Baeyer-Villiger mechanism, 3d metals display a computed advantage over their 4d and 5d counterparts. It is reasonable to assume, given the combination of results from this and past research that the weakness of the M–C bond is a major determinant of this trend. The prediction of weaker metal-oxo bonds being more favorable for hydrocarbyl migration is in seemingly contrast to previous work by Brown and Mayer; however, given the oxyl character of the Fe-oxo complex compared to diamagnetic Re(VII)-oxo complexes, differences in trends are not necessarily surprising.

(3) Contrary to what was determined from a study of oxy-insertion reactions for PtII complexes operating via an OMBV mechanism, introduction of an EWG (NO2) or an EDG (NMe2) into the para position of the phenyl ligand was calculated to have a minimal impact on activation barrier for the phenyl-to-oxo migration for Cp*Fe(CO)(O)Ar complexes. Substitution at the 4-position of the pyridine ring of the oxidant with these same EWD/EDG yielded a much greater Hammett impact on ΔG_{oxo}‡ as compared to what was previously computed for a PtII system operating via an OMBV mechanism. Also, a slightly larger inductive effect (assessed via meta substitution of these same functional groups) was computed. Furthermore, it was noted that the O–N_{py} distances in the FeII-mediated oxo formation transition states are decidedly shorter (~1.7 Å) than those
calculated for the Pt\textsuperscript{II}/OMBV transition states (~1.9 Å), implying an earlier transition state for the former and presumably greater potential for the oxidant leaving group to impact the course of the oxy-insertion above and beyond the intrinsic thermodynamic driving force derived from its OAT potential. Given the exergonicity of the overall oxy-insertion (L\textsubscript{n}M–R + YO → L\textsubscript{n}M–OR + Y), the hunt for catalytic (as opposed to stoichiometric) hydrocarbon oxidations will require milder oxidants, although this presents a balancing act as such systems are expected to increase the initial activation barriers for formation of metal oxo complexes.

(4) The role of CO as a co-ligand was also studied. Clearly in any experimental system one would expect oxidation of most \( \pi \)-acid co-ligands (CO, CNR, phosphine, \textit{etc.}) to compete with oxidation of the hydrocarbyl ligand. Indeed, activation of the C–H bond of a methyl group in Cp* would also be expected to be problematic, suggesting more research in that direction is also needed. Thus, while the studies of Cp*Fe(CO)(OPy)Ph reported herein indicate the viability of oxy-insertion into Fe–R bonds, experimental demonstration and extension to catalysis will likely require different supporting ligands less prone to oxidation.

Herein, substitution of CO with dimethylamide and NH\textsubscript{3} lowered the barrier for the initial oxo transfer (\( \Delta G_{\text{oxo}}^{\ddagger} \)), whereas Cl\textsuperscript{−} raised this barrier only slightly. The transition state for the second, phenyl migration step remained lower in free energy than the initial TS for oxo formation with S = Cl\textsuperscript{−}. When considering the L → LO side reaction, introduction of Cl\textsuperscript{−} as a co-ligand showed the most promise.

(5) Substitution of a phenyl with a methyl group in the R position raised the activation barrier for hydrocarbyl-to-oxo migration by only 1.3 kcal/mol. Calculated Fe–C bond dissociation free
energies imply that the Fe–R → Fe–OR transformation may have substantial radical character to it, especially for R = Me. Unlike the phenyl congener, the calculated bond dissociation free energy for Fe-methyl scission is substantially lower than the activation barrier for migration of the methyl to the oxo ligand. The Hammet studies may also be interpreted to imply radical character in the oxy-insertion transformations, and thus limited charge build-up in the hydrocarbyl group, in the migrating step for the 3d metal. If this radical reactivity could be harnessed, it may overcome one of the major challenges inherent in non-redox, Baeyer-Villiger pathways for oxy-insertion, i.e., the extreme reluctance of a nucleophilic methyl to transfer to an oxygen atom.

2.17 References

5. Perez, P. J. Alkane C-H Activation by Single-site Metal Catalysis; Springer: **2012**.


27. Frisch, M. J. *et al.* *Gaussian 09, Revision B.01*, Gaussian, Inc., Wallingford CT, **2009**.


Chapter 3
Oxygen Atom Insertion into Iron(II) Phenyl and Methyl Bonds via Phosphite Fe\textsuperscript{II} Complex\textsuperscript{2+}

3.1 Introduction

Insertion of oxygen atoms into metal–hydrocarbyl bonds is a vital step in developing catalysts for the oxidation of hydrocarbons as shown in Scheme 1-1. Currently there are few examples of nonradical conversion of M–R bonds and oxygen atom transfer reagents to M–OR. Chapter 2 showed a Cp*Fe(CO)(NCMe)Ph catalyst that energetically is feasible to fill that void. However, certain challenges must be overcome utilizing that catalyst. One specific example is the overoxidation of the carbonyl ligand. So, within this chapter we investigate a ligand that possesses more tunable properties as compared to CO.

Phosphines have been extensively studied within literature.\textsuperscript{1-9} Phosphines generally behave as spectator ligands as compared to active ligands. The steric and electronic properties of the phosphines can be manipulated based on the substituents attached to the PR\textsubscript{3} ligand.\textsuperscript{10} Stronger σ-donor substituents attached to the phosphines increase electron density at the metal center, which leads to a stronger metal to ligand π-back bonding. Being able to modulate the steric and electronic effects make phosphine ligands versatile in organometallic catalysis. Within this chapter the use of phosphine ligands coupled with the Cp*Fe(L)(NCMe)Ph (Chapter 2) catalyst is investigated.

\textsuperscript{2+} "Parts of this chapter was reprinted (adapted) with permission from (Oxygen Atom Insertion into Iron(II) Phenyl and Methyl Bonds: A Key Step for Catalytic Hydrocarbon Functionalization) Copyright (2014) American Chemical Society."
3.2 Computational Methods

Density functional theory (DFT) within the Gaussian 09 package\textsuperscript{11} was used for geometry optimization and vibrational frequency calculations. A standard level of theory was employed – B3LYP with a double zeta basis set with pseudopotentials and added d functions for group elements (\textit{e.g.}, CEP-31G(d)).\textsuperscript{12} This level of theory has been used in previous modeling of oxygen atom transfer and oxy-insertion reactions and shown to correspond well with experimental trends while maintaining reasonable computational cost.\textsuperscript{13} Tests with a larger, all-electron basis set – including diffuse functions on main group elements (B3LYP/6-31+G(d)) – as well as Truhlar's M06\textsuperscript{14} functional (M06/6-31+G(d)) did not yield significantly different calculated geometries or free energies.

The energies quoted are free energies that were calculated at 298.15 K and 1 atm. The stationary points were defined as minima or transition states (TSs) by the presence of 0 or 1 imaginary frequencies, respectively, as obtained from the calculated energy Hessians. Various spin states were studied with only results for the lowest energy spin state reported.
**Scheme 3-2.** DFT-calculated free energies for oxy-insertion into Fe-Ph bond via an oxo-mediated pathway. The most stable spin states for the respective stationary points are given in the box.

3.3 Oxy-insertion into an Fe-Ph bond via an oxo pathway

Cp*Fe[P(OCH$_2$)$_3$CEt]$_2$Ph is reacted with ONMe$_3$ oxidant to yield the phenoxide product Cp*Fe[P(OCH$_2$)$_3$CEt]$_2$(OPh), where the separated reactants are considered the free energy reference point (Scheme 3-1) for the DFT simulations. The former structure is calculated to be octahedral and in a singlet spin ground state. The average Fe—C (Cp*) bond distance was 2.3 Å. The average Fe—C (Cp*) bond distance in the Cambridge Database is 2.1 Å. The Fe was also bonded to Cp* in an η$^5$ fashion throughout the scheme. No evidence of “ring slippage” was seen in any of the oxy-insertion steps. The average Fe—[P(OCH$_2$)$_3$CEt] bonds are calculated to be ~2.2 - 2.4 Å depending on the coordination number and formal oxidation state of the intermediates and
TSs, implying weak coordination of the phosphite, which is consistent with the calculated free energies (see below). It is worth noting that the use of larger basis sets in conjunction with the M06\textsuperscript{14} functional, which is indicated to be superior to B3LYP for weak chemical interactions, yielded only marginally shorter (<0.1 Å) FeP bond lengths. This calculated bond distance is slightly elongated compared to the few Fe—[P(OCH\textsubscript{2})\textsubscript{3}CEt] bonds that have been synthesized within literature.\textsuperscript{16} Also, in the literature, two Fe—[P(OCH\textsubscript{2})\textsubscript{3}CCH\textsubscript{3}] bonds were found to be of similar distance, 2.217 Å and 2.171 Å.\textsuperscript{17,18}

Overall, the final Cp*Fe[P(OCH\textsubscript{2})\textsubscript{3}CEt]\textsubscript{2}(OPh), oxy-insertion product is highly exergonic relative to the starting structure (\(\Delta G_{\text{rel}} = -73.9\) kcal/mol). The first step within this two-step pathway is dissociation of one of the phosphite ligands and is found to be exergonic by 12.4 kcal/mol, indicating a weak Fe—P bond enthalpy with dissociation being entropically favored, consistent with the long calculated FeP bond lengths. The dissociation of phosphite leaves an open coordination site and a 16-electron Fe complex that allows for the coordination of ONMe\textsubscript{3}.

Upon dissociation of the phosphite ligand a spin “flip” from the singlet to a triplet spin state occurs. For a smaller model, CpFe(PH\textsubscript{3})\textsubscript{2}(CH\textsubscript{3}), the minimum energy crossing point (MECP) for the “spin flip” for phosphine loss was identified and found to lie \textit{ca.} 12 kcal/mol above ground state \(^1\text{CpFe(PH}_3)_2(\text{CH}_3)\). The MECP could not be found for P(OCH\textsubscript{2})\textsubscript{3}CEt dissociation from the larger, more conformationally complex Cp*Fe[P(OCH\textsubscript{2})\textsubscript{3}CEt]\textsubscript{2}(Ph), but the geometric and energetic data, in concert with the experimental data, indicate ready access to a 16-electron Fe intermediate.
Binding of ONMe₃ to Cp*Fe[P(OCH₂)₃CEt](Ph) was calculated to be endergonic by 6.6 kcal/mol, and is thus ΔG° = -5.8 kcal/mol compared to the starting complex. The metallo-Criegee intermediate (MCI) – so-called in analogy to the organic Baeyer-Villiger reaction - has now been formed, Cp*Fe[P(OCH₂)₃CEt](Ph)(ONMe₃). Another spin flip (triplet → quintet) accompanies the transformation of Cp*Fe[P(OCH₂)₃CEt](Ph) → Cp*Fe[P(OCH₂)₃CEt](Ph)(ONMe₃). Attempts to find phosphite/ONMe₃ dissociation via an associative mechanism were not successful, and thus the simulations imply a dissociative mechanism. More significantly, the calculations support the conclusion that exchange of phosphite by oxidant is facile in this Cp*Fe⁴⁺ system.

From the MCI an Fe⁴⁺-oxo, Cp*Fe[P(OCH₂)₃CEt](Ph)(O), intermediate is formed with a modest barrier of 8.6 kcal/mol and the oxo intermediate is exergonic by 34.3 kcal/mol relative to the MCI. The TS for this oxygen atom transfer was calculated to be a quintet spin state and entails another spin “flip” to a triplet upon formation of the oxo intermediate. The Fe of Cp*Fe[P(OCH₂)₃CEt](Ph)(O) has a spin density of 1.397, while the oxo has a 0.801 spin density. This suggests the oxo intermediate possesses oxyl (O•⁻) character. The spin density plot can be seen in Scheme 3-3, showing the alpha spin (orange) being shared between the oxyl and Fe while a small amount of beta spin (purple) is on the phenyl.
Scheme 3-2. DFT-calculated free energies for formation of phosphite via an oxo-mediated pathway (Blue) and a concerted mechanism (Red). The most stable spin states for the respective stationary points are given in the box.

Scheme 3-3. Spin density plot of oxo intermediate, Cp*Fe[P(OCH$_2$)$_3$CEt](Ph)(O), [scale: 0.33, contour value: 0.005787].

Aryl migration of the phenyl ligand to the Fe-oxo bond results in an effective calculated free energy barrier of 16.2 kcal/mol and was found to be exergonic by 44.9 kcal/mol upon formation of the quintet phenoxide product, Cp*Fe[P(OCH$_2$)$_3$CEt](OPh). Finally, association of the phosphite group back onto the unsaturated Fe intermediate complex was found to be endergonic
by 11.2 kcal/mol, mirroring the initial dissociation of this ligand from the starting iron-phenyl reactant.

![Diagram](image)

**Scheme 3-4.** Bond distances and angle of direct oxidation of phosphite from ONMe$_3$.

3.4 Oxy-insertion into an Fe-P bond via an oxo pathway

Once the oxidant, ONMe$_3$, has been coordinated, phosphite has the potential to become oxidized to form phosphate [O=P(OCH$_2$)$_3$CEt]. There are two routes in which this pathway can proceed. The first involves a concerted, Baeyer-Villiger mechanism in which no formal change in oxidation state of the Fe occurs, Scheme 3-2 (Red Pathway). The phosphite migrates to the O atom of the oxidant, which releases the leaving group (Y) from the oxidant (YO). This triplet TS has an effective barrier of $\Delta G^\ddagger = 14.6$ kcal/mol relative to the MCI. Relative to the initial starting structure, Cp*Fe[P(OCH$_2$)$_3$CEt]$_2$Ph, the concerted TS to form phosphate is 8.8 kcal/mol higher in energy. This barrier is also higher than that in which the oxo is formed ($\Delta G^\ddagger = 8.6$ kcal/mol vs. $\Delta G^\ddagger = 14.6$ kcal/mol), suggesting the oxo would be formed instead of phosphate.

As an aside, the transition state for direct oxidation of phosphite free ligand, absent of Fe complex, was calculated, Scheme 3-4. This oxo transfer had a free energy barrier of 20.7 kcal/mol and a
thermodynamic free energy that was calculated to be exergonic by 69.4 kcal/mol. Hence, it is quite conceivable that phosphate could be formed from free phosphite produced via initial dissociation of the latter from Cp*Fe[P(OCH$_2$)$_3$CEt]$_2$Ph.

Once the Fe$^{IV}$-oxo (ferryl) intermediate is formed, Cp*Fe[P(OCH$_2$)$_3$CEt](Ph)(O), the phosphite can migrate to the oxyl forming a phosphate, Scheme 3-2 (Blue Pathway), instead of phenyl migration forming phenoxide as was shown in Scheme 3-1. The effective calculated free energy barrier to form phosphate from ferryl was 8.4 kcal/mol (versus a calculated free energy barrier of 16.2 kcal/mol for phenyl migration to the oxo ligand), thus a $\Delta \Delta G^\ddagger = 7.8$ kcal/mol favoring phosphate formation. The formation of the phosphate oxy-insertion product Cp*Fe(OP(OCH$_2$)$_3$CEt)[OP(OCH$_2$)$_3$CEt]Ph is 66.8 kcal/mol exergonic in relation to the starting material [Cp*Fe[P(OCH$_2$)$_3$CEt]$_2$Ph]. These energetics suggest that the phosphite must be oxidized prior to phenoxide being formed.

3.5 Summary, Conclusions and Prospectus

Insertion of oxygen atoms into metal–hydrocarbyl bonds is a key step in the development of potential catalysts for the oxidation of hydrocarbons as shown in Scheme 3-1. Despite the potential importance of such oxygen atom insertion reactions, there are few examples of nonradical conversion of M–R bonds and oxygen atom transfer reagents to M–OR. Herein, it is demonstrated that Fe(II) hydrocarbyl (phenyl and methyl) complexes undergo C–O bond formation. The study indicates that Fe–oxo complexes as viable intermediates that precede net oxo insertion into the Fe–R bond. The calculations indicate that both Fe–oxo formation and the oxy-insertion into Fe–R bonds are thermally viable processes. Although the previous (limited) examples of O-atom
insertion into M–R bonds occur with metals that will not activate C–H bonds, use of Cp*Fe(P(OCH2)3CEt)2R complexes is promising because of the demonstrated ability of the related Cp*Fe(CO)(NCMe)Ph to activate C–H bonds. These studies establish the ability of d6 complexes to mediate O atom insertion into M–R bonds. Importantly, they also point the way to new ligand motifs that avoid (1) C–C coupling products, and (2) ligand oxidation.

3.6 References


Chapter 4

Computational Study of Carbon-Hydrogen Bond Deprotonation by Alkali Metal Superbases

4.1 Introduction

The exploitation of acidity or electrophilicity is a vital aspect of many chemical reactions as well as catalysis. Olah and coworkers were pioneers in the study of superelectrophiles. These researchers showed that such compounds, also known as “superacids,” possess the ability to accomplish chemistry that “normal” acids are unable to accomplish. A shining example includes Olah’s work in which he was the first to effectively stabilize carbocations and permit direct experimental characterization of many of their properties. These strong electrophiles/ acids have the ability, for example, to react with weakly nucleophilic/basic sites such as the $\pi$-electrons of alkenes or small hydrocarbon C—H bonds. Strong acids are vital in the transformation of typically inert hydrocarbon feedstocks into materials of economic importance. For example, “superacid” systems are able to crack or isomerize alkanes. Superacidic systems play a vital role in the production of valuable industrial compounds, e.g., ethylene, propylene and hence compounds derived from these olefins.

Although not as well studied as superelectrophilic/superacidic compounds, supernucleophilic/superbasic compounds effect interesting and important chemical transformations. A substantial body of work has been published by Streitwieser and coworkers concerning the kinetic acidities of alkanes, cycloalkanes and other very weak carbon acids using cesium cyclohexylamide (CsCyNH) as a “superbase.” Proton exchange kinetics have been

---

$^{\dagger}$ This chapter was reproduced from Reference “Computational Study of Carbon–Hydrogen Bond Deprotonation by Alkali Metal Superbases” with permission from The Royal Society of Chemistry.
reported for reactions of alkanes with CsCyNH in cyclohexylamine solvent.\textsuperscript{9,12} From this it was concluded that CsCyNH was monomeric in solution.\textsuperscript{9} Streitwieser \textit{et al.} evaluated dissociation constants derived from conductivity studies of alkali metal ion pairs in THF.\textsuperscript{22} This study indicated that these dissociation constants for lithium ion pairs are $10^2 - 10^3$ times greater than those of cesium salts. They reasoned that lithium salts of delocalized carbanions exist as solvent separated ion pairs in which dissociation is favored by weak metal-anion interactions and long interionic separations.\textsuperscript{23} In contrast, the cesium salts exist as contact ion pairs.\textsuperscript{24} The stronger metal-anion interactions and shorter interionic separations make dissociation less favored for cesium salts verses lithium salts. Although not d-block metal complexes, cesium amides hold considerable interest in the context of hydrocarbon cleavage.\textsuperscript{11,25} Specifically, cesium amides permit deprotonation of very strong C—H bonds including those of methane, the primary component of natural gas. Acid/base properties of transition metal organometallics have been demonstrated to be important in CH activation of methane.\textsuperscript{26-29} Study of cesium amides thus allows testing of one extreme in ligand basicity/nucleophilicity (and hence metal acidity/electrophilicity) as it pertains to the factors that control metal-mediated cleavage of C—H bonds.

Herein are reported the results of density functional theory (DFT) calculations of cleavage of the CH bonds of methane by CsNH\textsubscript{2} as well as derivatives with a larger hydrocarbyl substituent, Scheme 4-1, cyclohexyl (Cy). Also, Cs is replaced with other alkali metals. The influence of varying the acidity of the substrate was also studied with smaller model complexes. Although studied experimentally,\textsuperscript{7-12} the extreme reactivity of superbasic compounds has hindered the elucidation of some aspects of their chemistry requiring special experimental techniques. A computational study on the thermodynamics and barriers of hydrocarbon C—H bond cleavage by
these and related alkali metal compounds may provide important insight into harnessing superbasic properties of related transition metal complexes without the complications that may arise from the redox non-innocence of d-block metals.

\[
\text{CsNH}_2 + \text{CH}_4 \rightarrow \text{Cs}^+\text{(H}_2\text{N}---\text{H}--\text{CH}_3)\rightarrow^+ \rightarrow \text{CsCH}_3 + \text{NH}_3
\]

**Scheme 4-1.** Depiction of proposed cleavage of the CH bonds of methane by a model cesium amide complex.\(^\text{30}\)

4.2 Computational Methods

DFT within the Gaussian 09 package\(^\text{31}\) was used for geometry optimization and vibrational frequency calculations. B3LYP functional was employed. Also, an effective core potential basis set (LANL2DZ) was used for the alkali metals.\(^\text{32}\) All other atoms were calculated using the all-electron, 6-31+G(d,p) basis set. Tests with the M06\(^\text{33}\) functional [M06/LANL2DZ/6-31+G(d,p)] did not yield significantly different calculated geometries or free energies.

The energies quoted are free energies that were calculated at 298.15 K and 1 atm. Stationary points were defined as minima or transition states (TSs) by the presence of 0 or 1 imaginary frequencies, respectively, as obtained from calculated energy Hessians. The vibration associated with the single imaginary frequency confirmed that the calculated TS associated with C—H bond cleavage involved the transfer of hydrogen between the carbon (of the substrate) and nitrogen or oxygen of the alkali metal complex. All compounds are in the singlet spin state, unless stated otherwise. Implicit solvation calculations were performed with the SMD\(^\text{34}\) method. Geometries were optimized in the presence of the continuum solvent, butylamine, as this was the SMD-
parameterized solvent deemed closest to the cyclohexylamine solvent used by Streitwieser and coworkers.\(^6\)

4.3 Cleavage of Methane CH bonds

The computational methods described above were first employed to model the reaction coordinate for C—H cleavage of methane by CsNH\(_2\). The reaction, Cs(CH\(_4\)NH\(_2\) → Cs(CH\(_3\))NH\(_3\), was calculated to be endergonic by 11.7 kcal/mol (\(\Delta H = 11.0\) kcal/mol). Within the adduct, Cs(CH\(_4\))NH\(_2\), methane was only weakly bonded to Cs (Cs—C = 3.92 Å), Figure 4-1. The calculated Cs-amide nitrogen distance in the adduct was 2.92 Å. Upon C—H cleavage, Cs—C shortens by ~0.6 Å, to 3.28 Å, relative to this distance in the methane adduct. Gemund et al. reported a monomeric Cs—NR\(_2\) complex with a bond distance of 2.99 Å.\(^{35}\).

![Figure 4-1. DFT calculated bond lengths (Å) and bond angles (°) for methane adduct reactant, Cs(CH\(_4\))NH\(_2\) and the product, Cs(CH\(_3\))NH\(_3\).](image-url)
The transition state (TS) for the conversion of Cs(CH₄)NH₂ to Cs(CH₃)NH₃ was confirmed by the calculation of a frequency of ~ 1240 cm⁻¹, Figure 4-2a. Atomic motions within the TS normal mode are depicted in Figure 4-2b. This transformation entails the transfer of the hydrogen from methane to the amide N. The CH₃ ligand rearranges within the transition state mode in order to form a direct σ bond with the Cs. The TS thus closely corresponds to the exchange mechanism discussed by Streitwieser and coworkers.⁷

![Figure 4-2a (left) and Figure 4-2b (right). DFT calculated bond lengths (Å) and bond angles (°) of the TS for cleavage of the CH bond of methane for the conversion of Cs(CH₄)NH₂ to Cs(CH₃)NH₃ (left). Plot depicting atom motion in the imaginary mode for the same TS (right).](image)

The methane possesses a calculated Mulliken charge density of only 0.004 e⁻ (all charges quoted are the summation of C and bonded H’s) in the methane adduct, Cs(CH₄)NH₂, supporting the supposition of only weak interaction (minimal charge transfer). The methyl group has a charge of -0.83 e⁻ when the product, Cs(CH₃)NH₃, is formed. Interestingly, the methyl group of the TS has a calculated Mulliken charge of -0.69 e⁻. This suggests, therefore, a C—H bond cleavage event that is primarily a deprotonation, consistent with the superbasicity of cesium amides. The
calculated Mulliken charge on cesium is +0.85 e\(^-\) in both the reactant and product states, suggesting formulations for the above that may be better construed as \([\text{Cs}^+ (\text{NH}_2)^+] \cdots \text{CH}_4\) and \([\text{Cs}^+ (\text{CH}_3)^- \cdots \text{NH}_3\), respectively.

A 14.4 kcal/mol free energy barrier was calculated for the \(\text{Cs(CH}_4\text{)}\text{NH}_2 \rightarrow \text{Cs(CH}_3\text{)}\text{NH}_3\) reaction. The calculated transition state is depicted in Figure 4-2a. The Cs—C bond length in the transition state more closely resembles that of the Cs—C bond in the Cs(CH\(_3\))NH\(_3\) product complex (3.32 vs. 3.28 Å, respectively), whereas, the Cs—N bond is closer in distance to that calculated for the Cs(CH\(_4\))NH\(_2\) reactant adduct (3.01 vs. 2.92 Å, respectively). Thus, the calculated structural data are ambiguous with respect to the early/late nature of the transition state.

The computed \(\Delta G^\ddagger\) for methane C—H bond cleavage of 14.4 kcal/mol for cesium amide compares favorably to reported highly electrophilic (at the transition metal, hence highly nucleophilic at the imide N) d\(^0\) imidos,\(^{36-39}\) which are potent activators of the strongest C—H bonds, including those of methane.\(^{40-42}\) Previous computations\(^{36}\) show methane CH activation by d\(^0\) Group 4 mono-imidos with \(\Delta H^\ddagger\) from 7.3 - 14.5 kcal/mol relative to separated reactants (\(\Delta G^\ddagger\) is ~12 kcal/mol higher at STP due to entropy corrections). Cundari reported computations on Ti(OH)\(_2\)(=NH) in which the \(\Delta H^\ddagger_{\text{act}}\) = 19.8 kcal/mol (relative to adduct)\(^{37}\). Other research\(^{38}\) shows that d\(^0\), bis-imidos M(NH\(_2\))(=NH)\(_2\)(M = Nb, Ta, V) to have \(\Delta H^\ddagger_{\text{act}}\) = 16.2 to 20.7 kcal/mol (relative to adduct). Similar enthalpic barriers are seen for methane C—H activation by Group 6 d\(^0\) tris-imidos\(^{39}\). The study of d\(^6\) complexes by Grimes\(^{43}\) et al. [(Tab)M-(PH\(_3\))\(_2\)X]\(^q\) (Tab) tris-azo-borate; X = OH, NH\(_2\); q = -1 to +2; M = Tc\(^I\), Re\(^I\), Ru\(^II\), Co\(^III\), Ir\(^III\), Ni\(^IV\), Pt\(^IV\)) showed enthalpic barriers of ~ 19 kcal/mol → 35 kcal/mol for activation of benzene C—H bonds.
4.4 Method Sensitivity

The sensitivity of the methane CH cleavage reaction coordinate was addressed by comparing DFT stationary points to those obtained with a correlated wavefunction method, MP2 (Table 4-1). The energetics shown in Table 4-1 are derived from fully optimized geometries at each particular level of theory. MP2 calculations also assessed the SCS-MP2 (separate scaling of parallel- and antiparallel-spin pair correlation energies) correction.\(^{44}\) The barriers and thermodynamics obtained with B3LYP/6-31+G(d,p) are similar for Cs systems in comparison to more expensive MP2 methods.

**Table 4-1.** Comparing barriers (kcal/mol) and thermodynamics (kcal/mol) of CH cleavage of methane by CsNH\(_2\) using differing computational methods. LANL2DZ used for Cs basis set in all calculations.

<table>
<thead>
<tr>
<th>Method</th>
<th>(\Delta G^\ddagger)</th>
<th>(\Delta G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP2/aug-cc-pVDZ</td>
<td>13.9</td>
<td>10.8</td>
</tr>
<tr>
<td>MP2/aug-cc-pVTZ</td>
<td>14.0</td>
<td>11.1</td>
</tr>
<tr>
<td>MP2/aug-cc-pVQZ</td>
<td>16.6</td>
<td>13.2</td>
</tr>
<tr>
<td>M06/6-31+G(d,p)</td>
<td>13.3</td>
<td>10.0</td>
</tr>
<tr>
<td>SC-S-MP2/ aug-cc-pVDZ</td>
<td>15.8</td>
<td>12.0</td>
</tr>
<tr>
<td>SC-S-MP2/aug-cc-pVTZ</td>
<td>16.0</td>
<td>14.1</td>
</tr>
<tr>
<td>SC-S-MP2/aug-cc-pVQZ</td>
<td>18.6</td>
<td>14.4</td>
</tr>
<tr>
<td>B3LYP/6-31+G(d,p)</td>
<td>14.4</td>
<td>11.7</td>
</tr>
</tbody>
</table>

The average \(\Delta G^\ddagger\) was 15.3 ± 1.8 kcal/mol with the average \(\Delta G\) being 11.8 ± 1.3 kcal/mol, Table 4-1, for the different methods and basis sets evaluated. The largest difference between \(\Delta G^\ddagger\)'s, SCS-MP2/aug-cc-pVQZ and MP2/6-31+G(d,p), was 5.3 kcal/mol. Therefore, one may consider the sensitivity of the calculations reported employing B3LYP/6-31+G(d,p) to be ~ 5 kcal/mol. MP2 calculations change the weak Cs—CH\(_4\) bond distance the most, Table 4-2. However, this methane is obviously very weakly bound to the cesium-amide and the \(\Delta G\)'s are minimally affected, Table 4-1. Therefore, we utilized the B3LYP/6-31+G(d,p) level of theory in this research as it seems to
be reasonably accurate and computationally efficient in elucidating the chemistry of these Cs superbasic compounds.

4.5 Benzylic C—H Cleavage of Toluene

Methane was replaced with toluene as a model substrate to address the impact of a weaker C—H bond (105 kcal/mol for methane vs. 89 kcal/mol for toluene)\textsuperscript{45} would have on the energetics of CH bond cleavage for these alkali metal complexes.

**Table 4-2.** Comparing bond lengths (Å) of methane CH cleavage by CsNH\textsubscript{2} systems using differing computational methods. LANL2DZ used for Cs basis set in all calculations.

<table>
<thead>
<tr>
<th></th>
<th>MP2/aug-cc-pVDZ</th>
<th>MP2/aug-cc-pVTZ</th>
<th>MP2/aug-cc-pVQZ</th>
<th>M06/6-31+G(d)</th>
<th>B3LYP/6-31+G(d,p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cs(CH\textsubscript{4})NH\textsubscript{2}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r(Cs-C) Å</td>
<td>3.59</td>
<td>3.42</td>
<td>4.09</td>
<td>3.64</td>
<td>3.92</td>
</tr>
<tr>
<td>r(Cs-N) Å</td>
<td>2.93</td>
<td>2.88</td>
<td>3.01</td>
<td>2.90</td>
<td>2.92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MP2/aug-cc-pVDZ</th>
<th>MP2/aug-cc-pVTZ</th>
<th>MP2/aug-cc-pVQZ</th>
<th>M06/6-31+G(d)</th>
<th>B3LYP/6-31+G(d,p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r(Cs-C) Å</td>
<td>3.22</td>
<td>3.14</td>
<td>3.43</td>
<td>3.26</td>
<td>3.32</td>
</tr>
<tr>
<td>r(Cs-N) Å</td>
<td>3.05</td>
<td>2.99</td>
<td>3.20</td>
<td>2.99</td>
<td>3.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MP2/aug-cc-pVDZ</th>
<th>MP2/aug-cc-pVTZ</th>
<th>MP2/aug-cc-pVQZ</th>
<th>M06/6-31+G(d)</th>
<th>B3LYP/6-31+G(d,p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cs(CH\textsubscript{3})NH\textsubscript{3}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r(Cs-C) Å</td>
<td>3.18</td>
<td>3.08</td>
<td>3.37</td>
<td>3.23</td>
<td>3.28</td>
</tr>
<tr>
<td>r(Cs-N) Å</td>
<td>3.19</td>
<td>3.12</td>
<td>3.53</td>
<td>3.18</td>
<td>3.23</td>
</tr>
</tbody>
</table>
Additionally, employing toluene as a substrate affords the possibility of a Hammett analysis of C—H bond cleavage. The Cs⁺ ion interacts favorably with the π-cloud of the toluene, via a cation-π interaction,⁴⁶,⁴⁷ in all three calculated stationary points, Figure 4-3. Conformers in which the toluene phenyl group was rotated to be distal from Cs⁺ were either higher in energy (~10 kcal/mol) or reverted upon geometry optimization to the stationary points shown in Figure 4-3. Most interestingly, the Cs-ring centroid distance decreases upon benzylic C—H bond cleavage (3.63 Å for reactant, 3.43 Å for TS, and 3.25 Å for product). This result suggests that the cation-π interaction facilitates scission of the benzylic C—H bond. The CSD shows an average distance of 3.56(14) Å for Cs—toluene (ring centroid), consistent with the ground state reactant.⁴⁸

![Figure 4-3](image)

**Figure 4-3.** Calculated Cs (purple) to ring centroid (blue) distance (Å) for toluene substituted structures: reactant (left), transition state (center), and product (right).

The thermodynamics of C—H bond cleavage goes from being **endergonic** with methane (+11.7 kcal/mol) to being **exergonic** with toluene substrate (ΔG = -5.7 kcal/mol, ΔH = -6.5 kcal/mol). The C—H cleavage barrier is also greatly influenced by the change in substrate from methane, 14.4 kcal/mol, to only 3.1 kcal/mol (ΔH‡ = -6.5 kcal/mol) for toluene, hence ΔΔG‡ = 11.3 kcal/mol between the toluene and methane systems: ΔΔG‡ = 11.3 kcal/mol, ΔΔG = 17.4 kcal/mol, ΔΔBDE = 16 kcal/mol. The calculated free energy differences, both in barriers and thermodynamics, can
thus be directly correlated to the difference in C—H bond energies for the hydrocarbon substrates, implicating a Hammond Postulate-like origin for the computed trends.

4.6 Electronic Impact of Substrate Modification

Toluene was also used as the substrate with cesium cyclohexylamide as the base to model the reaction $\text{Cs(NHCy)(PhCH}_3\text{)} \rightarrow \left[\text{Cs(NH}_2\text{Cy)(benzyl)}\right]$, Cy = cyclohexyl. Upon geometry optimization of Cs(NHCy) it was found that the cyclohexyl group is most stable in the chair conformation, with the C—N bond in the equatorial conformation. The Cs—ring centroid distances were calculated to be 3.64 Å, 3.42 Å, 3.24 Å for the reactant, TS, and product, respectively. The Cs$^+$$\rightarrow$arene $\pi$-cloud interaction with the toluene substrate (discussed above for CsNH$_2$ as the base) remains little changed with the introduction of a cyclohexyl substituent on the amide N. Usage of Cs(NHCy) as base also had a slight impact on the energetics ($\Delta G^\ddagger = 3.9$ kcal/mol, $\Delta G = -5.5$ kcal/mol) ($\Delta H^\ddagger = 0.9$ kcal/mol, $\Delta H = -6.8$ kcal/mol) as compared to toluene CH cleavage by CsNH$_2$ ($\Delta G^\ddagger = 3.1$ kcal/mol, $\Delta G = -5.7$ kcal/mol). The similarity of these data for the smaller CsNH$_2$ and larger Cs(NHCy) imply minimal steric and electronic impact from the H to Cy replacement.

The Hammett impact of the substrate ($p$-X-C$_6$H$_4$CH$_3$ X = H, NMe$_2$, CN) was calculated with respect to the arene adducts. Placement of CN onto the para position of the toluene lowered the barrier by 3.3 kcal/mol relative to toluene, hence $\Delta G^\ddagger = 0.6$ kcal/mol for benzylic C—H cleavage. Introduction of the NMe$_2$ onto the para position of the toluene raised the barrier by 2.9 kcal/mol to 6.9 kcal/mol. The electronic impact between the modeled EDG and EWG was thus calculated to be $\Delta \Delta G^\ddagger = 6.3$ kcal/mol. The same EWG and EDG were placed at the meta position (Figure 4-
4) of the toluene. Introduction of CN at the *meta* position lowered the barrier by 1.4 kcal/mol relative to toluene, Δ\(G^\dagger\) = 2.5 kcal/mol.

Placement of NMe\(_2\) at the *meta* position raised the barrier, Δ\(G^\dagger\) = 5.2 kcal/mol. The electronic impact at the *meta* position between the EDG and EWG was calculated to be ΔΔ\(G^\dagger\) = 2.7 kcal/mol. The empirical sigma values \([σ_p = 0.66 \text{ (CN)}, -0.83 \text{ (NMe}_2\text{)}; σ_m = 0.56 \text{ (CN)}, -0.16 \text{ (NMe}_2\text{)}]\) were plotted versus calculated log(\(k_X/k_H\)) to obtain a Hammett graph, Figure 4-5.

The sign of \(ρ\) (the slope of the Hammett line) indicates whether a reaction is accelerated by EDGs or EWGs. For example, a positive \(ρ\) indicates that the rate will be accelerated by EWGs.\(^{50}\)

*Figure 4-4.* Substitutions made at the *meta* or *para* positions of toluene along with calculated benzylic C—H cleavage barriers.
The magnitude of $\rho$ reflects how sensitive a reaction is to the electronic effects of the substituents. Both the meta and para substituents display similar $\rho$ values. The $\rho$ values, $\rho_p = 3.2$ and $\rho_m = 3.3$, (Figure 4-5) suggest the reaction is accelerated by the presence of EWGs. The sign of $\rho$ is reasonable given that it implies that making the toluene C—H bond more acidic would accelerate the reaction. In addition, it is possible that EWGs also impact the cation-$\pi$ interaction in the transition state. From the similarity of the values of $\rho$ for meta- and para-substituted toluenes it can be hypothesized that there is similar sensitivity to inductive and resonance effects for the benzylic C—H bond cleavage.

\[ \rho_p = 3.2 \quad R^2=0.9841 \]
\[ \rho_m = 3.3 \quad R^2=0.9678 \]

Figure 4-5. Hammett plot of inductive ($\sigma_m$) and resonance ($\sigma_p$) effects (x-axis) versus relative rate (y-axis) for benzylic C—H cleavage of $p$-$X\text{C}_6\text{H}_4\text{CH}_3$ by cesium cyclohexylamide. The blue line represents the para substituted substrates while the green line denotes the meta substituted substrates.
4.7 Impact of Alkali Metal

The role of the alkali metal was addressed by substitution of different alkali metal ions for Cs⁺. The same ligand and substrate, cyclohexylamide and toluene, respectively, as was studied in the Hammett study, M(NHcy)(PhCH₃) → [M(NH₂Cy)(H₂CC₆H₅)], was investigated for M = Li, Na, K, Rb, Cs. The Li-substituted systems were calculated using the all-electron 6-31+G(d,p) basis set. The remaining metals were calculated in the same manner to the Cs complexes, _i.e._, with the LANL2DZ basis set on alkali metal.

The M—ring centroid bond distances for toluene benzylic C—H cleavage TSs were measured for each of the non-radioactive alkali metals. As expected, the bond distance increases down the alkali metal row (2.00, 2.53, 2.97, 3.19 and 3.42 Å, for Li, Na, K, Rb and Cs, respectively). This is obviously consistent with Cs⁺ having a larger ionic radius as compared to the other alkali metal ions. The M—ring centroid was plotted against the crystal ionic radii for each of the alkali metals, Figure 4-6, and this shows a similar linear correlation. Figure 4-7, shows the large differences of geometry between the Li and Cs TS congeners.

![R² = 0.9913](image)

**Figure 4-6.** Calculated M—Centroid distance (pm) versus crystal ionic radii (pm) for alkali metals.
Figure 4-7. Calculated Li (left) and Cs (Right) bond distances (Å) for TS of toluene CH cleavage.

<table>
<thead>
<tr>
<th>M</th>
<th>$\Delta G^\dagger$ (kcal/mol)</th>
<th>$\Delta G$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>15.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Na</td>
<td>8.5</td>
<td>-0.3</td>
</tr>
<tr>
<td>K</td>
<td>4.9</td>
<td>-4.2</td>
</tr>
<tr>
<td>Rb</td>
<td>4.6</td>
<td>-4.3</td>
</tr>
<tr>
<td>Cs</td>
<td>3.9</td>
<td>-5.5</td>
</tr>
</tbody>
</table>

Figure 4-8. Alkali metals and their influence on the calculated barriers and thermodynamics of toluene benzylic C—H cleavage

The energetics for toluene benzylic C—H cleavage trend similarly to the calculated bond distances just calculated, in that the Li amide complex had the highest barrier ($\Delta G^\dagger = 15.6$ kcal/mol) for toluene CH cleavage as well as being the only metal for which this reaction is
calculated to be endergonic (3.9 kcal/mol), Figure 4-7. Previous work done by Streitwieser et al. gave proton exchange rates for cesium cyclohexylamide to be ~10^4 times faster than that of lithium cyclohexylamide.\(^7,9\) The cesium complex has the lowest barrier for C—H cleavage as well as the most exergonic thermodynamics among the alkali metals, qualitatively consistent with the aforementioned experimental observations.

4.8 Solvent Effects

The impact of solvent was assessed using a cesium model, \([\text{Cs(CyNH)}(\text{toluene})] \rightarrow [\text{Cs(NH}_2\text{Cy)}(\text{benzyl})].\) Explicit as well as implicit solvation effects were examined (Figure 4-9). The implicit calculations were done with butylamine to model the CyNH\(_2\) solvent used experimentally.\(^10\)

Explicit solvation effects using NH\(_3\) and CyNH\(_2\) as the solvent models (Figure 4-9 with R = H or Cy) were calculated. The C—H cleavage barrier for this system was raised slightly (~ ½ kcal/mol) in comparison to the non-solvated complex (\(\Delta G^\ddagger = 4.5\) kcal/mol, \(\Delta G = -5.6\) kcal/mol), Figure 4-9 (R = H). With cyclohexylamine acting as the explicit solvent model, the C—H cleavage barrier increases by ~ 1 kcal/mol versus gas phase (\(\Delta G^\ddagger = 4.8\) kcal/mol; \(\Delta G = -5.9\) kcal/mol). Explicit solvation using both NH\(_3\) and CyNH\(_2\) models thus raised the free energy barriers only slightly. It may be concluded that the ligation of NH\(_3\) or CyNH\(_2\) to Cs\(^+\) makes the cyclohexylamide compound slightly less nucleophilic, thus marginally inhibiting its ability to deprotonate C—H bonds.

Gas-phase and implicitly solvated calculations were compared for the largest and smallest alkali metal ions with respect to the barriers for C—H cleavage, \([\text{M(CyNH)}(p-H_3\text{C}_6\text{H}_4\text{X})] \rightarrow\)
[M(NH₂Cy)(H₂CC₆H₄X)] (M = Li or Cs). These were then used to construct Hammett plots of inductive and resonance effects similar to Figure 4-6. The slopes (ρ values) obtained are collected in Table 4-3. In a global sense, the ρ values were little changed upon introduction of continuum solvent effects. Solvation of the lithium reactions slightly lowered the ρₚ value versus the gas-phase reaction (4.8 to 4.3), whereas the ρₘ value was raised for the same models, 3.2 to 5.3. The same trends in solvation were seen for the Cs solvated and nonsolvated models: ρₚ = 3.2 to 2.6 for the gas-phase and SMD butylamine simulations, respectively, with ρₘ showing the opposite trend upon inclusion of solvent effects: 3 to 4.0 for the Cs reactions. Given that ρₘ is meant to categorize inductive effects, the calculations suggest quite reasonably that continuum solvent effects will more greatly impact these than resonance interactions, Table 4-3. Calculated reaction barriers and reaction free energies (kcal/mol) with implicit and explicit solvation included for benzylic C—H cleavage of toluene.

The use of implicit solvation models had a minute influence on the geometry. The energetics of toluene CH cleavage by Cs(NHCl) were, however, effected to a high degree: implicitly solvated (ΔG°‡ = 11.0 kcal/mol; ΔG = -0.9 kcal/mol); gas phase calculation: (ΔG°‡ = 3.9 kcal/mol; ΔG = -5.5 kcal/mol). Implicit solvation thus raised the calculated barriers and made C—H scission less exergonic. Implicit solvation was also modeled for the Li system, [Li(CyNH)(toluene)] → [Li(NH₂Cy)(benzyl)]. Interestingly, continuum butylamine solvation had less impact on the calculated energetics than for the Cs congener: ΔG°‡ = 20.9 kcal/mol; ΔG 4.6 kcal/mol; gas phase calculation: ΔG°‡ = 15.6 kcal/mol; ΔG 3.9 kcal/mol.

4.9 Summary, Conclusions and Prospectus
A DFT study of C—H bond cleavage by “superbasic” alkali metal amides was reported. Several important conclusions were reached with respect to the specific case of superbase mediated C—H cleavage. Implications of the present research for transition metal mediated C—H activation are also discussed here.

(1) As expected, toluene was calculated to be easier to deprotonate compared to methane. The lower barrier (ΔΔG‡ ~ 11 kcal/mol) is attributed to the lower bond strength and greater acidity of a toluene (pKa ~ 43\textsuperscript{54}) versus methane (pKa ~ 56\textsuperscript{46}).

(2) Changes in the distances between Cs\textsuperscript{+} and the ring centroid of the toluene substrate along the reaction coordinate suggest that metal cation-π interactions facilitate scission of benzylic C—H bonds. Several C—H functionalizations have been reported\textsuperscript{55-57} in which Cs salts are required. The present calculations suggest a possible role for this alkali metal in facilitating such a transformation. One may also propose that similar interactions could be exploited in applications involving benzylic C—H functionalization by electrophilic transition metal amide/imide moieties.

(3) Comparing the barriers and thermodynamics to deprotonate toluene among the alkali metal cyclohexylamides, the Cs complex was calculated to be most active. This is consistent with Cs being the most electropositive of these metals, and hence cesium amide should be more basic than other alkali metal amides. The computations also agree with experiments by Streitwieser \textit{et al.}, who showed that Li(NHCy) was insufficient to measure the pKa of methane, while its Cs congener was sufficiently basic.\textsuperscript{58} The Mulliken electronegativity\textsuperscript{59} was plotted against the barriers, (Figure 4-7) for toluene CH cleavage by the alkali metal compounds, M(NHCy).
$$\Delta G^\ddagger \text{ (kcal/mol)} \Delta G \text{ (kcal/mol)}$$

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$\Delta G^\ddagger$</th>
<th>$\Delta G$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Solvent</td>
<td>3.9</td>
<td>-5.5</td>
</tr>
<tr>
<td>Implicit: Butylamine</td>
<td>11.0</td>
<td>-0.9</td>
</tr>
<tr>
<td>Explicit: NH$_2$(Cy)</td>
<td>4.8</td>
<td>-5.9</td>
</tr>
<tr>
<td>Explicit: NH$_3$</td>
<td>4.5</td>
<td>-5.6</td>
</tr>
</tbody>
</table>

**Figure 4-9.** Explicitly solvated structure with either NH$_3$ or CyNH$_2$ as the explicit solvent model and computed free energies of cleavage of toluene benzylic C—H bond.

**Table 4-3.** Slopes ($\rho_p$ and $\rho_m$) of Hammett graphs for deprotonation of benzylic C—H bond of toluene by Li and Cs cyclohexyl amide for solvated (SMD butylamine) and gas-phase) systems.

<table>
<thead>
<tr>
<th></th>
<th>$\rho_p$</th>
<th>$\rho_m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li$_{\text{gas}}$</td>
<td>4.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Li$_{-\text{SMD}}$</td>
<td>4.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Cs$_{\text{gas}}$</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Cs$_{-\text{SMD}}$</td>
<td>2.6</td>
<td>4.0</td>
</tr>
</tbody>
</table>
The correlation, Figure 4-10, reasonably suggests that more basic/nucleophilic character for the alkali metal amide affords a lower CH deprotonation barrier. However, the linear correlation is modest ($R^2 \sim 0.8$), suggesting that the decrease in barrier between Li and Cs amides is not merely a simple function of amide basicity. As a comparison, deprotonation of the methane C—H bond by “naked” NH$_2^-$ has a calculated $\Delta G^\ddagger = 16.8$ kcal/mol (SMD butylamine solvent) as compared to CsNH$_2$ with the same continuum solvent model $\Delta G^\ddagger = 19.4$ kcal/mol. Electronic analysis revealed that stabilization of the developing carbon anion and the alkali metal is trend setting for electrostatic interactions and consideration of electron-electron repulsion (Pauli repulsion) is also important in understanding the relative barriers.
(4) The use of implicit solvation (butylamine) raised the calculated toluene benzylic C—H cleavage barriers higher and made the thermodynamics less exergonic ($\Delta \Delta G^\ddagger = 7.1$ kcal/mol and $\Delta \Delta G = 4.6$ kcal/mol versus gas phase calculations for Cs(NHCy)). Interestingly, explicit solvation simulations (NH$_3$ and CyNH$_2$ were modeled) both raised the barriers slightly ($\Delta \Delta G^\ddagger \sim 1$). From the latter, we conclude in light of other pieces of evidence, that addition of any functionality that makes the Cs$^+$ system less nucleophilic will hinder its effectiveness in deprotonating C—H bonds. The impact of implicit solvation is intriguing as analysis of the dipole moments (~9.6 D for reactant adduct, ~ 8.4 for TS) and volumes (adduct ~ TS within 15%) show them to be similar.

(5) Hammett studies on benzylic C—H cleavage for both meta and para substituted toluenes indicate that EWGs at each of these positions will accelerate the rate of these reactions. The similar meta and para $\rho$ values (~ 3 in gas-phase simulations) suggests that the transition states for C—H bond cleavage are comparably impacted by both inductive and resonance effects. The magnitude of $\rho$ likewise is consistent with a reaction that is ostensibly a deprotonation. The former were enhanced, the latter reduced when continuum solvent (SMD, butylamine) effects were incorporated.

Interestingly, similar $\rho$ values to those calculated here for Cs and Li amide systems were seen by DeYonker et al. when ruthenium complexes were evaluated for arene C—H activation ($\rho = 2.6$ and $\rho = 3.2$).$^{60}$ The Ru complex being studied was TpRu(L)(η$^2$-C,H-C$_6$H$_5$X)Me; L = PMe$_3$ or CO, X = various EDG and EWG. The theorized reason for the high $\rho$ values in the activation by Ru is the lack of stabilizing solvent effects for those gas-phase calculations. However, the present $\rho$ values for C—H scissions, which are presumably more biased towards a deprotonation event as
compared to C—H addition across a Ru-methyl bond, vary by only ±1 when solvent effects are included, Table 4-3.

It is worth noting that the ρ values reported by DeYonker et al. and the values computed here in the Cs systems are higher than found in σ-bond metathesis pathways. Experiments by Bercaw for σ-bond metathesis with cyclopentadienyl scandium complexes showed insensitivity to substituted arenes, with $k_{X=NMe2}/k_{X=H} \approx 0.97$ and $k_{X=CF3}/k_{X=H} \approx 0.42$ for arene C—H cleavage of C$_6$H$_5$X (X = H, CF$_3$ or NMe$_2$). Herein, in both the Li and Cs amide systems, the calculations suggest that inductive (resonance) effects will be increased (lessened) in the presence of solvent. Thus, we must either conclude that the current reaction is either more of a homolytic scission event or that Hammond ρ values need to be viewed with caution. In view of the other pieces of data such as the calculated atomic charges and the correlation of C—H cleavage barriers with alkali metal ion size and electronegativity, currently the latter explanation is preferred. Further ADF-EDA analysis by Ess and coworkers of the LiNH$_2$/CH$_4$ transition state yields nearly equal stabilization from orbital and electrostatic interactions, which counteracts the usual assumption that deprotonation reactions are highly ionic and have little covalent character. This latter result is also consistent with the modest ρ values computed and experimentally measured for activation of C—H bonds by electrophilic transition metals with nucleophilic activating ligands.

4.10 References


Chapter 5

A Mechanistic Study on C-H Amination and Olefin Aziridinations via A Tripodal Cu(I) Reagent

5.1 Introduction

Metal-catalyzed nitrene/imido transfer reactions, such as aziridination of alkenes, and amination/amidation of alkanes, have valuable applications in organic synthesis.\textsuperscript{1-4} Specifically, the amination of saturated C–H bonds with high yield and high selectivity remains a difficult challenge. A methodology for the regio-, stero, and chemoselective introduction of a more abundant C–N bond into the less active C–H or C=C bond to construct the aminated/aziridinated product, respectively, is of great value.\textsuperscript{5-9} However, a reagent capable of these conversions at high turnovers, which is environmentally friendly as well as economical is still sought. The formation of new C–N bond functionalities is afforded by transition metal reagents, especially as of recently the versatility of utilizing coinage metals has been examined.\textsuperscript{10-20} Recently, these conversions have been accomplished through the use of nitrene precursors such as iminoiodanes PhI=NR or electron-deficient sulfonylamines, H\textsubscript{2}NSO\textsubscript{2}R. PhI=NTs (Ts = -SO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}CH\textsubscript{3})\textsuperscript{21-23} has been investigated within this study. In this chapter, a tripodal, economical, Cu\textsuperscript{I} reagent is studied that is capable of alkane amination as well as alkene aziridinations on a variety of substrates. This Cu\textsuperscript{I} reagent is sequestered by a tripodal C\textsubscript{3}-symmetric coordinate, highly basic, guadinate-rich ligand.\textsuperscript{5}

\textsuperscript{4*} “Sections of this chapter was reprinted (adapted) with permission from (“A Versatile Tripodal Cu(I) Reagent for C-N Bond Construction via Nitrene-Transfer Chemistry: Catalytic Perspectives and Mechanistic Insights on C-H Aminations/Amidinations and Olefin Aziridinations). Copyright (2014) American Chemical Society.”
A definitive mechanism for the conversion, C–H/C=C bonds → aminated/azirdinated products, utilizing earth abundant transitions metals is still debated in the literature.\textsuperscript{24,25,26} Herein, we investigate (1) the electronic description of the metal nitrene species (M=NR),\textsuperscript{6} (2) method in which insertion/addition of the nitrene occurs by the reagent.

5.2 Computational Details.

Density functional theory within the Gaussian 09 package\textsuperscript{27} was utilized for geometry optimization and vibrational frequency calculations. Stationary points were characterized as minima or transition states (TSs) on the basis of 0 or 1 imaginary frequencies, respectively. The B3LYP\textsuperscript{28,29} hybrid functional was employed, although tests with the BP86 functional were conducted as described. All atoms were calculated using the all-electron, 6-31G(d)\textsuperscript{30} basis set. When differing spin states were expected, all feasible possibilities were considered.

5.3 Calculated Ground State Cu\textsuperscript{I} Reagents.

Three variations of Cu\textsuperscript{I} catalysts were calculated with X = CH\textsubscript{3} (1), H (1-H) and CH\textsubscript{2}–NHTs (1-CH\textsubscript{2}-NHTs) (Figure 5-1, top). The former represents the intact catalyst 1, the other two denote potential \textit{in situ} modifications of 1. Similar Cu\textsuperscript{I}–N\textsubscript{equatorial} (Figure 5-1) bond distances were calculated for the singlet ground states with all being between 2.00 and 2.04 Å. The Cu–N\textsubscript{axial} distance was calculated to be 2.21 Å in each of the three catalyst variations, somewhat shorter than in the solid-state crystal. Copper had Natural Population Analysis charges of 0.51, 0.47, and 0.49 $e^-$, respectively, for 1, 1-H and 1-CH\textsubscript{2}-NHTs.
<table>
<thead>
<tr>
<th>Bond (Singlet)</th>
<th>Å</th>
<th>Bond (Triplet)</th>
<th>Å</th>
<th>ΔÅ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu-N(NTs)</td>
<td>1.79</td>
<td>Cu-N(NTs)</td>
<td>1.84</td>
<td>0.05</td>
</tr>
<tr>
<td>Cu-N₁(Equatorial)</td>
<td>1.98</td>
<td>Cu-N₁(Equatorial)</td>
<td>2.08</td>
<td>0.10</td>
</tr>
<tr>
<td>Cu-N₂(Equatorial)</td>
<td>2.19</td>
<td>Cu-N₂(Equatorial)</td>
<td>2.00</td>
<td>0.19</td>
</tr>
<tr>
<td>Cu-N₃(Equatorial)</td>
<td>2.98</td>
<td>Cu-N₃(Equatorial)</td>
<td>2.93</td>
<td>0.05</td>
</tr>
<tr>
<td>Cu-N(Axial)</td>
<td>2.04</td>
<td>Cu-N(Axial)</td>
<td>2.11</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Figure 5-1.** Compound 1 (top left) with X denoting the location in which variations were modeled. Bond lengths, and difference of lengths, of singlet and triplet nitrene $^3$[Cu]NTs (top right). Hydrogens are omitted from the figure for ease of viewing.

5.3 Computed Nitrene Intermediates.

Upon $^3$NTs ligation (Figure 5-1, right; bond lengths for singlet and triplet), the B3LYP/6-31G(d)-calculated copper Natural Population Analysis charges increased to 0.75, 0.76, and 0.75 $e^-$, respectively, for 1, 1-H and 1-CH₂-NHTs.
Figure 5-2. Important frontier alpha SOMOs for triplet [Cu]=N-Ts. Note the delocalization from the copper-nitrene active site to the sulfonyl, para-tolyl and TMG₃trphen moieties. Other relevant frontier MOs and the computed spin density plots are collected in Supporting Information. Contour value = 0.045.

The unrestricted Kohn-Sham formalism was used, and the computed spin density places ~1 unpaired $e^-$ on the nitrene nitrogen, $\sim^{2/3}$ unpaired $e^-$ on Cu, with the remainder spread over other atoms. Interestingly, upon ligation of $^3$NTs, one of the Cu–N$_{\text{equatorial}}$ bonds in each structure is lengthened to distances ranging from 2.81–3.03 Å. Concomitantly, the Cu–N$_{\text{axial}}$ distance is shortened upon formation of the nitrene intermediate, ranging from 2.08–2.11 Å. As expected, the Cu–NTs distance was calculated to be the shortest among all other Cu–N bonds (1.84 (1), 1.91 (1-H), 1.83 (1-CH$_2$NHTs) Å), albeit somewhat longer than that reported for terminal copper-nitrene moieties.$^{11}$ Optimized [Cu]–N–Ts bond angles were calculated to be 135° (1), 127° (1-H) and 142° (1-CH$_2$NHTs).

Shown in Figure 5-2 are two of the more revealing frontier molecular orbitals for $^3$[Cu]=NTs. Other frontier orbitals with significant composition on the copper-nitrene active site are shown in Figures 5-3 to 5-6 along with the computed spin density. What is of particular interest is the delocalization of the spin density from the copper-nitrene active site to the sulfonyl, $p$-tolyl and
TG3trphen moieties. Given the present computational results, in conjunction with previous computational efforts on the bonding and structure of hetero-substituted nitrenes and aryl nitrenes, it is reasonable to conclude that this delocalization of spin density stabilizes the putative nitrene intermediate enough to make it kinetically and thermodynamically accessible, but not much as to completely quench its reactivity for group transfer. Furthermore, the greater activity of Cu=N-alkyl complexes vis-à-vis Cu=N-aryl variants highlights the importance of the nitrene substituents in modulating the group transfer reactivity of the active species.

Upon nitrene binding, the singlet state of the [Cu] catalyst models changes to a triplet ground state for [Cu(NTs)]. Note that attempted isolation of the PhI=NTs adduct of complex I resulted in PhI dissociation upon geometry optimization. Attempts to find a k2-N,O-nitrene bound NTs resulted in rearrangement to the k1 arrangement shown in Figure 5-1. The computed ΔG’s indicated NTs ligation is exergonic by 23 (1), 27 (1-H), and 19 (1-CH2NHTs) kcal/mol. The ΔG difference between the corresponding singlet [Cu]NTs and triplet [Cu]NTs was 16 (1), 14 (1-H), and 20 (1-CH2NHTs) kcal/mol, hence the singlet copper-nitrene is substantially destabilized vs. the triplet ground state.

Amination Related Calculations. The amination of toluene by [Cu]NTs was calculated (Table 5-1 and Scheme 5-1) to have activation barriers for benzylic C-H bond activation of ΔG‡ = 29 (1), 25 (1-H), and 26 (1-CH2NHTs) kcal/mol relative to separated triplet copper-nitrene complex and toluene reactant; the transition states for toluene C–H activation (H-atom abstraction) were calculated to be a triplet. The majority of the spin density resides on Cu (0.7 e–), the nitrene N (0.6 e–) and the benzylic C of toluene (0.4 e–). The barrier was also computed using the BP86 functional,
yielding $\Delta G^\ddagger = 35$ (1), 29 (1-H), and 31 (1-CH$_2$NHTs). Hence, BP86 values are commensurate with those obtained with B3LYP in terms of catalyst ordering, being consistently higher by $\sim$5 kcal/mol.

A comparison of BP86 and B3LYP for the $^3$[Cu]NTs intermediate for 1, 1-H and 1-CH$_2$NHTs is shown in Table 5-2; the H-atom abstraction TS geometries are likewise similar. Notably, the $^3$TS for benzylic H-atom abstraction from toluene was lower in energy by $\sim$12 kcal/mol than the corresponding $^1$TS for all three catalyst variants modeled. Following the intrinsic reaction coordinate (triplet surface) from $^3$[Cu]NTs (for 1) in the reactant direction, showed its immediate precursor to be a weakly-bound adduct of toluene and $^3$[Cu]NTs. The computed $\Delta G$ for the formation of this adduct from toluene and $^3$[Cu]NTs is 8 kcal/mol. Computing the intrinsic reaction coordinate in the product direction (triplet surface) indicated formation of a $^3${[Cu]–NHTs–CH$_2$Ph} caged adduct intermediate ($\Delta G_{rel} = +4$ kcal/mol; Scheme 5-3, Figure 5-2). A constrained optimization (singlet) for the radical rebound (RR) step showed $\Delta G^\ddagger = 2$ kcal/mol relative to the caged adduct. The constrained triplet was calculated to be 26 kcal/mol higher than that of the constrained singlet, suggesting that the spin-flip occurs before the TS for radical rebound. A kinetic penalty must presumably be paid for the singlet-triplet spin flip. Finally, we note that $^3${[Cu]–NHTs–CH$_2$Ph} $\rightarrow$ $^1$[Cu$^\ddagger$]N(H)Ts(Bz) is 10 kcal/mol exergonic.
Figure 5-3. Plot of the total spin density (0.02 contour value) for triplet [Cu]=NTs at the B3LYP/6-31G(d) level of theory. The majority of the spin density is on the copper and nitrogen atoms of the copper-nitrene active site with a small amount of delocalization on to the sulfonyl moiety.
Figure 5-4. Frontier Kohn-Sham orbitals with significant density on the copper-nitrene active site of triplet [Cu]=N-Ts are plotted at a contour value of 0.045.
The orbital energies (eV) determined at the B3LYP/6-31G(d) level of theory are given and occupancy indicated.

**Figure 5-5.** The alpha and beta occupied orbitals (eV) at the B3LYP/6-31G(d) level of theory are given and occupancy indicated.
<table>
<thead>
<tr>
<th>#</th>
<th>( \epsilon ) (eV)</th>
<th>Occupancy</th>
<th>#</th>
<th>( \epsilon ) (eV)</th>
<th>Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>201</td>
<td>-10.01</td>
<td>Occ'd</td>
<td>201</td>
<td>-9.69</td>
<td>Occ'd</td>
</tr>
<tr>
<td>202</td>
<td>-9.72</td>
<td>Occ'd</td>
<td>202</td>
<td>-9.38</td>
<td>Occ'd</td>
</tr>
<tr>
<td>203</td>
<td>-9.44</td>
<td>Occ'd</td>
<td>203</td>
<td>-9.20</td>
<td>Occ'd</td>
</tr>
<tr>
<td>204</td>
<td>-9.37</td>
<td>Occ'd</td>
<td>204</td>
<td>-9.07</td>
<td>Occ'd</td>
</tr>
<tr>
<td>205</td>
<td>-9.20</td>
<td>Occ'd</td>
<td>205</td>
<td>-9.02</td>
<td>Occ'd</td>
</tr>
<tr>
<td>206</td>
<td>-9.04</td>
<td>Occ'd</td>
<td>206</td>
<td>-8.89</td>
<td>Occ'd</td>
</tr>
<tr>
<td>207</td>
<td>-9.02</td>
<td>Occ'd</td>
<td>207</td>
<td>-8.87</td>
<td>Occ'd</td>
</tr>
<tr>
<td>208</td>
<td>-8.90</td>
<td>Occ'd</td>
<td>208</td>
<td>-8.84</td>
<td>Occ'd</td>
</tr>
<tr>
<td>209</td>
<td>-8.88</td>
<td>Occ'd</td>
<td>209</td>
<td>-8.67</td>
<td>Occ'd</td>
</tr>
<tr>
<td>210</td>
<td>-8.80</td>
<td>Occ'd</td>
<td>210</td>
<td>-8.45</td>
<td>Occ'd</td>
</tr>
<tr>
<td>211</td>
<td>-8.54</td>
<td>Occ'd</td>
<td>211</td>
<td>-8.30</td>
<td>Occ'd</td>
</tr>
<tr>
<td>212</td>
<td>-8.49</td>
<td>Occ'd</td>
<td>212</td>
<td>-8.21</td>
<td>Occ'd</td>
</tr>
<tr>
<td>213</td>
<td>-8.27</td>
<td>Occ'd</td>
<td>213</td>
<td>-7.94</td>
<td>Occ'd</td>
</tr>
<tr>
<td>214</td>
<td>-8.24</td>
<td>Occ'd</td>
<td>214</td>
<td>-7.75</td>
<td>Occ'd</td>
</tr>
<tr>
<td>215</td>
<td>-7.98</td>
<td>Occ'd</td>
<td>215</td>
<td>-7.38</td>
<td>Occ'd</td>
</tr>
<tr>
<td>216</td>
<td>-7.81</td>
<td>Occ'd</td>
<td>216</td>
<td>-5.36</td>
<td>Unocc'd</td>
</tr>
<tr>
<td>217</td>
<td>-7.36</td>
<td>Occ'd</td>
<td>217</td>
<td>-5.24</td>
<td>Unocc'd</td>
</tr>
</tbody>
</table>

**Figure 5-6.** Frontier Kohn-Sham orbital energies. The occupied and unoccupied orbitals (eV) at the B3LYP/6-31G(d) level of theory are provided.

Dissociation of the radical pair, \(^3\{[\text{Cu}]-\text{NHTs}--\text{CH}_2\text{Ph}\} \rightarrow ^2[\text{Cu}]\text{N(H)Ts} + ^2\text{Bz},\) is 7 kcal/mol exergonic. Calculation of the separated radicals relative to 1, \(^3[\text{Cu}]\text{NTs} + \text{H}--\text{Bz} \rightarrow ^2[\text{Cu}]\text{NTs} + \text{•Bz},\) was shown to be exergonic by 3 kcal/mol. The reaction coordinate is summarized in Scheme.
5-3. These calculations thus imply a two-step amination sequence: H-atom abstraction followed by radical rebound, as opposed to a single-step insertion.

Table 5-1. B3LYP/6-31G(d) Computed \( \Delta G \)'s and \( \Delta G^\ddagger \)'s (kcal/mol) for the Steps shown in Scheme 5-1.

<table>
<thead>
<tr>
<th>( X )</th>
<th>( \text{Step 1} )</th>
<th>( \text{Step 2} )</th>
<th>( \text{RR} )</th>
<th>( \text{Step 3} )</th>
<th>( \text{Step 4} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>-27</td>
<td>25</td>
<td>-</td>
<td>-9</td>
<td>-17</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>-23</td>
<td>29</td>
<td>2</td>
<td>-6</td>
<td>-25</td>
</tr>
<tr>
<td>CH(_2)–NHTs</td>
<td>-19</td>
<td>26</td>
<td>-</td>
<td>-8</td>
<td>-27</td>
</tr>
</tbody>
</table>

Table 5-2. B3LYP/6-31G(d) calculated bond lengths (Å) and Cu–N–S \( \angle \) (°) of \( ^3\text{[Cu]NTs} \) comparing the BP86 and B3LYP functionals; N\(_2\), N\(_3\), and N\(_4\) being the equatorial nitrogens as seen in Figure 5-1 (top right), and N\(_1\) being the axial nitrogen as seen in the same figure.

<table>
<thead>
<tr>
<th>( X )</th>
<th>( \text{Functional} )</th>
<th>Cu–N(_1)</th>
<th>Cu–N(_2)</th>
<th>Cu–N(_3)</th>
<th>Cu–N(_4)</th>
<th>Cu–N (NTs)</th>
<th>N–S</th>
<th>( \angle ) Cu–N–S</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>B3LYP</td>
<td>2.08</td>
<td>2.01</td>
<td>2.02</td>
<td>2.81</td>
<td>1.91</td>
<td>1.62</td>
<td>127</td>
</tr>
<tr>
<td>H</td>
<td>BP86</td>
<td>2.11</td>
<td>1.99</td>
<td>1.99</td>
<td>2.93</td>
<td>1.81</td>
<td>1.62</td>
<td>134</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>B3LYP</td>
<td>2.11</td>
<td>1.99</td>
<td>2.08</td>
<td>2.93</td>
<td>1.84</td>
<td>1.62</td>
<td>135</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>BP86</td>
<td>2.13</td>
<td>1.99</td>
<td>2.02</td>
<td>3.01</td>
<td>1.79</td>
<td>1.63</td>
<td>137</td>
</tr>
<tr>
<td>CH(_2)–NHTs</td>
<td>B3LYP</td>
<td>2.11</td>
<td>2.00</td>
<td>2.07</td>
<td>3.03</td>
<td>1.83</td>
<td>1.62</td>
<td>142</td>
</tr>
<tr>
<td>CH(_2)–NHTs</td>
<td>BP86</td>
<td>2.15</td>
<td>1.99</td>
<td>2.02</td>
<td>3.06</td>
<td>1.79</td>
<td>1.63</td>
<td>142</td>
</tr>
</tbody>
</table>

The transformation \( ^3\text{[Cu]NTs} + \text{toluene} \rightarrow \text{\textsuperscript{1}[Cu]N(H)Ts(Bz)} \) was \textit{exergonic} by 6 (1), 9 (1-H), and 8 (1-CH\(_2\)NHTs) kcal/mol to form the singlet Cu\(^1\)-amine adduct, [Cu]N(H)Ts(Bz). The last step in Scheme 5-3 is the amine dissociation, which was computed to be exergonic by 25 (1), 17 (1-H),
and 27 (1-CH₂NHTs) kcal/mol, reflecting the extreme steric crowding in the amine adduct and the favorable entropic contribution of ligand loss.

The overall thermodynamics for nitrene insertion, $[^3\text{Cu}]\text{NTs} + \text{H–Bz} \rightarrow [^1\text{Cu}] + \text{N(H)Ts(Bz)}$, was thus computed to be exergonic by 31 (1), 26 (1-H), and 35 (1-CH₂NHTs) kcal/mol. Hence, the computations imply that after the initial H-atom abstraction to form a radical pair, namely Cu⁺-amide and benzyl radical, a radical rebound step occurs to give separated catalyst and amine product.

**Scheme 5-1**

```
[1][Cu] + [3]NTs $\rightarrow$ [3][Cu(NTs)]
[3][Cu(NTs)] + H-Bz $\rightarrow$ [1][CuN(Ts)=H–Bz]
{[3][Cu(NHTs)]-Bz} $\rightarrow$ [1][CuNH(Ts)=Bz]
[3][Cu(NTs)] + H-Bz $\rightarrow$ [1][Cu]$\xrightarrow{\text{H}}$ N$\xrightarrow{\text{Ts}}$ Bz
[1][Cu]$\xrightarrow{\text{Ts}}$ N$\xrightarrow{\text{Ts}}$ Bz $\rightarrow$ [1][Cu] + N(H)Ts(Bz)
```

For the radical clock reaction shown in Scheme 5-2, from the separated reactants to a triplet TS for H-atom abstraction, the computed, B3LYP/6-31G(d) $\Delta G^\ddagger = 28$ kcal/mol. This barrier resembles that computed for H-atom abstraction of toluene (Scheme 5-3). Thus, the cyclopropyl substrate must presumably go through a similar two-step process (H-atom abstraction followed by radical rebound), which is consistent with the experimentally observed ring-opening of this radical-clock substrate. The olefin product was computed ($\Delta G$) to be 5 kcal/mol more stable than the cyclopropane product.
5.4 Catalytic Aziridination Calculations.

The aziridination of styrene was investigated with the model catalyst 1. The optimized triplet TS is depicted in Figure 5-8 (A). What is particularly noticeable is the asymmetry of the C···N bonds between the nitrene nitrogen and the vinyl carbon atoms, $C_b···N_{Ts} = 2.31 \text{ Å}$, $C_a···N_{Ts} = 3.10 \text{ Å}$. Hence, the aziridination transition state geometry appears decidedly asynchronous with respect to the formation of the two carbon-nitrogen bonds.

**Scheme 5-2**

**Scheme 5-3**

---

5 Scheme taken from joint paper “A Versatile Tripodal Cu(I) Reagent for C-N Bond Construction via Nitrene-Transfer Chemistry: Catalytic Perspectives and Mechanistic Insights on C-H Aminations/Amidinations and Olefin Aziridinations”
The geometry of the TS thus raises the question of whether the aziridination is concerted or not, as does the inference from the toluene amination computations, which suggest a two-step (H-atom abstraction followed by RR) rather than one-step (direct insertion, albeit asynchronous) pathway.

The computed barrier from separated reactants to the triplet aziridination TS ($^3\text{azir-TS}$) is $\Delta G_{\text{az}}^\dagger = 24$ kcal/mol (Scheme 4). The $^3\text{Azir-TS}$ has spin density of 0.63 $e^-$ on Cu, 0.78 $e^-$ on N (NTs), 0.33 $e^-$ on $C_a$, and -0.10 $e^-$ on $C_b$. The corresponding singlet TS is 12 kcal/mol higher in free energy. This barrier was also calculated with the BP86 functional (reactants and TS geometries fully reoptimized), producing $\Delta G_{\text{az}}^\dagger = 25$ kcal/mol with that functional.

Going from the aziridination TS to an “open” triplet intermediate, Figure 5-8 (B) was exergonic by 22 kcal/mol (18 kcal/mol by virtue of BP86 modeling of this step). The “open” triplet intermediate has an electron spin density of 0.68 $e^-$ on Cu, 0.17 $e^-$ on the NTs nitrogen, and 0.76 $e^-$ on $C_a$. Thus, the spin density on the benzylic C has increased significantly vs. that of the triplet aziridination TS.

Going from the “open” triplet intermediate (B) to $k^1$-aziridine product in Figure 5-8 (D) is computed to be mildly endergonic, by +8 kcal/mol. $C_b$-$C_a$ bond rotation was considered for the
open triplet intermediate. Constrained optimizations (the H–C₆–C₇–C₁ dihedral was fixed to ±90°) yielded a free energy for rotation around the C₆–C₇ bond of 4 kcal/mol. A radical rebound TS (Figure 5-8, B → C) has ΔG‡ = 12 kcal/mol. These data thus imply potential rotation about the C₆–C₇ bond of the open triplet intermediate. The overall formation of aziridine, ³[Cu]NTs + styrene → aziridine + ¹[Cu]¹ is exergonic, with ΔG = -20 kcal/mol. As with the results for toluene amination, this suggests that dissociation of the nitrene-inserted product is facile. Interestingly, the C–N bond lengths in the k¹-aziridine product (Figure 5-8, D) are inequivalent, C₆–N_Ts = 1.49 Å, C₇–N_Ts = 1.56 Å. The computed C–N bond lengths in the isolated aziridine product (Figure 5-9) are C₆–N_Ts = 1.47 Å, C₇–N_Ts = 1.50 Å.

5.5 Calculated EWG/EDG Substituted Aziridinations.

For comparative purposes, aziridination transition state geometries (catalyst model 1) were obtained from the parent styrene TS by introducing an electron-donating (MeO) and an electron-withdrawing (CF₃) para-substituent and then initiating a new TS search. As for the unsubstituted olefin substrate discussed above, singlet TS’s are higher in energy than triplets for the para-CF₃ and para-OMe derivatives. The barriers for the initial C–N bond formation (³[Cu]=NTs] + p-Y-C₆H₄CH=CH₂ → ³Az) were calculated to be ΔG‡ = 24, 22, and 28 kcal/mol for Y = H, OMe, and CF₃, respectively, in accordance with the electrophilic nature of the reaction. The overall formation of aziridine product had ΔG = -20 kcal/mol for all three substituents modeled (³[Cu]=NTs] + p-Y-C₆H₄CH=CH₂ → ¹[Cu]¹ + aziridine).

Aziridination TS geometries (initial C–N bond formation) for p-Y-C₆H₄CH=CH₂ (Y = H, MeO, CF₃), by catalyst model 1 are shown in Table 5-3. Electron-donating p-OCH₃, associated with the
lowest C–N bond formation barrier, lengthened the N–C<sub>b</sub> and N–C<sub>a</sub> bond distances by ~0.05 Å vs. unsubstituted styrene. For the <i>p</i>-CF<sub>3</sub> substituent, N–C<sub>a</sub> and N–C<sub>b</sub> were similarly shortened. The modest change in the aziridination TS geometry with the introduction of para-substituents, along with the reasonable computed barriers for torsion about the C<sub>a</sub>–C<sub>b</sub> bond (see above), are consistent with the experimental observation of <i> cis/trans</i> isomerization in the aziridination of <i>trans</i>-<i>p</i>-Y-C<sub>6</sub>H<sub>4</sub>CH=CHD (Scheme 5-5) that does not change much with the <i>para</i>-substituent.

5.6 Conclusions.

Nitrene-transfer chemistry between donor imidiodinanes and acceptor C–H and C=C containing substrates was studied. Typically first-row transition metal reagents ligated to porphyrinoids are employed for this process. This chapter investigated a new C<sub>3</sub>-symmetric Cu<sup>1</sup> reagent bound to a highly basic, guadinate-rich ligand. The metal-nitrene moiety ([Cu=NTs]<sup>+</sup>) studied inserts NTs into C—H and C=C bonds. The calculations suggested that the Cu<sup>1</sup> reagent that possess one NTs-inserted arm (–NCH<sub>2</sub>NHTs in lieu of –NMe), and even a demethylated congener (–NH in place of –NMe), have the potential to be active precatalysts.

**Scheme 5-4**
Figure 5-8. B3LYP/6-31G(d) computed triplet TS for the aziridination of styrene (A) by \textbf{1}. “Open” triplet intermediate (B). Radical rebound TS (C). Singlet aziridine complex (D). Hydrogens are omitted from the figure for ease of viewing.

Figure 5-9. B3LYP/6-31G(d) calculated C\textalpha{}N\textsubscript{Ts}, C\textbeta{}N\textsubscript{Ts}, and C\textalpha{}C\textbeta{} bond lengths (Å) in isolated aziridine product.

Table 5-3. Aziridination Transition State (triplets) N–C (olefin) and C–C (Olefin) Bond Lengths

<table>
<thead>
<tr>
<th>para-Y</th>
<th>N–C\textbeta{}</th>
<th>N–C\textalpha{}</th>
<th>C\textalpha{}–C\textbeta{}</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>2.312</td>
<td>3.101</td>
<td>1.371</td>
</tr>
<tr>
<td>OCH\textsubscript{3}</td>
<td>2.351</td>
<td>3.163</td>
<td>1.370</td>
</tr>
<tr>
<td>CF\textsubscript{3}</td>
<td>2.268</td>
<td>3.029</td>
<td>1.373</td>
</tr>
</tbody>
</table>
The formed nitrene intermediate shows complete H-atom abstraction from the toluene which then forms a radical pair, Cu\textsuperscript{II}-amide and benzyl radical, for the amination reaction. This is followed by a radical rebound step and ultimately formation of the separated catalyst and product. Therefore, the results of the radical clock experiments by Stavropoulos and coworkers\textsuperscript{32} along with the toluene amination suggest that the reaction proceeds \textit{via} a two-step process.

The aziridination of styrene was investigated with the model catalyst 1. The C\textsubscript{1}=N bonds between the nitrene nitrogen and the vinyl carbon atoms of the transition state geometry appear to form asynchronously. Calculations showed rotation about the C\textsubscript{1}–C\textsubscript{2} bond is possible in the “open” styrene intermediate, which is consistent with experimental observations. Therefore, for both the amination and aziridination reactions by these copper catalysts, calculations suggest a two-step process is operative.

5.7 References

Chapter 6
Summary and Future Direction

This dissertation focuses on the fundamental aspects of C–H bond activation and functionalization utilizing an organometallic Fe^{II} complex and also by means of an alkali metal superbase. Also, C–N bond formation is addressed by amination and aziridination mechanisms. Based on the concluded research, future directions for C–H and C–C bond manipulation are suggested.

2.1 C–H Activation Employing Organometallic Complexes

C–H and C–C bond manipulation has challenged chemists for decades. The selective direct partial oxidation of C–H bonds at ambient temperatures (~200 °C) and pressures (< 500 psi) using dioxygen as the oxidant (either directly or indirectly) would prove extremely useful. One specific example being the conversion of methane to methanol.\(^1\) We have an abundance of domestic methane at our disposal.\(^2\) This gaseous fuel source could be converted to a liquid fuel source which our current infrastructure is designed to handle effectively. However, several challenges within the field of catalysis have yet to be overcome. Through the utilization and assistance of computational approaches, these challenges may be overcome.

A baseline Cp*Fe(CO)(OPy)Ph complex was modified to gain insight into the impact of modification of the chemical components on the thermodynamics and kinetics of oxy-insertion into the Fe–Ph bond. The calculations support a two-step (or redox) oxo-mediated pathway as more energetically favorable in comparison to a one-step (or non-redox) organometallic Baeyer-Villiger pathway. Moreover, the initial barrier to oxo formation \(\Delta G_{\text{oxo}}^{\ddagger} = 22.9 \text{ kcal/mol}\) marked
the highest point on the reaction coordinate while the transition state for phenyl migration is predicted to occur with a lower free energy of activation ($\Delta G_{\text{mig}}^{\ddagger} = 20.5$ kcal/mol). The oxo intermediate formed by the initial oxygen atom transfer from OPy to the metal is described as an oxyl ($\text{Fe}^{\text{III}}\text{O}^*$) as opposed to an oxide ($\text{Fe}^{\text{IV}}\text{O}_2^-$) or oxene ($\text{Fe}^{\text{II}}\text{O}^\cdot\cdot^\cdot$) intermediate. Also, it was shown that the 3d metal has a more favorable energetic barrier for the formation of the oxo intermediate as compared to 4d and 5d metals. The role of the coligand, CO, was also studied. Hence, moving forward, the study of Earth-abundant complexes of the middle and late 3d series would seem to be a profitable area for future research. Oxidation of the CO co-ligand was calculated to be energetically competitive with oxidation of the hydrocarbyl ligand. Hence, this is a key issue in moving forward using this and related iron complexes as oxidation catalysts. More oxidation resistant co-ligands such as N-heterocyclic carbenes would be worthy of investigation.

The calculated Fe–C bond dissociation free energies of the Cp*Fe(CO)(OPy)Me complex implied that the Fe–R → Fe–OR transformation may have substantial radical character to it, especially for R = Me. Unlike the phenyl congener, the calculated bond dissociation free energy for Fe-methyl scission was substantially lower than the activation barrier for migration of the methyl to the oxo ligand. The Hammett studies were also interpreted to imply radical character in the oxy-insertion transformations, and thus limited charge build-up in the hydrocarbyl group, in the migrating step for the 3d metal. Moving forward harnessing the high reactivity of this radical character could be highly useful in overcoming reluctance of a nucleophilic methyl to transfer to an oxygen atom.
The baseline complex from Chapter 2, Cp*Fe(CO)(OPy)Ph, was taken and converted to Cp*Fe[P(OCH₂₂)₂C₂t]₂Ph to investigate whether the coligand has a propensity for oxidation as was the case for the carbonyl coligand. Experimentally, it was demonstrated that Fe(II) hydrocarbyl (phenyl and methyl) complexes underwent C–O bond formation as predicted by the calculations. The study indicated that Fe–oxo complexes as viable intermediates that precede net oxo insertion into the Fe–R bond using the phosphite in place of the carbonyl coligand. The calculations indicated that both Fe–oxo formation and the oxy-insertion into Fe–R bonds are viable. Although the previous (limited) examples of O-atom insertion into M–R bonds occur with metals that will not activate C–H bonds, use of Cp*Fe[P(OCH₂₂)₂C₂t]₂Ph complexes is promising because of the demonstrated ability of the related Cp*Fe(CO)(NCMe)Ph to activate C–H bonds. This chapter established the ability of d₆ complexes to mediate O atom insertion into M–R bonds. Importantly, they also point the way to new ligand motifs that avoid (1) C–C coupling products, and (2) ligand oxidation. However, more research is needed to find a ligand motif that does not contain the susceptibility to oxidize the coligand during the catalytic cycle.

This chapter studied C–H bond cleavage by “superbasic” alkali metal amides, i.e., CsNH₂. The modeled substrate was toluene. It was computed that changes in the distances between Cs⁺ and the ring centroid of the toluene substrate along the reaction coordinate suggested that metal cation–π interactions facilitate scission of benzylic C–H bonds, which is interesting in light of experimental observations that C–H functionalizations sometimes require Cs salts, although the role of the cesium salt is typically view as a base. Moving forward it would be of interest to investigate the role of cesium at a deeper level in such organic transformations. Also, benzylic C—
H functionalization by electrophilic transition metal amide/imide moieties should be investigated as well to compare and contrast with s-block metals such as cesium, which, of course, cannot change their formal oxidation state.

Comparing the barriers and thermodynamics to deprotonate toluene among the alkali metal cyclohexylamides, the Cs complex was calculated to be most active. This is consistent with Cs being the most electropositive of these metals, and hence cesium amide should be more basic than other alkali metal amides. The Mulliken electronegativity was plotted against the barriers, for toluene CH cleavage by the alkali metal compounds, M(NHCy). The correlation reasonably suggested that more basic/nucleophilic character for the alkali metal amide afforded a lower CH deprotonation barrier. However, the linear correlation is modest ($R^2 \sim 0.8$), which suggested that the decrease in barrier between Li and Cs amides is not merely a simple function of amide basicity. The use of solvation, both implicit and explicit, raised the calculated toluene benzylic C—H cleavage barriers. The reaction was also made to be less exergonic upon introduction of the complex with solvent. It was concluded that any manipulation of the system that makes the complex less nucleophilic will hinder the effectiveness in deprotonating C—H bonds. Further study of the poor linear correlation of M(NHCy) would be of interest, for example, using more accurate wavefunction techniques such as MP2 and CCSD(T).

A Cu^I reagent ligated to a $C_3$-symmetric, highly basic, guadinate-rich ligand was investigated for the amination and aziridination of C–H and C=C bonds, respectively. The nitrene was deposited onto the Cu^I moiety by the assistance of PhI=NTs. This complex was shown to be an active precatalyst by our experimental collaborators. The formed nitrene intermediate shows complete H-atom abstraction from the toluene, which then forms a radical pair, Cu^II-amide and
benzyl radical, for the amination reaction. This is followed by a radical rebound step and ultimately formation of the separated catalyst and product. Therefore, the results of the radical clock experiments along with our modeling of toluene amination suggest the reaction to proceed via a two-step process.

The aziridination of styrene was also investigated with model catalyst 1. The C–N bonds between the nitrene nitrogen and the vinyl carbon atoms of the transition state geometry appear to be asynchronous with respect to the formation of the two carbon-nitrogen bonds. Calculations showed rotation about the C1–C2 bond is possible in the “open” styrene intermediate, which is consistent with experimental results that show cis and trans aziridine products in the catalytic amination of cis and trans alkenes. Therefore, for both the amination and aziridination the calculations and experiments provide strong evidence for a two-step process.

In conclusion, it was demonstrated that a CuI reagent accompanied by a tripodal C3-symmetric guadinate-rich ligand served as the catalyst for enantioselective nitrene transfer reaction (aziridination or C–H amination) using NTs as the nitrene source.

The inertness of alkanes has challenged catalysis scientists for decades. In the 1970’s, Shilov and coworkerd discovered a PtII/Cl4− system that could catalyze the functionalization of methane to methanol.8,9 Recently, Gunnoe et al. published a study showing Rh(III) bis(quinolinyl)benzene complexes that could potentially activate and oxidize for the C—H bonds of methane.10 Though, the mechanism of these two examples, as well the example provided herein is different, there are similarities among the three. These similarities are what need to be the focus in future catalyst design for alkane functionalization. First, the metal in all these
systems goes through varying oxidation states. Herein, iron is seen to go through variations of oxidation states, for example, from 2+ to 4+ and then back to 2+. The ease of moving among these formal oxidation states, which have differing acid/base properties, is key in future catalyst design. As seen in the Shilov catalyst, as well as the Rh catalysts, and the iron complexes studied here, the supporting ligands play a central role in the catalysis. The ligands are not merely “spectator” ligands but active ligands involved in the catalysis, even if indirectly. In future catalyst design, the ligand must be involved in key steps of the process. For example, a potential ligand that has the ability to be greatly withdrawing during coordination of the alkane to the metal complex while ceding that ability through the rest of the process. Redox active ligands can change their formal oxidation state and hence may be able to modulate the acid/base properties of the metal to greatly impact methane catalysis. This may also be accomplished by harnessing steric control of a ligand that is coordination “flexible” through the catalytic cycle, for example, a hemi-labile ligand in which one “arm” can come on and off during the catalytic cycle.

2.2 References


