The Study of Rhodium Complexes for C–H Bond Activation and Functionalization

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ABSTRACT

WEBSTER-GARDINER, MICHAEL S. The study of rhodium complexes for C–H Bond Activation and Functionalization (Under the direction of Professor T. Brent Gunnoe).

The production of alkyl arenes from arenes and olefins is a significant sector of the petrochemical industry. Typically, alkyl arenes are synthesized through acid-based methodologies such as Friedel-Crafts or zeolite catalysis. As a result of the mechanism for these processes, polyalkylation occurs, which necessitates a *trans*-alkylation step to yield the desired monoalkylated species, and there is poor control of the regioselectivity for substituted arenes. Further, acid-based catalysis cannot produce anti-Markovnikov addition products or vinyl arenes. Transition metal catalysts for the selective oxidative vinylation of arenes with olefins offer an alternate mechanism which circumvents the flaws of traditional methods. These catalysts operate through two fundamental steps: transition metal arene C–H activation and olefin insertion into an M–Ph bond. Current examples of transition metal catalysts for this transformation are typically based on Ru, Ir, Pt and offer marginal selectivity and efficiency. This Dissertation is focused on extension of oxidative vinylation of arenes with olefins to low valent rhodium species.

Initial studies focused on diimine rhodium complexes of the form (DAB)Rh(L)(TFA) (DAB = diazabutadiene, L = η^2 -COE or η^2 -C₂H₄, TFA = trifluoroacetate, COE = cyclooctene) for C–H activation. These catalysts were demonstrated to be active for the H/D exchange between benzene- d_6 and HTFA. However, these rhodium species were found to operate through protic electrophilic aromatic substitution and therefore formation of Rh–Ph was not observed. In addition,

we demonstrated that many common salt additives for *in situ* generated catalysts are efficient for the H/D exchange of arenes and acids.

These (DAB)Rh(η^2 -C₂H₄)(TFA) species were demonstrated to be efficient for the oxidative vinylation of benzene with ethylene. The most efficient catalyst, (^{FI}DAB)Rh(η^2 -C₂H₄)(TFA) (^{FI}DAB = *N*,*N'*-bis-(pentafluorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene), produces styrene in a single-step from benzene, ethylene, and Cu(OAc)₂ with > 95% selectivity and > 800 TOs. The oxidative vinylation of benzene with propylene revealed the formation of alkenyl products allylbenzene, *trans*- β -methylstryene, *cis*- β -methylstryene, and α -methylstyrene in linear to branched (L:B) ratios of > 8:1. Further studies revealed that the oxidative vinylation of both electron deficient and electron rich arenes with α -olefins is efficient when using commercially available [Rh(η^2 -C₂H₄)₂(μ -OAc)]₂ and Cu(II) carboxylate. [Rh(η^2 -C₂H₄)₂(μ -OAc)]₂ can successfully produce alkenyl arenes with over 1400 TOs and L:B ratios of 16:1. The similarities to the commercialized Wacker process highlight the potential of this rhodium based oxidative vinylation catalysis for further study.

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A wise man once told me that many people think a PhD is like running a marathon, and it can certainly sometimes feel that way; however, it is actually more like a series of sprints. You have to refine your technique during most of the time until finding those few successful results and then running with them. It is a race I did not think I would finish and I am grateful to so many people for helping me along this journey.

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1 Introduction

1.1 Overview of Catalysis

The development and utilization of catalysts is important for the global economy. An Organization of Economic Co-operation and Development (OECD) report from 1995 estimated that catalysts are involved in the syntheses of products which constitute more than 30% of the global GDP, with the full value of goods and services from catalysts worth approximately \$15 trillion annually.^{1,2} Catalysts are involved across many sectors in the production of fuels, food, materials, chemicals, and environmental cleanup. More than 80% of industrial chemical processes utilize catalysts in at least one step.^{3,4} Increased public and governmental concern over environmental issues has led to regulations that require the chemical and petrochemical industries to adjust their practices.⁵ To meet these requirements, industry has focused upon reaction optimization, recovery and recycling of catalysts, and the minimization of waste products. Catalysts can help achieve these goals.

Catalysts increase the rates of reactions by providing alternate mechanisms for reaction pathways that have lower activation barriers.⁶ This occurs because the catalyst either destabilizes the reactants and/or stabilizes transition states. The general criteria determining catalyst efficacy are activity, selectivity, and longevity. The activity of a catalyst is regularly reported by turnover frequency (TOF) which is the number of catalytic cycles per unit time. The selectivity is determined by the amount of conversion of starting materials to desired products. Longevity is often conveyed by turnover number (TON), the total number of turnovers before catalyst deactivation.

Commonly, catalysts are divided into two broad categories: homogenous and heterogeneous. As the name implies, homogenous catalysts operate in the same phase as the reactants. Conversely, heterogeneous catalysts operate in a different phase, typically solid catalysts with liquid or gaseous reactants. In spite of the advantages (see below) of using homogeneous catalysts, the chemical industry relies upon heterogeneous catalysts for over 75% of all chemical processes.⁷ The primary advantages of heterogeneous catalysts are stability and recovery.⁸ Well-known heterogeneous processes include catalytic converters in transportation, which convert NO_x, CO, and unburnt hydrocarbons to O₂, N₂, H₂O, and CO₂ using combinations of Pd, Pt, and Rh,⁹ and the Haber-Bosch process for the generation of ammonia from nitrogen and hydrogen over iron catalysts.^{7,10}

Homogenous catalysts are usually more active and selective, and also allow for simpler characterization and reaction monitoring.¹¹⁻¹³ This permits more facile determination of reaction kinetics and elucidation of the mechanisms of catalytic cycles. With an in-depth understanding of the mechanism, catalysts can then be rationally designed and optimized.¹⁴ Another advantage is that homogenous catalysts are easier to fine tune.

1.1.1 Overview of Key Industrial Examples of Homogenous Catalysts

While most industrial processes are based on heterogeneous catalysis, homogeneous catalysts are used in several significant commercial processes. The most prominent of these include hydroformylation, olefin polymerization, the Monsanto/Cativa acetic acid process, and the Wacker process for acetaldehyde production. These processes exemplify

the potential for homogeneous catalysis and the necessary requirements for commercialization of such processes.

Hydroformylation, also known as the "oxo-process," is the reaction of olefins with carbon monoxide and hydrogen with a rhodium catalyst to produce aldehydes, which have applications as substrates for organic chemicals, polymers, and the perfume industry.¹⁵⁻¹⁷ One of the most common olefins for this process is propylene, which is hydroformylated to produce butanal on a 5 million ton scale every year (Scheme 1.1).¹⁸ The process has high selectivity for the higher value linear isomers and exhibits high activity. One of the best rhodium catalysts [Rh(H)(CO)(PPh₃)₃] produces a linear to branched (L:B) ratio of 92:8.¹⁹ The selective production of the terminal linear isomer, relative to the internal isomer, is crucial for the commerciality because of its increased utility and therefore higher price.¹⁸



Scheme 1.1. Hydroformylation of propylene to give 1-butanal and 2-methylbutanal (or terminal and internal butanals).

In industry, the substrates are added to the reaction continuously while the products are simultaneously removed by distillation. Removal of the product stops possible side reactions and inhibition of the catalyst through product coordination. This allows for continuous production of butanal with minimal catalyst decomposition.¹⁸ For longer chain olefins, which are used to produce aldehydes for the manufacture of plastics and detergents, a $Co(H)(CO)_4$ catalyst is used because at the temperatures required to distill the longer chain products, the rhodium catalyst decomposes (Figure 1.1).²⁰ Relative to the

rhodium catalysts, the cobalt catalysts are less active and less selective for the terminal aldehyde, but can tolerate higher temperatures.



Figure 1.1. Cobalt and rhodium catalysts for hydroformylation.

The development of novel polymers and plastics via olefin polymerization is of significant interest to the chemical industry. A noteworthy development in the field of olefin polymerization is the Shell Higher Olefin Polymerization (SHOP) catalyst for the oligomerization of ethylene.^{3,21} This process uses a nickel-based catalyst to polymerize ethylene to produce α -olefins (Scheme 1.2). Unlike the Ziegler-Natta process, which generates very long chain polymers (C_{>25}), the SHOP catalyst produces α -olefins in the range of C₁₂ – C₂₀.²² SHOP also permits straightforward product separation through the use of highly polar alkanediols that solubilize the nickel catalyst but not the long chain α -olefin products.



Scheme 1.2. Typical Ni catalyst for ethylene polymerization (SHOP process).

A particularly instructive commercial example of homogeneous catalysis is the Monsanto process for the generation of acetic acid via the carbonylation of methanol. In 1966, Monsanto developed $[Rh(I)_2(CO)_2]^-$ to produce acetic acid, a chemical used as a raw material, utilizing methanol and carbon monoxide.²³ The catalytic cycle, shown in Scheme 1.3, makes use of fundamental organometallic steps including: 1) oxidative

addition of methyl iodide, 2) carbon monoxide insertion into the Rh–Me bond, 3) carbon monoxide coordination and 4) reductive elimination of acetyl iodide and subsequent catalyst regeneration. The acetyl iodide is then hydrolyzed to release acetic acid and hydrogen iodide. Methanol undergoes nucleophilic substitution with HI to give methyl iodide and water, completing the catalytic cycle.





Although used industrially, the rhodium catalyst suffers from water gas shift (WGS) reactions that lower the selectivity for the desired product. The Cativa acetic acid process, which uses $[Ir(I)_2(CO)_2]^-$ to prevent WGS, operates through the same basic principles as the Monsanto process with some important differences.^{24,25}

With the iridium catalyst, less water is required to activate and regenerate the catalyst; the WGS reaction is less significant and produces less of the propionic acid byproduct. In addition, with iridium the rate of migratory insertion of CO could be increased when using acidic solvents such as methanol.²⁶ In accordance with the benefits obtained from exchanging rhodium for iridium and the ability to utilize the same reactors, the Cativa process now accounts for most of the industrial production of acetic acid.²⁵

$$CO + H_2O \longrightarrow CO_2 + H_2$$

Scheme 1.4. Water gas shift reaction.

In 2003, the global production of acetaldehyde was approximately 1.2 million tonnes. The Wacker process is a major method for production of acetaldehyde and utilizes a simple palladium salt, $PdCl_4^{2-.27}$ Water reacts with the Pd center to release HCl and generate a Pd-OH. This species coordinates ethylene, which subsequently inserts into the Pd-OH bond to form acetaldehyde, which is then released, leaving Pd(0). The Pd(0) is then reoxidized to Pd(II) by 2 equivalents of CuCl₂.²⁸ The resulting copper salt, CuCl, is then reoxidized to CuCl₂ with molecular oxygen and the HCl produced from the reaction. Overall the process for the formation of acetaldehyde converts ethylene and molecular oxygen Scheme 1.5).²⁹



Scheme 1.5. Wacker process for the production of acetaldehyde. The net reaction is shown in the box.

A crucial characteristic of the Wacker process is that the copper oxidant can be regenerated using air or oxygen. The regeneration can occur by *in situ* regeneration in which the oxygen is introduced into the reaction concurrently, or alternatively, the CuCl can be removed and regenerated in a different reactor. Both methods are practiced industrially and each has advantages and disadvantages. Ultimately, the cost depends on the localized cost of purified oxygen versus air at the commercial plant. Purified oxygen is necessary for the *in situ* regeneration of CuCl₂, whereas air can be used in the two-step process.¹⁶

1.2 Transition Metal C–H Activation

The emphasis of this dissertation is on the utilization of carbon-hydrogen (C–H) activation as a methodology for the development of new catalysts for hydrocarbon functionalization. Although C–H bond breaking can be achieved through radical processes and use of superacids,³⁰⁻³² in this dissertation, C–H activation of R–H will be defined as the two-electron cleavage of a C–H bond by a transition metal to form a M–R bond. In the following sections a brief overview of four common modes of C–H bond activation (electrophilic activation, oxidative addition, σ -bond metathesis (SBM)), will be discussed.

1.2.1 Electrophilic Activation of C–H Bonds

Electrophilic activation of carbon-hydrogen bonds takes place when coordination of a C–H bond to a metal center renders the C–H bond acidic. The acidic C–H can then be deprotonated by a base (Scheme 1.6).³³ Traditionally, this mechanism has been observed in polar solvents like water or strong acidic media such as sulfuric acid.³⁴ Well-known

examples of this method for the functionalization of methane such as the Shilov and Catalytica systems are discussed in detail in Section 1.3.3.

$$M^{n} + R - H \longrightarrow \begin{bmatrix} M & \checkmark \\ H \end{bmatrix} \stackrel{X^{-}}{\checkmark} \longrightarrow M^{n} - R + HX$$

Scheme 1.6. Electrophilic activation of a C–H bond.

1.2.2 Activation of C–H Bonds by Oxidative Addition

Oxidative addition is a common type of C-H bond activation for low-valent, electronrich transition metal complexes. The C-H bond is activated by the donation of two electrons from the metal center to the σ^* anti-bonding orbital of the C–H bond followed by insertion of the metal into the C-H bond and oxidizing the metal center by two electrons (Scheme 1.7). These species often have to be generated in situ, like Bergman's $(\eta^5-C_5Me_5)-(PMe_3)Ir^{III}H_2$ ³⁵ Photochemical irradiation releases hydrogen gas leaving the highly reactive species $(\eta^5 - C_5 Me_5) - (PMe_3)Ir^I$. When exposed to hydrocarbons this Ir^I species undergoes oxidative addition to give $(\eta^5-C_5Me_5)-(PMe_3)Ir^{III}(R)(H)$.³³ Jones and Tp'Rh(C≡N-neopentyl) coworkers discovered the (Tp´ tris(3,5that = dimethylpyrazolyl)borate) fragment is active for the oxidative addition of C-H bonds.³⁶ These studies demonstrated for a range of hydrocarbons the relative activation barriers of oxidative addition to form Tp'Rh(C≡N-neopentyl)(H)(R). In benzene however, the fragment only produces Tp'Rh(C=N-neopentyl)(Ph)(H).³⁶

$$LnM^n + R-H \longrightarrow LnM^{-R} \longrightarrow LnM^{n+2}$$

Scheme 1.7. Oxidative addition of a C–H bond.

1.2.3 σ-Bond Metathesis of C–H Bonds

Traditionally, d^0 transition metals containing hydrides or alkyl ligands can initiate σ bond metathesis. The metal center cannot donate electron density into the σ^* anti-bonding orbital of the C–H bond and therefore goes through a 4-electron, 4-center transition state (Scheme 1.8).^{6,33,37,38} Coordination of the C–H bond to the metal center polarizes the C– H bond, which is subsequently deprotonated by the nucleophilic ligand. In the 1980s, Watson reported C–H bond activation with a Lu(III) species. Heating (Cp*)₂LuCH₃ (Cp* = pentamethylcyclopentadiene) with ¹³C-labelled methane produced CH₄ and (Cp*)₂Lu¹³CH₃.³⁸

$$M-R' + R-H \longrightarrow \begin{bmatrix} M-R'\\ \vdots & \ddots & \vdots\\ R-H \end{bmatrix} \longrightarrow M-R + R'-H$$

Scheme 1.8. Generic reaction showing SBM of a C–H bond.

1.3 Overview of Hydrocarbon Activation

Aliphatics, arenes, and olefins are the essential building blocks of the chemical industry as they are easily accessible from fossil resources. However, selective transformations of these hydrocarbons are difficult, in part due to the strength of the C–H bonds. The bond dissociation energies for methane and benzene are 104 and 113 kcal/mol, respectively.³⁹ Thus, high energy species such as free radical agents and superacids are often required to break these inert the C–H bonds.³¹ Another issue in selective functionalization of C–H bonds is that the products are often more reactive than the substrates. For example, methane has a C–H bond strength of 104 kcal/mol, but the C–H bond strength of methanol is 96 kcal/mol.³⁹ Thus, it is often a challenge to stop

further reactivity after the first the C–H functionalization. In addition, methane, for example, is non-polarized allowing for even fewer methods of functionalization.

1.3.1 Overview of Natural Gas and Current Technologies

Natural gas consists primarily of methane (approximately 87% by volume), ethane, propane and other light alkanes.⁴⁰ The energy in the alkane C–H bonds is a key reason why natural gas is a major source of power, accounting for 32% of electrical power for the US in 2014.⁴¹ The combustion of hydrocarbons produces substantial energy but converts all carbon and hydrogen to carbon dioxide and water, respectively (Scheme 1.9).

$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O + \triangle H = -891 \text{ kJ/mol}$$

combustion

Scheme 1.9. Complete combustion of methane to carbon dioxide and water with concomitant heat release.⁴²

Currently the majority of natural gas is used for power generation and heating; however, it is also a primary feedstock for the chemical industry. Often the ethane and propane are removed and used to generate ethylene and propylene, respectively.⁴³ Methane and water are reformed to generate synthesis gas, a mixture of H₂ and CO,⁴⁴ which can then be used to generate a variety of products including methanol (Scheme 1.10). This technology requires high temperatures (> 800 °C) and pressures.⁴⁰ In order to reach these conditions approximately half of the natural gas is burned in the process.⁴⁴

$$\sim 900 \,^{\circ}\text{C}$$
 $\sim 250 \,^{\circ}\text{C}$
CH₄ + H₂O $\xrightarrow{40 \text{ atm}}$ CO + 3 H₂ $\xrightarrow{50 \text{ atm}}$ CH₃OH + H₂O

Scheme 1.10. Current industrial production of synthesis gas and methanol.

There are huge natural gas deposits worldwide located in areas that are far removed from usable markets. It is expensive to transport this 'stranded natural gas'. Natural gas at remote locations is often flared; burning the gas to produce carbon dioxide rather than releasing methane. The United States alone flared an estimated 278,623 million cubic feet of natural gas in 2015, this was approximately 1% of total U.S. consumption.⁴⁵ The development of cost-efficient methods to utilize stranded natural gas remains a challenge. The construction of pipelines, which require specialized linings to avoid gas leakage, to transport natural gas is capital intensive. For example, the proposed Alaska gas pipeline was projected to cost \$35 billion; however, due to cheap shale gas near markets, the pipeline has been cancelled.⁴⁶ The capital and energy requirements for liquefaction, the process of cooling and pressurizing gas into a liquid, are prohibitive for all but the largest reserves.⁴³

One possible avenue to overcome these complications is to convert natural gas to a liquid in close proximity to the reserves. Obtaining a liquid product would alleviate challenges regarding transportation. The current method for conversion of natural gas to liquid, the synthesis gas process, requires very high pressures and temperatures, thus the industrial plants designed to accomplish this task are expensive, often prohibitively so. The Pearl Gas-to-Liquid (GTL) plant in Qatar, the largest of its kind with a production capacity of 140,000 barrels of petroleum liquids per day, epitomizes the capital-intensive nature of this liquefaction method. The final cost for the construction of this plant was \$19 billion.⁴⁷ Accordingly, simpler and more cost-effective processes for partial oxidation of methane to liquid fuels are highly desirable.

A particularly sought after conversion is the partial oxidation of methane to methanol, which is a liquid at room temperature. Its potential utility is so broad that people have advocated for the development of a 'methanol economy' in which methanol would be the primary source of fuel and raw material for fine chemical synthesis.⁴⁸ This idea has gained traction principally due to methanol's chemical versatility (Scheme 1.11). Methanol is a key commodity chemical; for example, acetic acid is produced by the carbonylation of methanol (see Section 1.1.1)²⁴ Formaldehyde, another commodity chemical, is also primarily synthesized from the oxidation of methanol.¹⁵ As a liquid, methanol can be transported using substantially more cost effective methods relative to methane. It can also be utilized as a fuel directly in both internal combustion engines, in direct methanol fuel cells and can be converted to gasoline.⁴⁹ Although methanol has lower volumetric energy content than gasoline, methanol has a higher octane rating allowing for increased efficiency.⁴⁸ A building block for fine chemical synthesis, methanol can be converted into olefins, dimethyl ether, and other widely used substrates.



Scheme 1.11. Common uses of methanol as a feedstock.

The extensive potential uses of methanol combined with the expansive reserves of natural gas has led to significant interest in the conversion of methane into methanol selectively at moderate temperatures and pressures (approximately 250 $^{\circ}$ C and < 1000 psi).

1.3.2 Methods to Functionalize Light Alkanes

Radical reactions have been used for the conversion of R–H to R–X. For example, radical chlorination using Cl₂ can convert methane into MeCl and HCl.⁴⁴ However, undesired over-oxidation of the hydrocarbon substrate occurs due to a subsequent decrease of bond strength as methane is chlorinated limiting the selectivity of these reactions. Because the bond strength of methyl chloride is 84 kcal/mol, substantially lower than that of methane (104 kcal/mol),⁵⁰ radical species will preferentially react with MeCl over CH₄.⁵¹ Consequently, radical chlorination produces a variety of products during reaction including chloromethane, dichloromethane, chloroform, and carbon tetrachloride. Oxychlorination operates in a similar manner except utilizing HCl and oxygen (Scheme 1.12).⁵² Typically oxychlorination is utilized because HCl is a common industrial byproduct of many different chemical processes and therefore is often less expensive than chlorine.^{53,54}

$$CH_4 + HCI + 1/2 O_2 \xrightarrow{>350 \circ C} RCI + RCI_2 + RCI_3 + RCI_4 + H_2O$$

 $CuCl_2 \text{ on}$
solid support

Scheme 1.12. Catalytic oxychlorination of hydrocarbons.

Nature selectively functionalizes methane to methanol through the use of transition metal containing enzymes. Methane monooxygenase (MMO) oxidizes methane to methanol under biological conditions utilizing an iron oxo species.⁵⁵ Although the exact mechanism of the process is debated, it is thought that the Fe oxo abstracts a H atom from

methane.⁵⁶⁻⁵⁹ Several research groups are attempting to mimic biological systems to functionalize alkanes.⁶⁰⁻⁶⁶ In addition, copper has also been implicated as the active catalyst of MMO.⁶⁷

Stucky and coworkers have shown that bromination of alkanes can result in remarkable selectivity for the mono-functionalized product. This is an attractive approach because methyl halides can be converted to olefins.^{68,69} However, at high conversions this method generates significant quantities of dibromomethane, an undesired byproduct that often ends up coking and poisoning the catalyst.⁷⁰ A method to inhibit this poisoning is to intercept the intermediate, dibromomethane, and transform it back to methyl bromide or to useful olefins directly. Dibromomethane can be converted to olefins with Pd₆C on Si or to methyl bromide and methane using silica supported Ru.⁷¹ Recently, iodine was found to convert dibromomethane and propane to methyl bromide, propylene, and hydrogen bromide, respectively.⁷²

1.3.3 Organometallic Routes to Methane Functionalization

Transition metals have been shown to be active catalysts for the selective transformation of alkanes to functionalized products.⁷³⁻⁷⁵ In the U.S.S.R. during the 1960s, Shilov developed his seminal work on the use of platinum salts for methane functionalization (Scheme 1.13).^{76,77} Using protic media and Pt(II) salts, the electrophilic substitution of methane was discovered. With a Pt(IV) oxidant and in aqueous media, the conversion of CH₄ to MeCl and MeOH was observed.⁷⁸ This system demonstrates the potential for transition metals to achieve this difficult transformation. The major problem with this platinum system is the required use of a stoichiometric platinum oxidant to
oxidize the Pt(II) to Pt(IV).⁷⁵ Multiple research groups have attempted to exchange the platinum oxidant for other chemical oxidants as well as electrochemical oxidants; however, none have been commercialized.

For the general mechanism for this reaction, shown in Scheme 1.13, Pt(II) electrophilically activates methane, the proposed rate-determining step, with subsequent oxidation of Pt(II)-CH₃ to Pt(IV)-CH₃ by the stoichiometric Pt(IV) oxidant, which is followed by the nucleophilic attack of the polarized and electrophilic methyl group by Cl⁻ or H₂O.^{79,80} However, the mechanism of methane activation has been debated, with computational studies finding the oxidative addition of CH₄ to be slightly lower in energy than the electrophilic substituion pathway.⁸¹



Scheme 1.13. Shilov system for the conversion of methane to CH_3X , where X = OH, Cl.

Following this work, multiple other systems based on transition metals have shown promise for selective methane functionalization. A key advancement in this field was developed by Periana and co-workers at Catalytica, Inc. The discovery of the (bpym)PtCl₂ system (bpym = 2,2'-bipyrimidine) for the efficient conversion of methane to methylbisulfate in fuming sulfuric acid, achieved high selectivity (> 90%) and yield (~ 70%) for one-pass methane functionalization (Scheme 1.14).



Scheme 1.14. Catalytica system for partial oxidation of methane in oleum.

This system was an influential advancement in the field. A common complication for this chemistry is that the solvent is more reactive than the methane. Oleum overcomes this challenge because its bonds are less reactive than the C-H bonds of methane toward electrophilic activation.⁸² In a crucial improvement over the Shilov system, in the Catalytica system sulfuric acid acts as the oxidant. The SO_3 in oleum forms Pt(IV) which allows for the reductive functionalization step. Furthermore, the SO₂ that is generated can be re-oxidized directly with molecular oxygen (Scheme 1.15). Possibly the most profound finding was the discovery that the bisulfate group deactivates the C–H bonds of the product toward further reaction. Indeed methane reacts 100 times faster than methylbisulfate.⁸³ Additionally, the methyl bisulfate can be hydrolyzed to release methanol and sulfuric acid. Moreover the addition of water dilutes the concentration of acid that the catalyst is no longer active. However, the challenges in the separation of the products from the acidic media, due to strong hydrogen bonding, the production of only 1 M methylbisuflate, and the dilution and reconstitution of the acid is expensive rendering this process unsuitable for commercialization.⁸⁴

SO₂ + 1/2 O₂
$$\xrightarrow{400 - 600 \text{ °C}}$$
 SO₃
V₂O₅ and K₂O
on silica supports

Scheme 1.15. Oxidation of sulfur dioxide to sulfur trioxide with oxygen.

Following the success of the Catalytica system, the study of methane functionalization using oleum has been extended to include mercury, palladium, gold, and iodine catalysts.^{83,85-88}. However, as stated above, the concentrated sulfuric acid media proved to be limiting due to product separation issues. Interestingly, the mercury catalyst was investigated for commercialization because natural gas would not have to be purified before use and residual mercury would simply become more catalyst.⁸⁹ Recently Pt salts were shown to be even more active in oleum than previously thought.⁹⁰ This study also found that increasing the concentration of SO₃ allows the TOF to reach the range required for industrial processes of approximately 1 TO per second.

Due to the aforementioned issues with concentrated sulfuric acid, research in this area has expanded to the use of non-superacidic media, which can provide similar beneficial effects. Trifluoroacetic acid (HTFA) has been investigated for this purpose. The conjugate base, trifluoroacetate, can deactivate the remaining C–H bonds of the product of CH₄ functionalization, methyl trifluoroacetate (MeTFA), from further C–H electrophilic activation. Further, MeTFA could be separated from the solution by distillation due to the large difference in boiling points between the product and the solvent, 43 °C for MeTFA versus 72 °C for HTFA. Moreover, as HTFA is a monoprotic acid rather than a diprotic acid like sulfuric acid, the hydrogen bonding is dramatically reduced.

Periana and co-workers recently published a report utilizing $Tl(TFA)_3$ and $Pb(TFA)_4$ complexes in HTFA for the efficient, albeit stoichiometric, conversion of methane, ethane, and propane to their respective trifluoroacetate ester products.⁹¹ In a significant

development, these Tl species have been shown to be oxidized from Tl(I) to Tl(III) by O_2 .⁹² Thus the conversion of methane to methanol using oxygen as the ultimate oxidant is possible and efforts toward catalytic implementation of this process are underway.

In 1987, Sen utilized Pd salts in HTFA to oxidize methane to methyl trifluoroacetate,⁹³ and subsequently extended this work to use hydrogen peroxide as the oxidant.⁹⁴ Cobalt salts and oxygen in HTFA with trifluoroacetic anhydride have also been found to convert methane to methyl trifluoroacetate.⁹⁵ However, precipitation of inactive cobalt fluorides hinders this process. Recently, the Strassner group published examples of *N*-heterocyclic carbene Pd complexes that can functionalize methane and propane in trifluoroacetic acid (Scheme 1.16). A key to the regeneration of the catalysts was the oxidation to Pd(IV) by Br₂.⁹⁶ Oxygen can then be used as the final oxidant.^{97,98}



Scheme 1.16. Generic catalytic cycle showing a Pd(NHC) (NHC = 1,10 -dimethyl-3, 3' -methylene-4-diimidazolin-2,2' –diylidene) complex functionalizing methane.

In addition, our group recently published the functionalization of light alkanes using iodate salts with a substoichiometric chlorine source in HTFA.⁹⁹ In the initial study, at optimized conditions a one pass yield of 24% (based on methane) with greater than 90% selectivity for methyl trifluoroacetate was achieved. A clear dependence on chloride,

versus other halogens, was shown. This system has been successfully expanded and improved using periodate salts (Scheme 1.17).¹⁰⁰ The exact mechanism of these processes is unknown; however, the high selectivity of these reactions points to a system that operates via a mechanism different than that of oxychlorination.

Scheme 1.17. Periodate and chloride functionalization of methane in trifluoroacetic acid.

Another example of selective homogenous methane activation includes the use of Ag complexes that convert alkanes to esters in supercritical carbon dioxide (Scheme 1.18).¹⁰¹ The use of carbon dioxide as a solvent is a notable advancement.⁹⁴ However, because the driving force for these reactions is the use of the high energy starting material, ethyl diazoacetate, which cannot be commercialized for high volume processes.

$$CH_4 + H \xrightarrow{N_2} O \xrightarrow{[Tp^{Br}Ag]} H_3C \xrightarrow{H} O \xrightarrow{H} N_2$$

Scheme 1.18. Silver catalyst for methane functionalization in supercritical carbon dioxide (TpBr = perbrominated tris(pyrazolyl).

1.4 Overview of Alkyl Arenes and Current Technologies

Alkyl arenes are key commodity chemicals that are used in the synthesis of a variety of fine chemicals and are used to produce plastics, fuels, and pharmaceuticals (Scheme 1.19).⁴⁴ Benzene is produced on a scale of 37 million tons per year.¹⁰² Approximately 72% of benzene is transformed in ethylbenzene and cumene. Over 95% of ethylbenzene is converted into styrene, which is used to produce polystyrene, a prevalent plastic.^{103,104} Ethylbenzene, cumene, and long chain (C_{10-20}) linear alkylbenzenes are produced by acid catalyzed alkylation.



Scheme 1.19. A selection of alkyl arenes produced from benzene and olefins, and common products prepared from those alkyl arenes.

Currently, the chemical industry produces alkyl benzenes through Friedel-Crafts and related catalytic alkylations. By using acid-catalyzed pathways, with both Brønsted (HF) and Lewis (AlCl₃) acids, high yields and rapid rates have been achieved. The process operates by electrophilic aromatic substitution, wherein the acid attacks the olefin to generate a carbocation, which then reacts with the electron-rich arene to give a Wheland intermediate (Scheme 1.20). Deprotonation of the Wheland intermediate by the conjugate base gives the alkyl benzene and regenerates the acid catalyst.



Scheme 1.20. Acid-based Friedel-Crafts alkylation of benzene with ethylene to produce ethylbenzene.

The alkyl benzene product is more electron-rich and is thus more reactive than benzene, resulting in the formation of undesired polyalkylated products. Ethylbenzene, for example, often reacts 2-3 times faster than benzene.¹⁰² In order to convert polyalkylated benzenes to the mono-functionalized product, they are removed from the reaction and are transalkylated in a separate high temperature and energy-intensive step.¹⁰⁵⁻¹⁰⁷ Another prominent drawback of Friedel-Crafts alkylation is its limited substrate scope. Electron-deficient arenes are either unreactive, like nitrobenzene, or react slowly, like chlorobenzene which reacts ~10 times more slowly than benzene.¹⁰⁸⁻¹¹⁰

Additional disadvantages of acid-based mechanisms include the inability to recycle the catalyst due to its neutralization during the product extraction process, the stoichiometric generation of halogenated waste, and the requirement of acid-resistant non-corrosive reactors.^{44,103,106,111}

When utilizing longer chain α -olefins, an additional limitation arises due to the generation of the carbocation intermediate. This carbocation rearranges to the more stable secondary versus primary carbocation.¹⁰² This subsequently results in the exclusive formation of branched alkyl benzene products. For propylene, only the branched product, cumene, is produced (Scheme 1.21). Cumene is then oxidized to generate phenol and acetone on a 6.7 million ton scale each year (Scheme 1.22).¹¹²



Scheme 1.21. Acid-based mechanism for the alkylation of benzene with propylene.



Scheme 1.22. Production of phenol and acetone from cumene oxidation.

True straight-chain alkyl benzenes must be produced through Friedel-Crafts acylation followed by a Clemmensen or Wolff-Kishner reduction (Scheme 1.23). However, the expense of the substrates for this method prohibits its use on an industrial scale.



Scheme 1.23. Current method for the synthesis of truly linear alkyl benzenes.

1.4.1 Zeolite Catalysts

In an attempt to overcome some of the deficiencies of Friedel-Crafts catalysis, solid acid catalysts have been used. These catalysts can be extracted from the reaction mixture easily; however, the acidity is reduced compared to mineral acids.^{102,113}

In 1975, Mobil developed a process with zeolites, microporous aluminosilicates based on interlocking chains of SiO_4^{4-} and AlO_4^{5-} , based on ZSM-5 (Figure 1.2).¹⁰⁴ Zeolites have also been synthesized using boron, iron, and titantium.¹⁰² The cations can be exchanged within the zeolite to modulate acidity.¹¹⁴ Additionally, the size of the porous channels can be modulated, typically within the range of 0.25 nm to 1 nm, in order to modulate the surface area and stability of the zeolites, which subsequently affect the selectivity and rate of the alkylation reaction.^{115,116} There has been considerable progress in the development of zeolite catalysis since its inception. The catalyst longevity has been advanced such that some types of zeolites only need to be regenerated after 3 years.¹¹¹ Additionally, the transalkylation step can also take place in the same reactor.^{103,104} Although traditional Friedel-Crafts catalysts are used in the production of greater than 20% of ethylbenzene worldwide, zeolite catalysts now have a majority of the market share for ethylbenzene.¹¹⁷



Figure 1.2. Depiction of a ZSM-5 zeolite catalyst (A) Structure looking from the top at zeolite channels (B) Looking side on at zeolite material, four pores are marked for orientation (a, b, c and d). Copyright 2009 Wiley. Used with permission from Macquarrie, D. J., Industrial Friedel-Crafts Chemistry, *Catalytic Asymmetric Friedel-Crafts Alkylations*, Wiley-VCH.

Although many of the problems associated with Friedel-Crafts chemistry have been addressed through the use of zeolites, the selectivity for branched product remains a challenge.¹¹⁸ In the 1960s, branched alkyl benzenes (BABs) were the backbone of the detergent industry. However, the highly branched nature of BABs rendered them resistant to biodegradation (Figure 1.3). This resulted in a high concentration of BABs in lakes, rivers, and streams, environmental regulations prompted a change in the industry.^{119 120} Therefore, the chemical industry developed linear alkyl benzenes (LABs), benzene rings

with C_8 - C_{16} alkyl substituents. LABs are then sulfonated *para* to the alkyl group and are key chemicals for the detergent and surfactant industries.^{121,120} LABs are produced through acid-based alkylation. Typically this alkylation is operates with anhydrous HF or AlCl₃. The isomer distribution is dependent on the acid catalyst, as shown in Table 1.1 for the reaction of dodecene and benzene with anhydrous HF or AlCl₃.¹²⁰ Moreover, the toxicity of the linear isomers must also be considered; in general, the toxicity increases with increasing linearity.¹²¹ Conversely, while they are more toxic, the more linear alkyl arenes are more rapidly decomposed in an aerobic environment than their branched counterparts.¹²⁰



Figure 1.3. Branched alkyl benzenes versus linear alkyl benzenes.

Table 1.1. Composition of phenyldodecane isomers from the alkylation of benzene with 1-dodecene using HF or $AlCl_3$.¹²⁰

Isomer of phenyldodecane	% Composition from HF	% Composition from AlCl ₃
1-Phenyldodecane	0	0
2-Phenyldodecane	18	29
3-Phenyldodecane	16	19
4-Phenyldodecane	17	18
5-Phenyldodecane	24	18
6-Phenyldodecane	25	17

Truly linear alkyl benzenes, like 1-phenyldodecane in Table 1.1, cannot be produced by an acid-catalyzed mechanism. But, these 1-phenyl substituted alkenes could be valuable to the increased detersive power in low concentrations when compared to more branched alkyl arenes.¹²²

1.5 Transition Metal Catalyzed Production of Alkyl Arenes

Transition metal catalysts can be used to synthesize alkyl arenes through non-acid based mechanisms, and therefore offer potential advantages over current technologies. Such reactions feature two key steps: olefin insertion and C–H activation. A simplified catalytic cycle for the production of ethylbenzene from benzene and ethylene using a transition metal catalyst is shown in Scheme 1.24. The catalytic cycle proceeds through ethylene coordination, which is followed by olefin insertion in the M-Ph bond. Benzene then coordinates, is subsequently C–H activated, and ethylbenzene dissociates to regenerates the catalyst.¹²³⁻¹²⁶



Scheme 1.24. Catalytic cycle for the hydrophenylation of ethylene to yield ethylbenzene using a transition metal catalyst that operates through metal mediated olefin insertion and arene C–H activation. Unwanted side pathways highlighted by numbers.

This mechanism has potential advantages over acid-based catalysts described above.

- Using transition metal based catalysis, monoalkylated products can be produced selectively. While for the acid-based mechanisms the alkylated product is more reactive than benzene resulting in polyalkylation,¹²⁷ changing the mechanism to transition metal mediated C–H activation could remove this rate enhancement (see below).
- 2) When dialkylbenzenes are desired, transition metals could bias the *ortho:meta:para* selectivity toward generating *meta* products.¹²⁰ In contrast, Friedel-Crafts reactions favors the formation of *ortho-* and *para-* dialkylbenzenes.
- 3) Transition metal catalysis can enable the alkylation of electron-deficient arenes. In acid-based mechanisms the arene acts as a nucleophile,¹¹⁰ thus electron-deficient arenes are difficult to alkylate due to the decreased arene electron density.¹²⁷
- 4) Because the transition metal cycle does not involve a carbocation intermediate, straight-chain alkyl arenes can be produced from α -olefins. Acid-based mechanisms produce a carbocation which results in exclusive production of branched products.¹²⁸
- 5) An additional advantage of the transition metal catalyzed pathway is its ability to perform direct oxidative vinylation of arenes to produce vinyl or allyl arenes. Currently, alkyl benzenes must undergo a separate dehydrogenation step to produce vinyl arenes. For the production of styrene, over 95% of ethylbenzene is directly dehydrogenated.^{44,129} Transition metals in the presence of an oxidant can produce

vinyl arenes directly. This could allow for the direct generation of substrates which are difficult to synthesize such as anethole and estragole (Figure 1.4).¹³⁰



Figure 1.4. Anethole and estragole.

Despite the potential of transition metal catalysts for olefin hydroarylation, substantial challenges remain such as preventing unwanted side reactions. Scheme 1.24 shows a catalytic cycle with four likely side reactions: 1) olefin C–H activation, 2) β -hydride elimination, 3) olefin polymerization and 4) irreversible oxidative addition. Efficient activation of arene sp^2 C–H bond, while avoiding activation of olefin sp^2 C–H bonds is a challenge. Benzene and ethylene have BDEs of 112 kcal/mol and 111 kcal/mol, respectively.³⁹ Therefore the ΔG^{\ddagger} for benzene activation must be significantly less than the ΔG^{\ddagger} of ethylene activation or insertion. This was shown with our groups TpRu(L)(NCMe)(Ph) complexes (see Section 291.6.2); electron rich ligands increase the $\Delta\Delta G$ = for ethylene insertion versus benzene activation.¹³¹ Further, controlling β -hydride elimination from the phenylalkyl species is important. Depending upon desired product, catalysts can be designed to produce ethylbenzene or styrene. If ethylbenzene is desired then β -hydride elimination must be reversible and disfavored; as β -hydride elimination can result in the formation of a catalytically inactive hydride species. Moreover, if vinyl or allyl species are preferred, the catalyst must be able to regenerate the hydride species to the catalytically active species. Controlling this step can be achieved by modulating the electronics of the metal center through ligand design. Olefin polymerization can occur if the rate of olefin insertion is too rapid. This can generate polyethylene or can lead to M– Butyl ligands which retard catalysis. Moreover, irreversible oxidative addition of the arene can generate species containing two M–Ph bonds which can reductively eliminate biphenyl and/or generate species which are inactive for catalysis.

1.6 Transition Metal Complexes for Olefin Hydroarylation

1.6.1 Transition Metal C–H Activation: Acid-Catalyzed Mechanism

Tilley and coworkers have reported olefin hydroarylation using a platinum complex $[2-(2-pyridyl)indole]Pt(Cl)(C_2H_4)$.¹³² In conjunction with AgBF₄, the hydrophenylation of olefins including propylene, norbornene, and cyclohexene was observed (Scheme 1.25).¹³² However, the reaction of propylene or norbornene with benzene produced the branched, isopropyl benzene ~8 TOs, or *exo* species, *exo*-phenylnorbornane ~9 TOs, exclusively. Further, when no silver salt was added no reaction occurred. The reaction of toluene and cyclohexane gave an *ortho:meta:para* ratio of 31:6:63. This branched formation is typical of acid-based mechanism.



Scheme 1.25. Norbornene hydrophenylation with $[2-(2-pyridyl)indole]Pt(Cl)(C_2H_4)$ and AgBF₄ salt.

Tilley and coworkers later investigated the mechanism of Pt mediated hydrophenylation with cyclohexene using (COD)Pt(OTf)₂ and (tbpy)PtOTf₂ (tbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl).¹³³ An important point was that (COD)Pt(OTf)₂ with cyclohexene was observed to produce an equivalent of HOTF *in situ*. Catalysis with HOTF was discovered to undergo Friedel-Crafts based alkylation rather than explicit transition metal C–H activation (Scheme 1.26). Therefore the platinum metal center could not impact the regioselectivity of reaction.



Scheme 1.26. Generation of an equivalent of HOTf and a Pt allyl species from $(COD)Pt(OTf)_2$ species and cyclohexene (COD = 1,5-cyclooctadiene, OTf = trifluoromethanesulfonate).

1.6.2 Transition Metal Mediated Olefin Hydroarylation: Non-Acid-Based Mechanism

Periana, Matsumoto and coworkers reported catalytic hydrophenylation of olefins using a dinuclear Ir species, $[Ir(\mu\text{-}acac\text{-}O,O,C^3)\text{-}(acac\text{-}O,O)(acac\text{-}C^3)]_2$ (acac = acetylacetonato).¹³⁴ Catalytic reactions using $[Ir(\mu\text{-}acac\text{-}O,O,C^3)\text{-}(acac\text{-}O,O)(acac\text{-}C^3)]_2$ in benzene under 1.9 MPa of ethylene at 180 °C resulted in 50 TOs after 20 minutes and 455 TON after 3 hours. The apparent TOF is approximately equivalent using the TO after 20 min and 3 hours, $418 \times 10^{-4} \text{ s}^{-1}$ versus $421 \times 10^{-4} \text{ s}^{-1}$, respectively. The reaction of benzene and propylene gave 13 TOs of alkyl arene products after 20 minutes, significantly less than was observed for ethylene. The ratio of *n*-propylbenzene:cumene was 1.6:1. Using 1-hexene as the olefin produced 8 TON of 1-phenylhexane and 2phenylhexane in a 2.2:1 ratio. Importantly, the reaction using AlCl₃ showed 100% branched species, highlighting the difference between iridium and Friedel-Crafts catalysis. Further, the hydroarylation of ethylene with toluene produced *m*-ethyltoluene and *p*-ethyltoluene in a 63:37 ratio with no *o*-ethyl toluene observed (Scheme 1.27).



Scheme 1.27. $[Ir(\mu-acac-O,O,C_3)-(acac-O,O)(acac-C_3)]_2$ for the hydroarylation of ethylene with toluene shows selectivity for the para and meta species.

Experimental and computational studies were conducted to determine the active catalyst species. The active catalyst was proposed to be an mononuclear iridium species generated *in situ* from ethylene coordination and C–H activation,¹³⁵ which prompted the synthesis of the monomeric iridium (III) complex, of the form *trans*-[(acac)₂Ir(Ph)(L)] (L = H₂O, pyridine), which were found to be catalytically active (Figure 1.5). ^{136,137}



Figure 1.5. Catalytically active monomeric iridium species for the hydroarylation of olefins.

A proposed mechanism for this catalytic process is shown in Scheme 1.28. Olefin insertion into the Ir-Ph bond requires a *cis* configuration between olefin and aryl. The

trans-[(acac)₂Ir(Ph)(L)] (L = H₂O, pyridine) isomerizes under catalytic conditions to yield *cis*-[(acac)₂Ir(Ph)(L)] (L = H₂O, pyridine). Ethylene replaces the labile ligand and subsequently inserts into the Ir-Ph bond yielding an Ir-phenethyl fragment. Benzene coordinates and undergoes C–H activation to release ethylbenzene. Ethylene coordinates to regenerate the catalyst. Interestingly, the Ir-phenethyl species was shown to undergo reversible β-hydride elimination based on deuterium labelling studies.¹³⁷ However, only saturated alkyl arenes are produced under reaction conditions due to prohibitively high kinetics barriers from the hydride species. In contrast to our platinum systems, olefin insertion is the rate determining step for the iridium catalyst.¹²³⁻¹²⁵



Scheme 1.28. Catalytic olefin hydroarylation mechanism for trans- $[(acac)_2 Ir(Ph)(L)]$ (L = H₂O, pyridine).

Calculations suggested that a less electron-rich metal center would increase the rate of insertion,¹²⁴ κ^2 -0.0-1.1.1.5.5.5olefin therefore hfac-O.O (*B*-diketonate hexafluoroacetylacetonate) was attempted as a ligand. Although attempts to synthesize the Ir species were unsuccessful, the rhodium species, trans-(hfac-O,O)₂Rh(Ph)(py), was successfully synthesized (Figure 1.6).¹³⁸ Although this complex is active for C-H activation, which is evident from H/D exchange studies between C_6H_6 and toluene- d_8 , only stoichiometric olefin hydroarylation was observed. Other less electron donating species were investigated including trop (κ^2 -O,O-tropolonato) ligands. The complex *trans*-[(trop)₂Ir(Ph)(Py)] was synthesized and is catalytically active for the hydroarylation of olefins, albeit less effectively than the *trans*- $[(acac)_2 Ir(Ph)(L)]$ (L = H₂O, pyridine) system. At 200 °C, the hydroarylation of ethylene produced 27 TO of ethylbenzene after 30 minutes, while the hydroarylation of propylene gave 8 TO of propylbenzenes in a 61:30 L:B ratio. This is a similar rate and ratio to the $[(acac)_2 Ir(Ph)(Py)]$ species and therefore both species undergo similar mechanisms.



Figure 1.6. Monomeric catalyst species for attempted olefin hydroarylation with electron-deficient ligands.

Our group has published a series of Ru(II) complexes that catalyze the hydroarylation of olefins.^{126,131,139-148} The initial report showed olefin hydroarylation using TpRu(CO)(NCMe)Ph (Tp = hydridotris(pyrazolyl)borate). At 90 °C, benzene, 25 psi ethylene, and 0.1 mol % TpRu(CO)(NCMe)Ph gave 77 TO of ethylbenzene after 24

hours. The reaction of propylene and benzene yielded 10 TO of *n*-propylbenzene and cumene products in a 1.6:1 ratio. Interestingly, a nearly quantitative amount of *trans-\beta*-methylstyrene (based on Ru) was observed. Computational studies in conjunction with experimental results support the mechanism depicted in Scheme 1.29. The catalyst enters the catalytic cycle following the dissociation of acetonitrile and the coordination of ethylene. Ethylene then inserts into the Ru-Ph bond to give a phenethyl intermediate. A second equivalent of ethylene can reversibly coordinate to take the catalyst in an off-cycle step, or in a productive step, benzene can coordinate. Rate determining arene C–H activation followed by ethylene coordination and ethylbenzene dissociation regenerates the catalyst. Computational studies indicated that olefin insertion would be rate limiting.^{125,149} However, a KIE of 2.1(1) was found through competition experiments between C₆H₆ and C₆D₆, which suggests that benzene C–H activation is rate limiting.¹⁴⁵



Scheme 1.29. Mechanism for olefin hydroarylation by TpRu(CO)(NCMe)Ph.

The TpRu(L)(NCMe)Ph motif allows for structural modifications to gain a further understanding of structure and activity relationships. Figure 1.7 shows the possible adjustments to the catalyst. Importantly, the ligand L can be modulated to affect the steric and electronic properties.



Figure 1.7. Catalyst structural features for TpRu(L)(NCMe)Ph complexes.

The impact of the steric and electronic effects was investigated by modulating the L group in the series L = CO, PMe₃, P(*N*-pyrrolyl)₃, P(OCH₃)₂Et, and P(O)(OCH₂)₂CMe). The relative sterics was determined by using the Tolman cone angles for each phosphorus species,¹⁵⁰ while the variation in the electronics of the complex was analyzed by cyclic voltammetry using the Ru(III/II) potentials. The Ru(III/II) potentials give a measure of the electron density of the metal center; increased electron density decreases the potential whereas decreased electron density increases the potential. Table 1.2 compares the impact of the varying ligands, L, on the production of ethylbenzene.

Table 1.2. Comparison of various L groups for TpRu(L)(NCMe)Ph species and their effects on sterics, electronics, and catalytic activity for the hydroarylation of ethylene.^{131,150}

	L=	O □C		0 0 P-0		CH₃ H₃C╲│╱CH₃ ₽╱CH₃
N Ph Ru-NCMe	E _{1/2} (V)	1.03	0.82	0.69	0.54	0.29
	Cone Angle (^o)	95	145	108	101	118
н —	TON	415	0	90	20	0

We found that too much steric bulk hinders catalysis. For P(N-pyrrolyl)₃, with the largest cone angle of the ligands studied, produced no ethylbenzene because the steric bulk of the ligand was found to hinder ethylene coordination.¹⁴⁰ In general, increased electron density produced fewer TON of ethylbenzene. Moreover for all TpRu(L)(NCMe)Ph catalysts, another equivalent of ethylene was inserted and subsequently activated the olefinic C–H bond which decomposed to inactive TpRu(L)(η^3 -C₃H₄Me).

Because the less electron-rich catalysts, among TpRu(L)(NCMe)Ph, were found to give higher TON of ethylbenzene, $HC(pz^5)_3$ ($HC(pz^5)_3$ = tris(5-methyl-pyrazolyl)methane) was exchanged for Tp. This caused the catalyst to be cationic rather than neutral, which removed additional electron density, as evidenced by the Ru(III/II) of 1.06 $E_{1/2}$ (V). [$HC(pz^5)_3$)Ru(P(OCH₂)_3CEt)(NCMe)Ph][BAr¹⁴] is highly active for ethylene hydroarylation generating 565 TON of ethylbenzene with a 95% yield based on ethylene (Scheme 1.30).^{146,147} This is in contrast to TpRu(P(OCH₂)_3CEt)(NCMe)Ph which only produces 20 TO. Efforts to synthesize even less electron-rich Ru(II) centers using the $HC(pz^5)_3$ framework are underway including altering the L group to carbonyl or nitrosyl.



Scheme 1.30. Hydroarylation of ethylene with $[HC(pz_5)_3)Ru(P(OCH_2)_3CEt)(NCMe)Ph][BAr'_4].$

In 2008, Goldberg and coworkers reported the first Pt complexes for olefin hydroarylation involving transition metal C–H activation.¹⁵¹ The complexes, $[(dmpp)Pt(SMe_2)Ph]$ and $[(dmpp)PtMe_3]$ (dmpp = 3,5-dimethyl-2-(2-pyridyl)pyrrolide) (Figure 1.8), are capable of catalytic hydrophenylation of ethylene. The reaction of ethylene and benzene at 100 °C in the presence of $[(dmpp)Pt(SMe_2)Ph]$ or $[(dmpp)PtMe_3]$ gave 36 and 26 TON after 50h of ethylbenzene, respectively.



Figure 1.8. Platinum catalysts for the hydroarylation of unactivated substrates.

Utilizing propylene as the olefin gave a ratio of 15:85 *n*-propylbenzene:cumene using [(dmpp)PtMe₃] as catalyst. In addition, hydroarylation of propylene using toluene with [(dmpp)Pt(SMe₂)Ph] produced an *ortho:meta:para* ratio of 9:66:25 with 3 TON of 84:16 Icumene:*n*-propylbenzene substituted arenes. Acid-based mechanisms give predominately ortho and para selectivity due to the electrophilic aromatic substitution mechanism. Both of these reactions provide evidence against an acid-based mechanism due to the presence of some linear alkyl benzene (i.e. *n*-propylbenzene) and the formation of meta-substituted products for reaction with toluene. Scheme 1.31 provides a possible catalytic cycle using benzene and ethylene. The key steps involve ethylene insertion into the Pt-Ph bond with subsequent cyclometallation by oxidative addition of the phenylethyl fragment. Reductive elimination with concomitant benzene coordination is followed by benzene C–H activation. Finally, ethylene coordination regenerates the catalyst species and releases ethylbenzene.151



Scheme 1.31. Mechanism proposed for ethylene hydroarylation using Pt(dmmp).¹⁵¹ Goldberg and coworkers pursued further optimization studies of the reaction in an effort to optimize the conversion of arenes and substituted olefins to anit-Markovnikov products.¹⁵² By modulating the substituents on the bidentate nitrogen chelate, the ratio of anti-Markovnikov to Markovnikov or L:B products could be changed (Scheme 1.32). Removing the methyl ligands from the dmmp backbone enhanced the L:B ratio for propylene hydrophenylation to *n*-propylbenzene:cumene from 15:84 to 48:52. Interestingly, substituting the *ortho* position of the ligand's phenyl ring with a methyl group decreased the TON and L:B ratio but also generated 80% vinyl arenes. This provided proof of concept that ligand modification can modulate the L:B ratio of products from α -olefin hydroarylation.



Scheme 1.32. Effect of ligand substitutions on the TON and L:B ratio for Pt(dmmp) precatalysts for propylene hydrophenylation.

Our group has recently published a series of papers detailing ligand effects, substrate scope, and mechanistic details of Pt(II) catalysts for olefin hydroarylation.¹⁵³⁻¹⁵⁸ The first Pt catalyst reported is [('bpy)Pt(Ph)THF][BAr'₄] ('bpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine, Ar' = 3,5-bis(trifluoromethyl)phenyl). Using 0.1 mol % [('bpy)Pt(Ph)THF][BAr'₄] (relative to benzene) at 100 °C after 16 hours with ethylene (15 psi) gives 65.8 TO of ethylbenzene and 34.6 TO of diethylbenzenes. An inverse dependence of rate on ethylene pressure was observed. Extending the catalyst scope to the α -olefin propylene gave 33.5 TO of *n*-propylbenzene and cumene products with a L:B of 1:3. Mechanistic and computational studies elucidated that C–H activation is the rate determining step.¹⁵⁴ The studies suggested that the formation of dialkylbenzenes results from a second C–H activation that competes with ethylbenzene dissociation. Moreover, the rate of ethylbenzene formation is ~4.5 times than dialkylbenzenes.

The 2,2'-bipyridine ligand motif allows for modulation of the steric and electronic profiles of the catalyst; specifically, modulating the 4,4' substituents as well as the ring

chelate size (Figure 1.9). Varying the substituents in the 4,4' positions, we found that decreasing the electron density of the metal increases the production of styrene relative to ethylbenzene. The β -hydride elimination to form styrene also produces Pt-H which leads to catalyst decomposition. For instance, for $[(^{x}bpy)Pt(Ph)THF][BAr'_{4}]$ (where x = 4,4' substituents on the bpy ligand) when $X = NO_2$, the ratio of styrene to ethylbenzene is 10:1, while for X = OMe the ratio is 1:30.¹⁵⁷ By modulating 4,4' substituents on the bpy ligand, the L:B selectivity using propylene we found that the ratio of *n*-propylbenzene to cumene (L:B products) decreases with electron withdrawing ligands. For example, when $X = NO_2$, the L:B ratio decreases from 1:3 to 1:4.6 where $X = {}^{t}Bu.{}^{158}$ Moreover, by increasing the chelate size from 5- to 6-membered rings, the catalytic activity and longevity increased substantially. The [(dpm)Pt(Ph)(THF)]BAr'₄ (dpm = dipyridylmethane) complex achieves 469 TON after 110 hours.¹⁵⁶ The dpm ligand is a larger chelate ring size, compared to that of ^tbpy, providing an entropic advantage, which results in increased catalytic activity.



Figure1.9.Structure[(dpm)Pt(Ph)(THF)][BAr'_4].

1.7 Summary and Thesis Aims

The research presented in this dissertation is to probe transition metal catalysts for selective alkane and arene functionalization, with a primary focus on the development of rhodium catalysts for C–H activation. The successful catalyst for C–H activation will

then be studied for methane functionalization and the oxidative vinylation of benzene. Rhodium complexes were investigated because C–H activation can take place at Rh(I) or Rh(III).¹⁵⁹⁻¹⁶⁴ Further, air or oxygen regenerable oxidants, like copper(II) salts, have been shown to oxidize rhodium.^{165,166} In addition, the formation of Rh(s) is less likely relative to Pt(s).¹⁶⁷ Initial studies, by monitoring H/D exchange reactions, were focused on understanding the effect of bidentate nitrogen donor ligand systems on Rh(I) catalysts for efficient C–H activation. Mechanistic studies revealed that many standard organometallic complexes and transition metal salts are active for H/D exchange through electrophilic acid-catalyzed mechanisms. Concurrent experiments with the Rh(I) complexes found that styrene could be produced directly from ethylene, benzene, and copper(II) oxidants. The effect of varying substituents on the diimine ligands was examined as was the use of other nitrogen donor frameworks. Extending this unique reactivity to longer chain aolefins revealed that the catalysts achieved unprecedented linear to branched ratios of 10:1. Further, commercially available Rh(I) salts were found to be active for oxidative vinylation, however the carboxylate moiety appears to be required for efficient C-H activation. The reactivity of these complexes and salts were studied with a range of olefins. Further, electron-poor and electron-rich arenes were investigated.

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2 The Development and Study of Rh(I) Complexes for Arene C–H Activation

2.1 Introduction to Studies of Hydrogen/Deuterium

As discussed in Chapter 1, the C–H activation of hydrocarbons is an area of intense study in academic and industrial chemistry.¹ For example, the development of a catalyst to selectively and directly functionalize light alkanes would have wide-ranging implications. It would enable the use of prevalent hydrocarbon feedstocks and revolutionize the natural gas and petrochemical industries, fine chemical production and the commodity chemical sector.²⁻⁶

In order to develop an efficient catalyst for this hydrocarbon functionalization, the mechanism of C–H bond activation must be studied in detail. R–H activation by a transition metal species often proceeds through formation of an M–R species. This M–R bond can then be protonated to release the hydrocarbon. Thus, if an R–H bond is activated and the M–R species is protonated by deuterium, the conversion of R–H and DX to give R–D and HX provides a method to monitor C–H activation Hydrogen/deuterium (H/D) exchange reactions are commonly used in organometallic chemistry to gather evidence regarding bond activation and to elucidate mechanistic details by monitoring the exchange of an isotopically labelled species with non-labelled substrates.⁷⁻⁹ This method is particularly prevalent in the field of hydrocarbon functionalization due to the particular significance of the C–H(D) bond breaking step.¹⁰⁻¹⁴ In addition, this technique is widely prevalent in the pharmaceutical industry.¹⁵

Due to the relative difficulty of working with light alkanes at high pressures and temperatures, academic groups have largely focused on developing catalysts for the activation of benzene C–H bonds as a model for methane. The C–H bond dissociation energy (BDE) of benzene is greater than that of methane (113 kcal/mol and 104 kcal/mol, respectively). Unlike light alkanes, specialized equipment is not necessary as benzene is a liquid at room temperature. Product analysis is also facile via ¹H NMR spectroscopy or GC-MS without the need for high pressure NMR tubes or gas tight syringes. Indeed a simple Excel® program was developed to deconvolute the mass fragmentation patterns of benzene and deuterated benzenes ($C_6H_{6-n}D_n n = 0 - 6$) from GC-MS data.¹⁶

However, using benzene as a model for methane is not universally suitable as there are significant differences in the binding modes between alkanes and arenes with metal centers. Alkanes are poor ligands and often coordinate to a metal center through an η^2 -C,H σ -complex, whereas arenes can coordinate through π electrons and form relatively stable η^2 arene species.

Fundamental studies of C–H activation have revealed an interesting observation. Oxidative addition reactions of hydrocarbons with transition metals are sometimes kinetically selective for stronger C–H bonds. Bergman discovered that activation of *n*-alkanes with Cp*Ir(PMe₃)H₂ preferentially activated the primary versus secondary position.¹⁷ This is partially due to the larger difference in bond energy between C_{primary}–H and M_{primary}–C than C_{secondary}–H and M_{secondary}–C.¹⁸ Further, Jones and coworkers compared the oxidative addition of hydrocarbons to (C₅Me₅)Rh(PMe₃).^{18,19} These results estimated that (C₅Me₅)Rh(PMe₃)(C₆H₅)H is 16-17 kcal/mol more stable than (C₅Me₅)Rh(PMe₃)(CH₂CH₂CH₃)H. Jones and coworkers further only observed primary activation of propane not secondary.¹⁸ Therefore, the propensity toward C–H activation

can depend on the strength of the incipient M–R bond that is formed. In addition, a weak incipient M–R bond may increase the energy of the transition state and therefore the activation barrier. Further, if the M-R bond is sufficiently weak and the reaction is highly endothermic, C–H activation may not be observed. The simpler experimental methods, different binding mode, and formation of more stable species are some reasons why the transition metal activation of benzene is substantially more prevalent than alkanes.

Although transition metal mediated C–H activation can be identified with H/D exchange, strong acids are also capable of arene H/D exchange.²⁰ Notably, nitric and sulfuric acids are capable of protonating benzene directly through electrophilic aromatic substitution.^{20,21} Although trifluoroacetic acid is much weaker, it has also been shown to protonate benzene, albeit very slowly.²² Meanwhile, superacids, such as "magic acid" (SO₃H·SbF₅) and trifluoromethanesulfonic acid (HOTf), have been shown to protonate light alkanes directly, a much more challenging task.^{23,24}

2.2 Examples of Arene Activation with Palladium and Platinum

Electrophilic catalysts can break hydrocarbon bonds by coordinating the C–H bond and releasing H⁺, as shown in Chapter 1. However, weakly basic solvents can inhibit C–H bond activation because the solvent can bind to the electrophilic catalyst. Therefore the general concept was to use a strongly acidic solvent such as oleum or concentrated sulfuric acid. This strategy enabled C–H functionalization catalysis with $Pt(bpym)(Cl)_2$ but also Pd, Hg, and Au.²⁵⁻²⁸ However, the challenge with this strategy is that non-superacidic media dramatically retards or stops C–H activation.

Due to the historical success of utilizing platinum and palladium species in hydrocarbon C–H activation (see Chapter 1), a large number of Pt and Pd complexes have been investigated for H/D exchange of hydrocarbons and acids. Building off the success of the Pt(bpym)(Cl)₂ catalyst of methane functionalization,²⁹ the Periana group investigated a tridentate monoanionic donor ligand, κ^3 -6-phenyl-4,4'-di-*tert*-butyl-2,2'bipyridine (NNC).¹⁶ One problem with the Pt(bpym)(Cl)₂ catalyst is that the reactivity is hindered by non-superacidic media. The Pt(NNC)TFA complex was designed to increase the electron density at the metal center, in order to reduce the electrophilicity of the metal and, hence, to enhance tolerance of less acidic solvents.



Figure 2.1. Pt(bpym)(TFA)₂ and Pt(NNC)TFA (bpym = 2,2'-bipyrimidine, TFA= trifluoroacetate, NNC = κ^3 -6-phenyl-4,4'-di-*tert*-butyl-2,2'-bipyridine) complexes for hydrocarbon activation.¹⁶

The reaction of Pt(bpym)(TFA)₂ or Pt(NNC)TFA in DTFA with CH₄ produced no H/D exchange products (CH₃D, CH₂D₂, etc.). Interestingly, changing the solvent to D₂SO₄ did produce deuterated methane isotopologues. After 10 hours at 180 °C with 500 psi CH₄, Pt(NNC)TFA achieved 61.7 turnovers (TO) of methane H/D exchange with approximately 14% of the methane converted to deuterated analogs (CH₃D 5.39%, CH₂D₂ 2.53%, CHD₃ 2.3%, CD₄ 4.2%). Although H/D exchange was achieved, less than 2 TO of methylbisulfate, the desired methane functionalized product, were observed. Importantly, D₂SO₄ in the absence of a Pt catalyst was found to achieve H/D exchange of

methane, although at a slower rate. In order to elucidate the C–H activation pathway for Pt(NNC)TFA, the complex was studied for benzene C–H activation. At 180 °C with a 1:4 ratio of benzene:DTFA, 14.7 TO of C_6H_5D were observed after 30 minutes. The Pt(NNC)TFA complex is not a better catalyst for methane functionalization than Pt(bpym)(Cl)₂.¹⁶

Sanford and coworkers also designed ligand sets based on the bpym motif.³⁰ The ligands were designed to withdraw electron density from the metal center, in a similar manner to the bpym ligand, when operating in acidic media. To achieve this effect the ligand, $2,2^{"},4,4^{"},6,6^{"}$ -hexaphenyl-[1,4':2',2":4",1"'-quaterpyridine]-1,1"'-diium *bis*-tetrafluoroborate, incorporated positively charged quartenized nitrogens (Scheme 2.1). This ligand coordinated to Pt and Pd, with the *in situ* addition of AgBF₄, initiates H/D exchange between benzene and acetic acid – d_4 . The Pt and Pd complexes achieve TOF of 0.1 s⁻¹ and 0.05 s⁻¹, respectively. The Pd ligated species was also tested for benzene functionalization. By combining benzene, the ligand and Pd(OAc)₂, using PhI(OAc)₂ as the oxidant, in acetic acid, produces 35 TO of PhOAc which is a 70% yield based on oxidant.



Scheme 2.1. Cationic pyridinium ligands coordinated to Pt and Pd. These catalysts are active for H/D exchange between benzene and CD_3O_2D as well as for benzene functionalization with PhI(OAc)₂.³⁰

Sanford and coworkers also designed a catalyst screening system to determine the efficacy of a broad range of catalysts for the H/D exchange of benzene with deuterated trifluoroacetic acid, acetic acid, and trifluoroethanol.³¹ The study focused on bidentate nitrogen donor ligands coordinated to platinum to give catalyst precursors of the type $(N_2)PtCl_2$ (N_2 = diazobutadienes (DABs), bipyridines, bipyrimidine). The study found that under the conditions (2 mol % Pt relative to benzene, with 2 equivalents of AgOAc to Pt, with 25 equiv TFA- d_1 or CD₃O₂D to benzene at 150 °C for 24 h) an electron-deficient diimine ligand, ^{2,6-Cl}DAB = *N*,*N*-bis-2,6-(dichlorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene, produced the most active catalyst for the H/D exchange between TFA- d_1 or CD₃O₂D and benzene (Scheme 2.2). Key to this system is the use of silver salts to remove coordinated chloride *in situ*, which generates an open coordination site. However, a small background reaction was observed with silver salts in trifluoroacetic acid. An investigation into the H/D exchange of arenes with trifluoroacetic and acetic acid by salts is shown in Chapter 3.



Scheme 2.2. Pt catalyzed H/D exchange with silver(I) acetate for *in situ* halide abstraction.

2.3 Rhodium Complexes for Arene C–H Activation

To overcome the issue of product or solvent inhibition of catalysis, our group sought to develop catalysts with earlier transition metals (i.e. earlier than group 10). By using earlier, less electronegative transition metal centers, the propensity toward Lewis base coordination should be minimized. By improving the tolerance to Lewis bases, the catalytic C–H activation and functionalization could, in principle, be performed using less acidic media. While earlier transition metals have been shown to activate C–H bonds,^{11,32-38} most of these reactions are in the absence of oxidants, such as chemical oxidants or acidic solvent. A concern with earlier metals is the propensity toward coxidation of the metal to a state that is incapable of C–H activation (Scheme 2.3).^{12,32,39-48}

$$\begin{bmatrix} active \\ for C-H \\ activation \end{bmatrix} M^{n} \cdot X \xrightarrow{HX} \begin{bmatrix} H \\ M^{n+2} \cdot X \\ X \end{bmatrix} \xrightarrow{inactive \\ for C-H \\ activation \end{bmatrix}$$

Scheme 2.3. Oxidation of the metal center in acidic media could lead to complex that is inactive for C–H activation.

Rhodium catalysts are attractive targets because C–H activation can potentially take place at Rh^{I49-52} or Rh^{III33,38} centers. In addition, air recyclable oxidants such as Cu^{II} salts have been shown to be oxidize Rh^{I,53-55} which enables the development of catalysts

that use air or oxygen as the terminal oxidant. Since oxygen or air can reoxidize, in the presence of acid, Cu° or Cu^{I} to Cu^{II} and H_2O , the net oxidation reaction converts $\frac{1}{2}$ oxygen to water (Scheme 2.4).

 Cu^{0} + 2 HOAc + 1/2 O_{2} \longrightarrow $Cu(OAc)_{2}$ + H₂O Scheme 2.4. Oxidation of Cu^{0} to Cu^{II} by oxygen and acetic acid.

Several rhodium species have been shown to activate C–H bonds of hydrocarbons. A PNP (PNP = 2,6-bis[(di-*tert*-butylphosphino)methyl]pyridine)) ligated rhodium catalyst achieved H/D exchange between D₂O and benzene at 100 °C with a TOF of 2.8 x 10⁻⁵ s⁻¹.^{56,57} [Rh(bdmpza)Cl₃]⁻Na⁺ (bdmpza = bis(3,5- dimethylpyrazol-1-yl) acetate) was combined with silver triflate to generate an active catalyst for H/D exchange between benzene and TFA- d_1 at 100 °C, where a TON of 119 was observed.³³

A comparison of selected Rh, Pd, and Pt catalysts for the H/D exchange between benzene and D₂O/TFA- d_1 /AcOD is provided in Table 2.1. The most active catalysts are Pd and Pt species with electron deficient bidentate nitrogen chelates. Pt^{(2,6dichloro-}DAB)Cl₂ and 2 equivalents of AgOAc is the most active catalyst for H/D exchange between benzene and AcOD which produces a TOF of 0.2 s⁻¹. In contrast the most active Rh species is two orders of magnitude slower with a TOF 1.0×10^{-3} s⁻¹. Importantly, most of the complexes use silver salt additives to generate the active catalyst species.

Table 2.1. Comparison of selected catalysts for H/D exchange in protic solvents.

Entry	/ Catalyst	Additive	Solvent	Temp	TOF
	-			(°C)	(s^{-1})
1	Rh(PNP)Me ^{56a}		D_2O	100	2.8×10^{-5}
2	Rh(pyridinium)Cl ₃ ³⁸	AgOAc	AcOD	150	4.8×10^{-4}
3	Rh(bdmpza)Cl ₃ ^{33b}	AgOTf	$TFA-d_1$	100	1.0×10 ⁻³
4	Pd(pyridinium)Cl ₂ ³⁰	AgBF ₄	AcOD	150	5×10 ⁻²

5	$Pt(^{2,6-Cl}DAB)^{31c}$	AgOAc	TFA- d_1	150	5×10 ⁻²
6	Pt(pyridinium)Cl ₂ ³⁰	AgBF ₄	AcOD	150	1×10 ⁻¹
7	Pt ^{(2,6dichloro-} DAB) ^{31c}	AgOAc	AcOD	150	2×10 ⁻¹

^{*a*} (PNP = 2,6-bis[(di-tertbutylphosphino)methyl]pyridine). ^{*b*} (bdmpza = bis(3,5-dimethylpyrazol-1-yl)acetate, OTf = triflate). ^{*c*} ($^{2,6-Cl}DAB = N,N$ -bis-2,6-(dichlorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene)

The goal of this project is to develop rhodium catalysts that display a similar rate of H/D exchange catalysis between arenes and TFA- d_1 as the Pd and Pt species in Table 2.1. Taking inspiration from the most active Pt complex, Pt^{(2,6dichloro-}DAB), we sought to develop rhodium catalysts that incorporate similar electron-deficient bidentate nitrogen ligands. In addition, we wanted to avoid the use of additives for catalysis due to the noted background reactions. Therefore, we attempted to incorporate the conjugate base, trifluoroacetate, of the acid and solvent utilized, trifluoroacetic acid, which should minimize the anion's influence on catalysis. Our basic structural motif is shown in Figure





Figure 2.2. Structural motif of the desired rhodium catalysts.

2.4 Results and Discussion

2.4.1 Synthesis and H/D exchange between benzene and TFA- d_1 by Rhodium Catalysts We compared the efficacy of two ligands coordinated to $[Rh(\mu-TFA)(\eta^2-COE)_2]_2$

(COE = cyclooctene), ^{Fl}DAB (*N*,*N*-bis-(pentafluorophenyl)-2,3-dimethyl-1,4-diaza-1,3-

butadiene) and BOZO (bis(2-oxazolin-2-yl)). The ^{FI}DAB ligand was chosen due to electron-withdrawing perfluorphenyl groups and the ease with which steric and electronic modifications can be made. The BOZO ligand was selected due to its possible propensity to protonate the oxygen atoms in acidic media; in a manner similar to protonation of the bipyrimidine nitrogens in the Pt(bpym)(Cl)₂ catalyst.⁵⁸ This protonation would withdraw electron density making the metal center more electrophilic. The complexes (^{FI}DAB)Rh(η^2 -COE)(TFA) (**2.1**) and (BOZO)Rh(η^2 -COE)(TFA) (**2.2**) were synthesized by combining [Rh(μ -TFA)(η^2 -COE)₂]₂ in THF with two equivalents of ligand at room temperature (Scheme 2.5).¹³ Upon the addition of the ligand, the yellow-brown solutions became purple instantly. After evaporating the THF and washing with pentane which removes free COE, the complexes were isolated as purple solids in 58% (**2.1**) and 78% (**2.2**) yield overall.



Scheme 2.5. Synthesis of $(^{Fl}DAB)Rh(\eta^2 - COE)(\mu TFA)$ (2.1) and $(BOZO)Rh(\eta^2 - COE)(\mu - TFA)$ (2.2) catalysts.



Figure 2.3. ¹H NMR spectrum of (^{FI}DAB)Rh(μ -TFA) in THF- d_8 . After extensive drying to remove cyclooctene. * represent residual THF.



Figure 2.4. ¹³C NMR spectrum of (^{FI}DAB)Rh(μ -TFA) in DMF- d_7 . After extensive drying to remove cyclooctene. * represent residual DMF.





Figure 2.6. ¹H NMR spectrum of (BOZO)Rh(η^2 -COE)(μ -TFA) in C₆D₆. * represent residual C₆H₆.



Figure 2.7. ¹³C NMR spectrum of (BOZO)Rh(η^2 -COE)(μ -TFA) in THF- d_8 . * represent residual THF.

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Figure 2.8. ¹⁹F NMR spectrum of (BOZO)Rh(η^2 -COE)(μ -TFA) in C₆D₆.

The initial screening for H/D exchange using TFA- d_1 and C₆H₆ was successful (Scheme 2.6). After 2 hours at 130 °C with 1.6 mol % Rh in benzene with 17.5 equivalents of TFA- d_1 relative to benzene, 82(8) and 91(11) TO were observed for **2.1**

and 2.2, respectively. To determine the TO, 1 μ L of reaction mixture is analyzed by GC-MS and the fragmentation pattern of the benzene peak is deconvoluted. Standard deviations of three independent experiments are given in parenthesis. The control reaction with [Rh(μ -TFA)(η^2 -COE)₂]₂ produced minimal (<10) TO under the same conditions.



Scheme 2.6. Screening conditions for H/D exchange between benzene with TFA-d₁ using catalysts 2.1 and 2.2.

The effect of temperature on catalysis was subsequently investigated; revealing that the highest TOs for **2.1** are obtained at 150 °C whereas **2.2** gives the highest TO at 130 °C and 150 °C (Figure 2.9). Both catalysts exhibit decreased TO at lower temperatures. However, the catalysts are also produce less TO at temperatures greater than 150 °C, which is most likely due to catalyst decomposition. In addition, the decreased TO at higher temperatures for **2.2** versus **2.1** is suggestive of improved thermal catalytic stability for the diazabutadiene (DAB) ligand when compared to the bisoxazoline (BOZO) ligand. Additionally, as temperature is increased, the background reaction of C_6H_6 with TFA- d_1 is enhanced dramatically. In the absence of Rh catalyst, H/D exchange between C_6H_6 with TFA- d_1 produced <10 TO at 150 °C versus 90(10) TO of at 180 °C.



Figure 2.9. Effect of temperature on the TOs of H/D exchange between benzene and TFA- d_1 with **2.1** and **2.2**. Reaction conditions: 1.6 mol % Rh in C₆H₆ with 17.5 equivalents of TFA- d_1 after 2 hours. Background reactions have been removed from the TO.

Following the optimization of the reaction temperature, the effect of catalyst concentration on H/D exchange was studied. Halving the concentration of **2.1**, from 1.6% to 0.8%, using the optimal temperature (150 °C) gave a two-fold increase in TOs (Figure 2.10). Decreasing the catalyst loading of **2.1** further to 0.4 mol % resulted in an increased 456(3) TOs and a TOF of 0.06 s⁻¹. Because decreasing the catalyst loading led to an increase in TOs, it is possible that **2.1** may undergo a binuclear decomposition pathway. A binuclear decomposition occurs when two catalysis species combine and subsequently deactivate, thus increased catalyst concentration would increase the likelihood of deactivation. Therefore, fewer TOs would be expected at higher catalyst concentrations. Consequently at lower catalyst concentrations more TOs could potentially be observed.



Figure 2.10 Effect of catalyst (^{FI}DAB)Rh(COE)(TFA) (**2.1**) concentration on TO of benzene H/D exchange. Reaction conditions: 1.6, 0.8 or 0.4 mol % Rh in C_6H_6 with 17.5 equivalents of TFA- d_1 relative to benzene at 150 °C for 2 hours.

We explored the possibility of recycling complex **2.1**. In order to study recyclability, glass walled pressure tubes, with a volume of 20 mL, were necessary. This is required to allow for evaporation of volatiles and addition of new solvent in the same reactor. Utilizing 0.4 mol % of complex **2.1**, the tubes were placed in an oil bath at 150 °C. After 24 hours, the tubes were cooled to room temperature, brought into the glovebox as to not poison the catalyst with oxygen, sampled and analyzed. The volatiles were then removed *in vacuo* and fresh TFA- d_1 and benzene were added, and the experiment was repeated. Complex **2.1** was successfully recycled 3 times (Figure 2.11).



Figure 2.11. Successful recycling trials of catalyst (^{FI}DAB)Rh(COE)(TFA) (**2.1**) with TOs after 24 hours. Reaction conditions: 0.4 mol % Rh in C_6H_6 with 17.5 equivalents of TFA- d_1 per benzene at 150 °C after 24 hours.

2.4.2 Effect of Cyclooctene on Catalysis

Since cyclooctene is bound to the rhodium center, the influence of cyclooctene on the H/D exchange between C_6H_6 with TFA- d_1 was probed. Additional cyclooctene decreased TOs for complex **2.2**. Under the following conditions (1.6 mol % **2.2** in C_6H_6 with 17.5 equivalents of TFA- d_1 relative to C_6H_6 , 2 hours, 130 °C), the addition of one equivalent of cyclooctene relative to **2.2** decreased TOs from 91 to 32. Catalyst inhibition, because of the increased cyclooctene concentration, could be due to COE preventing the coordination of benzene to the rhodium center.

Because cyclooctene was shown by Winemiller in 1984 to add trifluoroacetic acid across the olefin double bond to form cyclooctyl trifluoroacetate,⁶⁰ further investigation into the fate of cyclooctene was warranted. Thus, complex **2.2** in HTFA was monitored over time by ¹³C NMR spectroscopy. In order to lock and shim the NMR, a sealed D_2O

insert was added to the NMR tube. Figure 2.12 shows the comparison between free cyclooctene in HTFA to complex **2.2** in HTFA by ¹³C NMR spectroscopy. Cyclooctyl trifluoroacetate forms immediately at room temperature (bottom spectrum, Figure 2.12), and production increases over time. As the concentration of cyclooctene increases, cyclooctene may coordinate to the metal center inhibiting catalysis, before producing cyclooctyl trifluoroacetate and the active catalyst. Therefore the presumed active catalysts are (^{FI}DAB)Rh(HTFA)(TFA) or (BOZO)Rh(HTFA)(TFA) (Scheme 2.7).



Figure 2.12. Comparison of cyclooctene versus with complex (BOZO)Rh(COE)(TFA) (2.2) in HTFA by 13 C NMR spectroscopy. The bottom spectrum is complex 2.2 after immediately following dissolution in HTFA. Spectra 2 and 3 are after 40 minutes or 2 hours of reaction, respectively. The top spectrum is cyclooctene in HTFA.



Scheme 2.7. Generation of the presumed active catalysts after cyclooctyl trifluoroacetate formation.

2.4.3 Computational Study of H/D Exchange by Catalysts 2.1 and 2.2

With our computational collaborators at the California Institute of Technology, Professor Goddard's group, the mechanism of H/D exchange was explored using DFT calculations at the M06 level of theory. The reference complexes for the calculations are (^{FI}DAB)Rh(HTFA)(TFA) and (BOZO)Rh(HTFA)(TFA), the presumed species after cyclooctyl formation. In the initial report, the lowest energy pathways were calculated to oxidative addition and intramolecular electrophilic substitution.¹³ Scheme 2.8 shows the calculated reaction pathways for both oxidative addition and intramolecular electrophilic substitution.



Scheme 2.8. Comparison of C–H activation pathways for benzene by $(^{Fl}DAB)Rh(TFA)(TFAH)$. The top shows the oxidative addition of benzene to $(^{Fl}DAB)Rh(TFA)(TFAH)$ followed by internal protonation. The bottom shows intramolecular electrophilic substitution. Values are given in kcal mol⁻¹.

The calculations found that both oxidative addition and intramolecular electrophilic substitution are plausible. Interestingly, the replacement of HTFA with benzene is calculated to be energetically favorable by 1.3/2.2 kcal/mol at 298/498 K (Scheme 2.8). The free energy of the lowest transition state for oxidative addition is 20.9/21.5 kcal/mol at 298/498K, which is followed by internal protonation with a transition state free energy of 32.4/29.9 kcal/mol at 298/498K. Whereas, as shown on the bottom of Scheme 2.8, intramolecular electrophilic substitution has a slightly lower transition state barrier of 32.6/28.7 kcal/mol at 298/498K. While these results seemed

plausible at the time of publication, results from addition studies (see below) point to a different pathway for the H/D exchange catalyzed by these rhodium species.

2.4.4 Ligand Screening for H/D Exchange: Modulating the Steric and Electronic Effects

As previously shown, (^{FI}DAB)Rh(COE)(TFA), (**2.1**), was found to be an active catalyst for H/D exchange between benzene and TFA-*d*. The nature of the synthesis of the DAB ligands enables relatively facile modifications to the steric and electronic properties. As a variety of substituted anilines are readily available, a variety of ligands can be synthesized (Scheme 2.9). Although this synthetic pathway was effective for many DAB ligands, the syntheses of those containing nitro groups required the use of more forcing conditions, including the use of stronger acids and a Soxhlet extraction (Scheme 2.10).



Scheme 2.9. General synthesis of DAB ligand variants. R = alkyl group, X = nitro or fluorine.



Scheme 2.10. General synthesis of 4-NO₂-2,6-diisopropylDAB.

A range of DAB proligands were synthesized to study a broad range of steric and electronic effects (Scheme 2.11).¹⁴ The impact of the quantity and position of fluorine substituents was also evaluated.



Scheme 2.11. Proligands that were synthesized to evaluate the impact of electron donation, steric profile, and fluorine substituents on Rh(I) catalyst precusors (iPr = isopropyl). On the bottom is shown the general synthesis of *in situ* generated catalyst precursors from the coordination of DAB ligands with $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$. When the numbers 2.3 – 2.13 are used in this chapter they refer to the proligands complexed rhodium species as shown in on the bottom.

It was discovered that the DABs could be coordinated to rhodium *in situ* and used for catalysis directly. This is advantageous because the olefin was found to be a labile

ligand; under vacuum or nitrogen purging, the olefin often dissociates complicating isolation of Rh(DAB)(TFA)(η^2 -C₂H₄) catalyst precursors. Jones and coworkers also discovered this complication with isolating Rh(I) olefin complexes.⁶¹ Therefore in this chapter, complexes **2.3-2.13** refers to the ligands shown coordinated to rhodium as in in Scheme 2.11.

The catalyst screening conditions utilized were 0.05 mol % Rh relative to benzene and 20 equivalents of TFA- d_1 relative to benzene for 4 hours at 120 °C, 150 °C or 180 °C (Scheme 2.12). Background reactions in the absence of Rh catalyst produced the equivalent of 7(1), 15(4) and 96(9) TO of H/D exchange at 120 °C, 150 °C and 180 °C, respectively. Accordingly, these background reactions have been subtracted to obtain the reported catalytic TOs.

Scheme 2.12. Conditions for H/D exchange with $(DAB)Rh(TFA)(C_2H_4)$ complexes.

The results of the catalyst screening are shown in Figure 2.13 for the catalytic H/D exchange between benzene and TFA- d_1 . Complexes **2.4-2.6** and **2.8** showed minimal activity for all temperatures studied. It was found that 150 °C was the optimal temperature for all active catalysts (**2.3**, **2.7**, **2.9-2.13**). While these catalysts are also catalytically active at 120 °C, at 180 °C, several (**2.3**, **2.10**, and **2.12**) are inactive. This is presumably due to catalyst deactivation at higher temperatures.



Figure 2.13. The TO of H/D exchange for the reaction of benzene with TFA- d_1 using catalysts **2.3-2.13.** Conditions: 0.05 mol % Rh relative to benzene with 20 equivalents of TFA- d_1 relative to benzene after 4 hours at 120 °C, 150 °C, or 180 °C.

These data indicate that coordination of electron-withdrawing ligands provides more efficient catalysts. The apparent TOF for each complex at each temperature is reported in Table 2.2. Complex 2.13, (^{FI}DAB)Rh(TFA)(C_2H_4), is the most efficient catalyst precursor with 140(14) TO at 150 °C, which corresponds to an apparent TOF of 9.7(9) x 10⁻³ s⁻¹. The complex with phenyl substituent on the DAB ligands, 2.3, is approximately 5 times less effective, 25(7) TO, relative to the pentafluorophenyl DAB, 2.13. The complexes with varying number and positioning of fluorine substituents, 2.10-2.12, show intermediate catalytic activity relative to 2.3 and 2.13. Interestingly, the position of the fluorine atoms does not make a significant difference to catalysis. Complexes 2.11 and 2.12, with 2,4- versus 2,6-difluoro substituents, gave statistically identical TO for H/D exchange at 150 °C. This is in contrast to Sanford and coworkers results with Pt catalysts, in which halogens at the 2,6-positions were found to increase H/D exchange dramatically.³¹ The impact of electron-withdrawing groups on the DAB ligands is particularly evident through the comparison of complexes 2.4 (3.5-methyl substituents) and 2.7 (3,5-trifluoromethyl substituents), since the steric profiles of the substituents, CH₃ and CF₃, respectively, are similar whereas the electronic profile is different. Complex 2.4 reveals no catalytic activity while 2.7 shows 55(2) TO after 4 hours at 150 °C. In addition, installing a nitro group in the 4-position, 2.9, greatly enhances catalysis by producing 82(2) TO at 150 °C. Further, the negative impact of alkyl substituents is demonstrated by complexes, 2.4 (3,5-methyl substituents), 2.5 (2,4,6methyl substituents), 2.6 (2,6-isopropyl substituents), and 2.8 (4-nitro-2,6-isopropyl substituents), and were found to be inactive. The electron donation of the alkyl groups may make the rhodium center insufficiently electrophilic preventing C–H(D) activation. An interesting comparison comes from 2.6 and 2.8, as both species contain isopropyl groups in the 2,6-positions while **2.8** also contains an electron-withdrawing nitro group in the 4-position. However, neither species reveals TO for H/D exchange above background reactivity. The nitro group removes enough electron density to achieve catalysis, as evidenced by 2.9; however, complex 2.8 still is not an effective catalyst precursor. This provides evidence that the steric bulk of the isopropyl groups might inhibit coordination of trifluoroacetic acid or benzene (see below).

Catalyst Precursors	120 °C (s ⁻¹)	150 °C (s ⁻¹)	180 °C (s ⁻¹)
2.3	6(3) x 10 ⁻⁴	1.7(9) x 10 ⁻³	0
2.4	0	0	0
2.5	0	0	0
2.6	0	0	0
2.7	2.5(2) x 10 ⁻³	3.8(2) x 10 ⁻³	1.8(8) x 10 ⁻³
2.8	0	0	0
2.9	2.3(1) x 10 ⁻³	5.7(2) x 10^{-3}	3.3(7) x 10 ⁻³
2.10	$1.3(5) \ge 10^{-3}$	4(1) x 10 ⁻³	0
2.11	1.5(7) x 10 ⁻³	2.9(6) x 10 ⁻³	1.6(8) x 10 ⁻³
2.12	2(1) x 10 ⁻³	3(1) x 10 ⁻³	0
2.13	5(2) x 10 ⁻³	9(2) x10 ⁻³	5.2(7) x 10 ⁻³

Table 2.2. Apparent TOFs at various temperatures after 4 hours using 0.05 mol % Rh relative to benzene with 20 equivalents of TFA- d_1 relative to benzene at 120 °C, 150 °C, or 180 °C. Background reactivity of 7, 15 and 96 TO of H/D exchange at 120 °C, 150 °C and 180 °C, respectively, has been subtracted.

Three rationalizations for the increased catalytic activity of electron-withdrawing ligands are proposed. 1) The active catalyst species is in the Rh(I) oxidation state and electron-withdrawing ligands stabilize this species in the oxidizing solvent, HTFA. In contrast the electron-donating ligands would increase the likelihood of oxidation to an inactive Rh(III) species. 2) Less electron-rich metal centers undergo C–H activation through an electrophilic substitution mechanism that is enhanced by further decreasing the electron density at the metal center. 3) The H/D exchange reaction occurs through an electrophilic substitution mechanism, which is impacted by the increase in

acidity resulting from the use of electron-deficient rhodium species. We found no evidence for the oxidation of any of the Rh(I) species to Rh(III) in HTFA, specifically no color change was observed as would be expected if the oxidation occurred.

2.4.5 Extension of H/D exchange catalysis to other hydrocarbon substrates and deuterated acids

H/D exchange catalysis between sp³ hybridized C–H bonds and TFA- d_1 , with the most effective catalyst precursors **2.9** and **2.13**, was attempted. 100 psig of methane was added to the reactors with 0.05 mol % Rh relative to TFA- d_1 at 120 °C, 150 °C, or 180 °C. After 4 hours, 5 µL of reactor headspace was analyzed by GC-MS. Unfortunately, H/D exchange was not observed, as there were no isotopologues of methane (outside of the natural abundance) according to the GC-MS data. The same conditions that were successfully utilized for benzene were pursued for cyclohexane, 0.05 mol % Rh relative to cyclohexane at 120 °C, 150 °C, or 180 °C. However, no H/D exchange above background reactivity was observed with either catalyst.

To help elucidate mechanistic details, toluene was selected as the substrate. Organometallic catalysts for toluene C–H activation, that proceed through formation of an M–Ar bond, often favor *meta* and *para* activation, in contrast to, electrophilic aromatic substitution mechanisms with toluene which favor *ortho* and *para* positions; thus H/D exchange with toluene can be used to differentiate these pathways.^{34,62,63} The catalyzed H/D exchange between toluene- d_8 and HTFA was evaluated with complexes 2.3-2.13 (Scheme 2.13). The regioselectivity of the catalytic reaction was determined via ¹H NMR spectroscopy.



Scheme 2.13. The H/D exchange between toluene- d_8 with HTFA catalyzed by Rh complexes.

Catalyst precursors **2.3-2.13**, $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$, and the reaction in the absence of Rh were analyzed to determine the *ortho:meta:para* selectivity of the reaction (Table 2.3). Entry 1 shows the reaction of the toluene-*d*₈ with HTFA in the absence of Rh, which is highly selective for the *ortho* and *para* products. Reactions containing any Rh species (entries 2-13) show similar selectivity for the *ortho* and *para* products. This regioselectivity is consistent across all three temperatures studied (120 °C, 150 °C and 180 °C). Further, the methyl group of toluene was never observed to undergo H/D exchange. The similar *ortho:meta:para* ratios between acid (entry 1) and the rhodium catalysis (entries 2-13) highlights that electrophilic aromatic substitution is the most likely mechanism. Thus the rhodium species are likely not proceeding through an Rh-Ph bond in trifluoroacetic acid.

Entry	Catalyst Precursor	Ratio of <i>o:m:p</i>			
		120 °C	150 °C	180 °C	
1	HTFA $[Rh(u-TFA)(n^2-$	8(2):1:7(2)	12(1):1:11(1)	9(0.2) : 1 : 7(0.4)	
2	$[1cl((\mu H H H))(\eta C_2H_4)_2]_2$	8(0.3) : 1 : 7(0.3)	14(0.7): 1: 13(0.5)	12(1):1:9(1)	
3	2.3	12(3):1:16(3)	5(1):1:6.4(1)	8(2):1:8(2)	
4	2.4	5.8(1):1:7(2)	9(2):1:9(2)	12(4):1:10(3)	
5	2.5	4(2):1:3(2)	9.1(1):1:9(1)	11(1):1:10(1)	
6	2.6	5(2):1:6(2)	8(2):1:8(1)	7(1):1:6(1)	
7	2.7	9(0.2) : 1 : 8(0.2)	16(2):1:14(2)	14(2):1:10(1)	
8	2.8	9(0.1):1:9(1)	10(0.4) :1 : 10(0.3)	10(1):1:10(0.3)	
9	2.9	7(2):1:8(0.3)	7(0.03) : 1 : 7(0.2)	14(2):1:15(2)	
10	2.10	6(1):1:7(0.1)	8(0.3):1:8(0.3)	9(0.2):1:10(1)	
11	2.11	9(0.4) : 1 : 9(0.1)	8(1):1:7(1)	9(1):1:7(1)	
12	2.12	4(2):1:3(1)	9(0.7):1:9(1)	11(1):1:10(1)	
13	2.13	9(2):1:8(2)	10(0.3) : 1 : 9(0.3)	12(2):1:10(1)	

Table 2.3. Ortho:meta:para ratios from H/D exchange between toluene- d_8 with HTFA using Rh catalyst precursors. Conditions: 0.01 mol % Rh relative to toluene- d_8 in HTFA.

Ison and coworkers discovered that the mechanism of action for H/D exchange between arenes and acids is strongly dependent on the identity of the acidic media.⁶⁴ Studying Cp*Ir(III) complexes for CH activation an Ir-Ph bond was found to form in acetic acid and methanol. This Ir-Ph is subsequently deuterated, by AcOD or CD₃OD, to release deuterated benzene. In contrast, no Ir-Ph bond was formed when catalysis with Cp*Ir(III) in HTFA was investigated; instead an electrophilic aromatic protonation mechanism is active.
Therefore to provide additional evidence for the hypothesis that our rhodium catalysts H/D exchange reactivity between benzene and TFA- d_1 is electrophilic aromatic protonation we attempted H/D exchange of benzene with other acidic solvents. The most effective catalyst precursors, **2.9** and **2.13**, were also examined for benzene H/D exchange with D₃PO₄, D₂SO₄, CD₃COOD, CH₃OD, CF₃OD, and D₂O. Using D₃PO₄ and D₂SO₄ H/D exchange was observed; however, the reactivity did not exceed that of the control reaction without Rh complex. Moreover, no H/D exchange above background was observed in AcOD, CH₃OD, CF₃OD or D₂O. We hypothesize that this is due to the insufficient acidity of the media such that electrophilic aromatic substitution cannot occur.

2.4.6 Computational Investigation of Electrophilic Aromatic Substitution Mechanism

DFT calculations were performed, by our collaborators Dr. Fu, Dr. Nielsen, and Professor Goddard III at the California Institute of Technology, to further elucidate the mechanism of the rhodium species with benzene and toluene in acid. These computations confirm that the mechanism of action is electrophilic aromatic substitution, and that the rhodium complexes increase the acidity of the solution. Table 2.4 shows the calculated free energies of the formation for the arenium ions of benzene and toluene from H₂TFA⁺ and HTFA (Table 2.4, Columns 3 and 4). In the presence of the rhodium catalyst, H₂TFA⁺ is formed by [Rh]ⁿ⁺ + 2HTFA \rightarrow {[Rh]-TFA}⁽ⁿ⁻¹⁾⁺ + H₂TFA⁺. However, the autoionization of HTFA (in neat HTFA), is high (45.8 kcal/mol) and therefore the ΔG for arenium formation is high (Table 2.4, Column 4). As expected, the ΔG 's for the *ortho*- (-12.1 kcal/mol) and *para*-substituted (-13.4 kcal/mol) positions are decreased relative to the *meta*-substituted position (-8.1 kcal/mol). This is because of the increased stability of the carbocation resonance intermediate for the *ortho* and *para* positions in electrophilic aromatic substitution. Further, the similar ΔG 's for *ortho*- and *para*-substituted products, is in agreement with the comparable regioselectivity of the two substituted products that was determined experimentally, as shown in Table 2.3. Interestingly, the ΔG of protonation of the *meta* position is similar to that of benzene.

Entry	Reaction	ΔG (kcal/mol)	ΔG (kcal/mol)
		$\mathbf{X} = \mathbf{TFAH}$	$\mathbf{X} = \mathbf{TFA}^{-}$
1	$ + XH^{+} \longrightarrow \begin{bmatrix} H & H \\ \vdots & \vdots \end{bmatrix} + X $	-9.7 kcal/mol	36.0 kcal/mol
2 (ipso)	$H^{+} \xrightarrow{Me} H^{+} \xrightarrow{H} X$	-2.8 kcal/mol	43.0 kcal/mol
3 (ortho)	$+ XH^{+} \longrightarrow + XH^{+}H$	-12.1 kcal/mol	33.6 kcal/mol
4 (meta)	$ + XH^{+} \longrightarrow H^{+} XH^{+} H^{+} H^{$	-8.1 kcal/mol	37.6 kcal/mol
5 (para)	$ + XH^{+} \longrightarrow H^{+} + X $	-13.4 kcal/mol	32.4 kcal/mol

Table 2.4. DFT calculated free energies for the formation of arenium ions in HTFA. The temperature was set to 423.15 K.

To probe the argument that $[Rh]^{n+} + 2HTFA \rightarrow \{[Rh]-TFA\}^{(n-1)+} + H_2TFA^+$, DFT calculations with catalyst **2.13** were undertaken (Scheme 2.14). The rhodium species is a

very strong Lewis base and is calculated to have two HTFA molecules coordinated. This $(^{FI}DAB)Rh(TFAH)_2^+$ species then releases H_2TFA^+ with a ΔG of only 12.3 kcal/mol. Since this ΔG is significantly lower than that of the autoionization of HTFA, these findings provide an explanation for the increased H/D exchange TO between benzene and TFA- d_1 using (^{FI}DAB)Rh(COE)(TFA) relative to acid alone. In addition, this activation barrier, 12.3 kcal/mol, is significantly lower than the 28.7 kcal/mol previously calculated for H/D exchange through intramolecular electrophilic substitution (see Section 2.4.3).



Scheme 2.14. DFT calculations showing the coordination of HTFA by complex 2.1. Free energies calculated at 423.15 K.

2.4.7 Attempted Methane Oxidation in Acidic Media

Concomitant with the mechanistic studies of benzene H/D exchange were attempts to functionalize hydrocarbons. A specific push was to develop methane functionalization chemistry as part of the Center for Catalytic Hydrocarbon Functionalization.⁶⁵ Complex **2.1** was used for these studies as this was the most effective catalyst for H/D exchange between benzene and TFA- d_1 . Standard conditions that were

used to test for methane functionalization are shown in Scheme 2.15. The oxidant screens were originally limited to those that can be regenerated with oxygen or air directly, with a focus on Cu(II) salts and sulfur trioxide. None of the tested copper salts (Cu(TFA)₂, Cu(OAc)₂, Cu(IO₃)₂, CuCl₂ or CuO) produced any MeTFA within the temperature range of 150 - 220 °C. Furthermore, no methane functionalization was observed with the silver salts (AgCl, Ag₂O or AgTFA) or with the organic oxidants (PhI(OAc)₂, sulfur trioxide pyridine complex (py-SO₃) and DMSO) at 150 or 180 °C. Indeed even varying the temperature from 150 to 235 °C, or increasing the time to 6 hours using AgTFA or py-SO₃, had no impact on catalysis.

Based on results from a post-doctoral researcher in our lab, Dr. Matthew O'Reilly, who found that iodide had a significant enhancement for the reductive functionalization of MeX from rhodium species,⁴⁵ iodide was tested as an additive. Catalysis was attempted with a 1:1 ratio of Rh:I⁻ by the addition of NaI or MeI using Cu(OAc)₂ as the oxidant. However, no MeX was observed.

Scheme 2.15. General screening conditions for methane functionalization.

The positive results in our lab regarding reductive functionalization from (4,4',4''-nitroterpy)Rh(Cl)(terpy = 2,2';6',2''-terpyridine) with MeI species led to attempts to functionalize methane using this complex as catalyst (Scheme 2.16).⁶⁶ Under the screening conditions, (4,4',4''-nitroterpy)RhCl was added to an oxidant, either copper(II)

or silver(I) salts or py-SO₃, in HTFA at 150 °C. No MeX was observed in any case. The addition of one equivalent of iodine or an iodide source, I_2 or NaI, did not result in methane functionalization. Increasing the temperature to 180 °C and using 50 equivalents of iodine source was not successful.



Scheme 2.16. Attempted methane activation using (4,4',4''-nitroterpy)RhCl (terpy = 2,2';6',2"-terpyridine) complex with iodine sources. Iodine sources = NaI or I₂, Oxidant = Cu(TFA)₂, Cu(OAc)₂, AgTFA, Ag₂O, or py-SO₃.

As Periana and coworkers have shown that catalysts that achieve benzene H/D exchange in HTFA are also active in H_2SO_4 ,¹⁶ complex **2.1**, was tested for methane functionalization in sulfuric acid and oleum under the conditions shown in Scheme 2.17. Complex **2.1**, in concentrated H_2SO_4 or 20% oleum, at 150 °C did not produce any methyl bisulfate (MBS, MeOSO₂OH) by ¹H NMR spectroscopy. Analysis of the reaction mixtures was achieved by addition of a MeNO₂ standard to the reaction the mixture and stirred. After 2 minutes of stirring, an aliquot (0.5 mL) of the mixture was added to an NMR tube with a C₆D₆ capillary. *Warning, the combination of a touch sensitive explosive if heated.*⁶⁷



Scheme 2.17. Conditions tested for sulfuric acid or oleum methane functionalization.

Following the lack of methane functionalization at 150 °C with complex 2.1, higher temperatures were investigated for catalysis (Figure 2.14). However, due to decreased H/D exchange catalysis at high temperatures with complex 2.1, the (4,4',4''nitroterpy)RhCl₃ was initially studied due to its high thermal stability.^{44,45} After 1 hour. 1 mM (4,4',4''-nitroterpy)RhCl₃ in 20% oleum (104% sulfuric acid) produced 0, 20(4) and 6(2) TO of MBS at 180 °C, 200 °C and 220 °C, respectively (Figure 2.14). The highest molarity of MBS detected was 0.02 M, at 200 °C, which is significantly less than the ~1 M reported by Periana and corworkers using Pt(bypm)(Cl)₂.²⁹ In addition, running the same conditions with concentrated sulfuric acid (98% sulfuric acid) led to no MBS formation. The control reaction utilizing $RhCl_3 \cdot 3(H_2O)$ produced no reactivity at 180 °C or 200 °C. The reaction at 220 °C produced 11(3) TO of MBS. Dr. Samantha Burgess, in our group, showed that $[Rh(^{t}bpy)_{2}OMe_{2}]OTf(^{t}bpy = 4,4'-di-tert-butyl-2,2'-bipyridyl)$ was successful in 1,2-addition dihydrogen activation chemistry thereby making it a viable candidate for methane functionalization.⁶⁸ [Rh(t bpy)₂Cl₂]Cl produced 30(8), 4(1) and 12(4) TO of MBS at 180 °C, 200 °C and 220 °C, respectively.



Figure 2.14. Rhodium species tested for methane functionalization in 20% oleum after 1 hour.

The successful generation of MBS with all species at 220 °C led us to analyze the possibility that the SO₃ combined with a CI⁻ source might react similarly to methane functionalization with iodate/chloride.^{69,70} The Gunnoe group demonstrated that the combination of iodate or periodate salts with a substoichiometric chlorine source in HTFA is an effective catalysis for methane functionalization; achieving a 42% yield of MeTFA in one pass yield. Therefore we hypothesized that the SO₃ with CI⁻ might operate in a similar manner to IO₄/IO₃ with CI⁻. Therefore, the screening experiments were extended to CuCl₂ and KCl. Using 0.3 M of CuCl₂ in 20% oleum at 220°C for 1 hours with 500 psi of CH₄ led to the production of 0.22(8) TO and 0.067 M of MBS. The reaction with KCl did not produce MBS, even when increasing the KCl concentration to 1 mM. The success with CuCl₂, but not KCl, combined with Pedro Perez' successful methane functionalization with Cu,⁷¹ led to the hypothesis that Cu, rather than Cl, is responsible for the observed catalytic activity. Thus we tested analytically pure (99.999%) CuO in 20% oleum. This produced 0.34(9) TO and 0.13 M of MBS after 1

hour at 220 °C. The molarity of methylbisuflate significantly surpassed the results with the Rh complexes. Accordingly, we believe that copper in combination with 20% oleum is active for methane functionalization but substantially slower than other examples of catalytic methane functionalization in oleum.^{25-27,29}

With promising results regarding copper species in 20% oleum, we sought to benchmark the Catalytica system under our conditions. The catalyst, Pt(bpym)Cl₂, was synthesized and found to produce 120(20), 1940(300) and 3670(800) TO of MBS in 1 hour at 180 °C, 200 °C and 220 °C, respectively (Scheme 2.18). These correspond to MBS concentrations of 0.15 M, 1.94 M, and 3.67 M, respectively, where the latter two are substantially higher than was achieved in the original report.²⁹ However, the reproducibility of the reaction was limited, as is evident from the large standard deviations. The dependence on SO₃ concentration was found to be crucial and difficult to control. For example, results changed dramatically depending on how old the bottle of 20% oleum was; presumably due to H₂O in the atmosphere diluting the SO₃ content. Indeed, Schüth and coworkers found that the Pt salt, H₂O, and SO₃ concentrations as well as the temperature all play a crucial role in the production of methylbisulfate.⁷² Further, Schüth and coworkers discovered that most Pt sources can catalyze the production of MBS in oleum.⁷²



Scheme 2.18. $Pt(bpym)Cl_2$ catalyzed methane functionalization under our screening conditions.

2.4.8 Attempted Arene Oxidation in Acidic Media

The selective functionalization of arenes is also highly sought after. Two desired industrial processes are direct oxidation of benzene to phenol and the oxidative vinylation of benzene to styrene.⁷³⁻⁷⁶ After efficient H/D exchange between benzene and HTFA was observed with complexes 2.9 and 2.13, they were examined for benzene oxidation with a number of chemical oxidants. Experimental issues with reproducible stirring in the stainless steel reactors necessitated the use of glass pressure tubes for these experiments. A 0.05 mol % solution of 2.13 in HTFA with 50 equivalents of benzene and 100 equivalents of copper(II) acetate was heated to 150 °C for 4 hours. After cooling to room temperature, an aliquot of the reaction mixture was analyzed by GC-MS. No evidence of benzene functionalization, specifically PhOAc, PhTFA or biphenyl, was observed. Extending the reactivity to silver oxidants (AgTFA, Ag₂O) also did not produce PhX (X = TFA, OH). Sanford and coworkers have successfully used hypervalent iodine(III) compounds, such as (Ph)I(OAc)₂, with Pt and Pd catalysts for benzene functionalization.^{30,77} Therefore, we extended the oxidant screen to include (Ph)I(OAc)₂ with our catalysts. However, no formation of PhX (X = I, OAc) was observed above the control reaction.

2.4.9 Attempted Arene Oxidation in Non-Acidic Media

Because our mechanistic studies showed the most likely mechanism for H/D exchange between benzene and HTFA, using our rhodium complexes, is by electrophilic aromatic substitution (see page 84-89) with no formation of Rh-Ph bonds, arene functionalization was attempted in non-acidic media. Therefore, a 0.05 mol % solution of **2.9** or **2.13** in benzene with 100 equivalents of copper (II) acetate was heated to 150 °C or 180 °C for 4 hours. GC-MS analysis revealed the formation of biphenyl and phenyl acetate at 180 °C (Scheme 2.19); however, no products from benzene functionalization were detected following the reaction at 150 °C. The control reaction at 180 °C without rhodium produced similar quantities of phenyl acetate, but, no biphenyl was observed. Catalysts **2.6** and **2.9** as well as $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$ were found to produce biphenyl in the same quantities.



Scheme 2.19. Formation of PhOAc and biphenyl from complexes 2.6, 2.9, 2.13 and $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$ with Cu(OAc)₂.

We believe that the PhOAc is formed through radical decomposition of $Cu(OAc)_2$. A similar process for the decomposition of CuF_2 to produce PhF has been shown.⁷⁸ To study this process, toluene was utilized as a substrate (Scheme 2.20). A radical process would be likely to preferentially attack the methyl group of toluene (C–H bond strength of 88 kcal/mol) rather than the arene C–H bond (111 kcal/mol).⁷⁹ This hypothesis was confirmed, by GC-MS, from the reaction in toluene which produced

significantly more benzylic acetate than tolylacetate, as was expected for a radical-based reaction mechanism.



Scheme 2.20. Generation of benzylic acetate and tolylacetates from the radical decomposition of $Cu(OAc)_2$.

2.5 Conclusions

A variety of rhodium complexes were effective H/D exchange between TFA- d_1 and benzene. Initially, it was postulated that the H/D exchange mechanism operated through an intramolecular electrophilic substitution mechanism. However, experiments using toluene as the substrate revealed similar H/D exchange ortho:meta:para ratios as acid-based mechanisms, inconsistence with this theory. H/D exchange for aliphatic hydrocarbons was not observed. Further, weaker acids (e.g. acetic acid, methanol, and water) were not active for H/D exchange. Computational studies are consistent with electrophilic aromatic substitution; not through the desired formation of a Rh-Ph bond. A screening of rhodium complexes for hydrocarbon functionalization using a variety of oxidants was undertaken. No methane functionalization was observed in HTFA, while minor quantities of MBS were observed in 20% oleum. In comparison to the Catalytica system, which achieved ~1 M MBS, the effectiveness of the rhodium complexes was dramatically reduced, ~0.03 M MBS. Under our conditions, Pt(bpym)Cl₂ in oleum can generate significantly higher concentrations of methyl bisulfate >1.8 M MBS. This is in agreement with Schüth and coworkers recent report.⁷² One of the goals of this research was to develop rhodium catalysts for C–H activation through Rh-Ph bond formation. Although this goal was not achieved in acidic media, the functionalization of benzene to biphenyl provides evidence for possible rhodium mediated arene functionalization.

2.6 Experimental Methods

2.6.1 General Information

Unless otherwise noted, all synthetic procedures were performed under anaerobic conditions in a nitrogen-filled glovebox or by using standard Schlenk techniques. Glovebox purity was maintained by periodic nitrogen purges and was monitored by an oxygen analyzer ($O_2 < 15$ ppm for all reactions). Tetrahydrofuran and *n*-pentane were dried by distillation from sodium/benzophenone. Benzene was purified by passage through a column of activated alumina. C₆D₆ and DMSO-d₆ were used as received and stored under a N₂ atmosphere over 4Å molecular sieves. TFA- d_1 and DMF- d_7 was used as received. Argon was purchased from GTS Welco and used as purchased. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury Plus 300 MHz spectrometer (75 MHz operating frequency for ¹³C NMR), Varian Inova 500 MHz spectrometer (75 MHz operating frequency for ¹³C NMR), Bruker Avance DRX 600 MHz spectrometer (201 MHz operative frequency for ¹³C NMR), or Bruker Avance III 800 MHz spectrometer (201 MHz operative frequency for ¹³C NMR). All ¹H and ¹³C NMR spectra are referenced against residual proton signals (¹H NMR) or the ¹³C resonances of the deuterated solvent (¹³C NMR). ¹⁹F NMR (operating frequency 282 MHz) spectra were obtained on a Varian Mercury 300 MHz spectrometer and referenced against an external standard of hexafluorobenzene (δ -164.9). GC-MS analysis was performed using a Shimadzu GCMS–QP2010 Plus system with a 30 mm \times 025 mm RTx-Qbond column with 8 µm thickness using electron impact ionization. All other reagents were used as purchased from commercial sources. (COE)₂Rh(TFA) was made following the literature procedure using AgTFA instead of AgPF₆.⁸⁰ Elemental analyses were performed by Atlantic Microlabs, Inc.

2.6.2 Ligand Synthesis

Most of the diimine ligands (diazbutadienes, or DABs) were synthesized following a modified literature procedure:⁵⁹ To a round-bottom flask, 2.1 equivalents of the aniline, 1 equivalent of 2,3-butanedione, 0.1 equivalents of *p*-toluenesulfonic acid and 4 equivalents of trimethylorthoformate were combined in 10 mL of anhydrous methanol under air. The reaction mixture was stirred for 8 hours accompanied by the precipitation of a yellow solid. The solid was collected by filtration, washed with 5 mL of cold methanol, and dried under vacuum. The identity of the DABs was confirmed by comparison to reported NMR data for 3,5-diMeDAB = N,N'-bis-(3,5-dimethylphenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene),⁸¹ PhDAB = N,N'-bis-(2,3-dimethyl-1,4-diaza-1,3butadiene),⁸² 2,6-dippDAB = N,N'-bis-(2,6-diisopropylphenyl)-2,3-dimethyl-1,4-diaza-1.3-butadiene).⁸² 2.6-diClDAB = N.N'-bis-(2.6-dichlorophenyl)-2.3-dimethyl-1.4-diaza-1,3-butadiene),⁸³ 3,5-diCF₃DAB = N,N'-bis-(3,5di(trifluoromethyl)phenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene),⁸⁴ 2,6-diFlDAB = N,N'-bis-(2,6-difluorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene),⁸⁵ (2,4-diFlDAB = N,N'-bis-(2,4-difluorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene) and (4-FlDAB = N,N'-bis-(4-fluorophenyl)-2,3-dimethyl-1,4diaza-1,3-butadiene),⁸⁶ (^{FI}DAB = N,N'-bis-(pentafluorophenyl)-2,3-dimethyl-1,4-diaza1,3-butadiene).⁵⁹ The ligands (2,6-dip-4-nitroDAB = N,N'-bis-(2,6-diisopropyl,4nitrophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene) and (4-nitroDAB = N,N'-bis-(4nitrophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene) were prepared according to literature procedures,⁸⁷ and 4-nitroDAB was confirmed to reported NMR data.⁸⁸

2.6.3 Synthesis of Rhodium Catalysts

 $(^{FI}DAB)Rh(\mu-TFA)$ (2.1). To a round-bottom flask was added a stir bar, [Rh(TFA)(COE)₂]₂ (270 mg, 309 µmol) and 10 mL of THF to give a brown/yellow solution. Then ^{FI}DAB (258 mg, 619 µmol) was added, and the solution immediately turned dark purple. The solution was stirred for 1 hour before the solvent was removed in vacuo. The residue was washed with 10 mL of pentane. The purple solid was dried under vacuum (274 mg, yield of 58%) and stored in the glovebox freezer. Extensive time under vacuum results in the removal of cyclooctene. ¹H NMR (600 MHz, THF- d_8) δ -0.44 (s, 6H, CH₃). ¹³C NMR (201 MHz, DMF-d₇) δ 163.8 (imine N=C-CH₃), 142.0 (d, ³J_{CF} = 7.7 Hz, $o-C_6F_5$), 140.8 (d, ${}^{3}J_{CF} = 5.0$ Hz, $o-C_6F_5$), 139.6 (t, ${}^{3}J_{CF} = 13.3$ Hz, $p-C_6F_5$), 139.0 (t, ${}^{3}J_{CF} = 14.6$ Hz, $m - C_{6}F_{5}$), 137.8 (t, ${}^{3}J_{CF} = 12.7$ Hz, $m - C_{6}F_{5}$), 129.9 (*ipso-C*₆F₅), 115.78 (q, ${}^{1}J_{CF} = 292.9$ Hz, *C*F₃ TFA), 20.8 (s, *C*H₃), 13.7 (q, ${}^{3}J_{CF} = 22.6$ Hz, *C*=O TFA). ${}^{19}F$ NMR (282 MHz, DMSO- d_6) δ -74.0 (s, TFA), -151.9 (dd, ${}^{3}J_{\text{FF}} = 24$, 6 Hz, p C–F), -162.3 (t, ${}^{3}J_{\text{FF}} = 23$ Hz, m C–F), -163.4 (td, ${}^{3}J_{\text{FF}} = 23$, 6 Hz, o C–F). Analytical Calc. (without COE, which is removed upon extended drying in vacuo) C: 34.20 H: 0.96 N: 4.43 Found: C: 33.61 H: 1.05 N: 4.14.

(BOZO)Rh(COE)(TFA) (2.2). To a round bottom-flask was added a stir bar, $[Rh(TFA)(COE)_2]_2$ (99 mg, 114 µmol), and 10 mL of THF to give a purple solution.

BOZO (32 mg, 227 µmol) was added, and the solution immediately turned dark purple. The solution was stirred for 1 hour before the solvent was removed in vacuo. The residue was then washed with 10 mL of pentane. The purple solid was dried under vacuum (59 mg, 73%) and stored in the glovebox freezer. Attempts to obtain clean elemental analysis data were thwarted by the instability of complex **2**. In addition, *in vacuo* complex **2** slowly releases cyclooctene, which complicates efforts to remove solvent. ¹H NMR (600 MHz, C₆D₆) δ 3.48 (t, ³*J*_{HH} = 10 Hz, 2H, O–C*H*₂), 3.27 (m, 4H, O–C*H*₂ and N–C*H*₂, coincidental overlap), 2.27 (bs, 4H, COE), 2.12 (t, ³*J*_{HH} = 10 Hz, 2H, N–C*H*₂), 1.58 (bs, 10H, COE). ¹³C NMR (201 MHz, DMSO-*d*₆) δ 160.2 (O-*C*=N), 158 (*C*=O of TFA), 129.7 (*C*=*C* of COE), 114.9 (q, ¹*J*_{CF} = 290 Hz, CF₃), 72.7 (O–CH₂), 53 (N–CH₂), 28.7 (α –CH2 of COE), 25.6 (β –CH₂ of COE), 24.9 (γ –CH₂ of COE). ¹⁹F NMR (282 MHz, C₆D₆) δ -74.7 (s, C*F*₃). We were unable to obtain satisfactory combustion analysis. NMR spectra are shown below.

In Situ Generated Catalysts

Under nitrogen, the diimine ligand (2 equiv, 414.5 μ mol) in THF (10 ml) was added to a stirring solution of [Rh(μ -TFA)(η^2 -C₂H₄)₂]₂ (1 equiv, 207 μ mol) in THF (15 mL). The solution immediately became deep purple to black. After 1 hour the solvent was removed *in vacuo*, and the resulting solid was washed with *n*-pentane (20 mL) and then dried under vacuum to yield the corresponding *in situ* rhodium catalyst.

Other Catalyst Species

The $(4,4',4''-nitroterpy)RhCl_3$ was synthesized by Dr. Matthew O'Reilly. The $[Rh(^tbpy)_2Cl_2]Cl(^tbpy = 4,4'-di-$ *tert*-butyl-2,2'-bipyridyl) was provided by Dr. Samantha Burgess. The $(bypm)PtCl_2$ was synthesized according to literature procedure.²⁹

2.6.4 General Procedure for H/D Exchange

2.6.5 Representative Procedure for Benzene H/D Exchange.

Stainless steel pressure reactors were used for H/D exchange reactions (Figure 2.15). All pressure reactors bottoms and stir bars were treated with 35% hydrogen peroxide, washed with acetone and dried before use. To a 2 mL pressure reactor was added a small stir bar. A stock solution was made by placing 7.7 mg (0.01 mmol of **2.1**) into a glass vial and dissolving in 6.58 mL (86 mmol) of TFA- d_1 . Benzene (200 µL, 2.2 mmol) was then added to the stock solution. 1 mL of stock solution was added to each pressure reactor, which was sealed under N₂, pressurized with 800 psi argon, and placed in a heating block set to 150 °C. At the end of the reaction, the pressure reactor was cooled to room temperature, slowly vented, and opened. 1 µL of the reaction mixture was then analyzed by GC–MS. This was achieved by using an excel sheet program developed by Periana and coworkers.¹⁶ These reported TO take into account those resulting from the background reaction.



Figure 2.15. Pressure reactors used in H/D exchange. Left – Unassembled reactor parts. Middle - Assembled reactor. Right – Fully assembled reactor in aluminum heating block.

2.6.6 Representative Procedure for Toluene H/D Exchange.

To a glass vial, a stock solution was made by dissolving 12 umol of Rh catalyst in 7.8 mL

of trifluoroacetic acid and 240 μ L of toluene- d_8 . Then, 0.8 mL of stock solution was

placed into a J-Young NMR tube. The J-Young NMR tube was then placed in an oil bath

at 120 °C, 150 °C or 180 °C. After 15 minutes, the J-Young NMR tube was removed

from the high temperature oil bath, allowed to cool to room temperature, and then a

capillary tube filled with DMSO- d_6 was added. The reaction mixture was then analyzed

by ¹H NMR spectroscopy, and a representative NMR spectrum is shown in Figure 2.16.



Figure 2.16. Representative ¹H NMR spectrum of H/D exchange of toluene- d_8 in HTFA.

2.6.7 General Procedure for Aliphatic H/D Exchange

Stainless steel reactors were used for H/D exchange reactions. All pressure reactors and stir bars were treated with 35% hydrogen peroxide, washed with acetone and dried at 180 °C before use. For liquid aliphatics (cyclohexane) the same procedure described for benzene was used. For methane, the following procedure was followed: A stock solution was made by placing 0.02 mmol of Rh catalyst into a glass vial and dissolved into 6.2 mL (80.4 mmol) of TFA- d_1 . Then, 1 mL of the stock solution was added to each reactor, which was sealed under N₂, pressurized with 100 psi of methane, and placed in a heating block set to 120 °C, 150 °C or 180 °C. At the end of the reaction, the reactor was allowed to cool to room temperature. Then, 2 µL of reactor headspace was analyzed by GC-MS. Extent of H/D exchange was analyzed by deconvolution of the GC-MS spectrum using an Excel® spreadsheet developed by Periana, Goddard and coworkers.¹⁶

2.6.8 General Procedure for Methane Functionalization in HTFA

Stainless steel reactors were used for methane functionalization reactions. All pressure reactors and stir bars were treated with 35% hydrogen peroxide, washed with acetone and dried at 180 °C before use. A stir bar, Rh, 500 equivalents of oxidant relative to Rh, and HTFA were loaded into a tight-fitting Teflon liner. The reactor was sealed, purged with methane, pressurized to 800 psi, and subsequently placed in a preheated aluminum block at the appropriate temperature. The reactor was stirred (600 rpm) at this temperature for 2 h. After this, it was removed from the heating block and placed in front of a fan for 30 min to cool to room temperature. The reactor was vented and then opened. Nitromethane was added as a standard and the contents were allowed to stir. A 2 mL aliquot of reaction mixture was removed, centrifuged, and 0.5 mL of the liquid placed in an NMR tube containing a capillary filled with C_6D_6 and analyzed by ¹H NMR spectroscopy.

2.6.9 General Procedure for Methane Functionalization in Sulfuric Acid or Oleum

Stainless steel reactors were used for methane functionalization reactions. All pressure reactors and stir bars were treated with 35% hydrogen peroxide, washed with acetone and dried at 180 °C before use. A stir bar, 5 mL of a 1 mM solution Rh or Pt catalyst in 20% oleum or concentrated sulfuric acid, were loaded into a tight-fitting Teflon liner. The reactor was sealed, purged with methane, pressurized to 500 psig and

stirred under pressure for 20 seconds, and subsequently placed in a preheated aluminum block at the appropriate temperature. The reactor was stirred (10 Hz) at this temperature for 1 h. After this, it was removed from the heating block and placed in front of a fan for 30 min to cool to room temperature. The reactor was vented and then opened. Nitromethane was added as a standard and the contents were allowed to stir. A 2 mL aliquot of reaction mixture was removed, centrifuged, and 0.5 mL of the liquid placed in an NMR tube containing a capillary filled with C_6D_6 and analyzed by ¹H NMR spectroscopy.



Figure 2.17. Sample ¹H NMR spectrum with assignments for methane functionalization $Pt(bpym)Cl_2$ in 20% oleum.

2.6.10 Details of the DFT Calculations

All computational details were performed by the Goddard group at the California Institute of Technology. DFT calculations were carried out using the Jaguar software version 8.4 developed by Schrödinger Inc.⁸⁹ Geometry optimizations were carried out on initial guess structures, and vibrational frequencies were calculated to confirm the

optimized geometries as intermediates (no negative curvatures) and to calculate the zeropoint energy, entropy, and temperature corrections to obtain the free energy profile. Solvation energies were calculated using the PBF Poisson-Boltzmann implicit continuum solvation model ^{90,91} in Jaguar, with a dielectric constant of 8.55 and a probe radius of 2.451 Å based on trifluoroacetic acid. All geometry optimization and vibrational data were calculated using the double- ζ basis set 6-31G^{**} ^{92,93} for all elements except Rh, and the double- ζ basis set and pseudopotential LACVP** for Rh.⁹⁴ The B3LYP density functional⁹⁵⁻⁹⁷ was used for Rh species whereas M06 ^{98,99} was used for the organic molecules. In both cases, the Grimme post-SCF D3 correction for van der Waals interactions was added a posteriori.¹⁰⁰ After geometry optimization and vibrational calculations, single point gas-phase and solvated energies were calculated using M06- D3 with the triple- ζ Los Alamos basis set and pseudopotential (LACV3P**++) modified to include f functions and diffuse functions for rhodium [8],¹⁰¹ and the $6-311G^{**++}$ basis set^{102,103} [9] for the other atoms. The enthalpy for each molecular species in solution was calculated using the formula $H = Egas + \Delta Esolv + ZPE + Htot$, whereas the free energy was calculated using the formula G = H - TStot + RTln(34.7), where the last term represents the free energy change of compressing 1 mol of an ideal gas (volume 34.7 L at 150°C) to 1 L (for 1 M standard concentration). Note that all calculations were performed with T set to 423.15 K (150 °C).

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3 Proton catalyzed H/D exchange of arenes in acidic media

3.1 Introduction

As discussed in Chapter 2, H/D exchange is a common method for monitoring C–H activation. Moreover, as shown in Chapter 2, these data can be deceiving. For example, we originally believed our rhodium catalysts, for the H/D exchange of benzene and HTFA, were activating C–H bonds through formation of Rh–Ph bonds. However, investigations later revealed that the rhodium catalysts were increasing the acidity of the solvent and that the H/D exchange operated through protic electrophilic aromatic substitution.¹

Coordination of a C–H bond, to a transition metal, polarizes the bond and makes the C–H bond acidic, rending it susceptible to deprotonation. A dissociated basic species can then deprotonate the coordinated C–H bond.^{2,3} Acidic media can help dissociate anionic ligands and stabilize the resulting transition metal species. To probe hydrocarbon activation acidic solvents are often used.^{4,5} Common acids used for C–H functionalization catalysis include oleum/sulfuric acid,⁶⁻⁹ trifluoroacetic acid (HTFA),¹⁰⁻²⁰ and acetic acid.²¹⁻²⁵

Transition metal catalysts that activate C–H bonds through electrophilic mechanisms often rely on the generation of electron-deficient catalysts.²⁶⁻³² To generate electron-deficient metal species, often a halide extracting salt is added to the reaction *in situ*. These salts often contain weakly coordinating anions such as BAr^{F-} , BF_4^{-} , or OTf $(BAr^{F} = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, <math>BF_4 = tetrafluoroborate, OTf =$

trifluoromethanesulfonate).^{23-25,33-38} The abstraction of the halide causes the transition metal to coordinate a protic solvent molecule and leads to *in situ* generation of a strong acid (Scheme 3.1). As discussed in Chapter 2, strong acids are capable of H/D exchange with arenes. These observations, combined with experiments in the Gunnoe group (discussed in Chapter 2),^{39,40} lead us to analyze a variety of catalysts for H/D exchange.⁴¹

L_mMX	+	AgOTf	>	L _m M _n ⁺ OTf ⁿ⁻	+	AgX
$L_m M_n^+ O^-$	Tf ⁿ⁻	+ HTFA	<u> </u>	L _m MTFA +	H* +	OTf [–]

Scheme 3.1. Halide extraction and *in situ* generation of a strong acid.

3.2 Results and discussion

The research presented here is a collaboration between Dr. Dominik Munz and myself with the delineation of labor such that Dr. Munz developed the rate and a majority of the HTFA with toluene- d_8 H/D exchange experiments while I researched H/D exchange with acetic acid, methanol, and the remainder of the HTFA experiments. Screening conditions were 21 umol of AgX with 28 uL of toluene- d_8 at 80 °C in 0.8 mL of HTFA for 17 hours (Scheme 3.2). These experiments were run in high pressure J-Young tubes to allow for easy analysis and allow use of high temperatures. The background reaction without any AgX also revealed H/D exchange between toluene- d_8 and HTFA. The initial screen of silver salts revealed that AgOTf and AgBF₄ are active for the H/D of toluene (Figure 3.1). However, other anions (OAc, Cl, PF₆, TFA, NO₂) of Ag⁺ gave no enhanced reactivity over the background reaction. An interesting observation is that the catalytic activity appears to be partially dependent upon the conjugate acid of the anion. Thus HBF₄, is less effective than HOTf.⁴²



Scheme 3.2. Screening conditions for toluene H/D exchange with silver salts.



Figure 3.1. Silver salt catalyzed H/D exchange of toluene- d_8 with HTFA. Conditions: 28 µL toluene- d_8 , 21 µmol silver salt, 0.8 mL HTFA, 80 °C, 17 h. Error bars are standard deviations of multiple experiments. Background reaction had no silver salt.

To highlight the effectiveness of AgOTf on H/D exchange, a variety of transition metal compounds and salts were examined with and without the addition of AgOTf (Figure 3.2). Upon addition of AgOTf, the precipitation of AgCl/AgBr was observed for all transition metal complexes. Moreover, Ru(PPh₃)₄Cl₂ also formed another precipitate. In all cases, except Ru(PPh₃)₄Cl₂, the addition of AgOTf increased the TO of H/D exchange between toluene- d_8 and HTFA dramatically. The second row transition metals showed increased activity versus the third row counterparts. For example, [Rh(η^2 -COE)(μ -Cl)]₂ showed increased TOs compared to [Ir(η^2 -COE)(μ -Cl)]₂, 43 and 34 TOs, respectively. Thereby the nature of the cation affects the effectiveness of catalysis. Further, by comparing $Pd(NHC)_{2}Br_{2}$ $(NHC)_2$ 1,1'-dimethyl-3,3'methylenediimidazoline-2,2 '-diylidene) with Pd(PhCN)₂Cl₂, 56(12) TOs versus 43(2) TOs, respectively, the ligands can be seen to impact catalysis. However, this effect does

not hold for all species transition metal complexes. For example, the TO of AuCl and Au(PPh₃)Cl are statistically identical. Comparing AuCl₃ to AuCl reveals that the oxidation state also has an impact with Au(III), 48(1) TOs, being more effective than Au(I), 43(2).



Figure 3.2. Comparison of transition metal compounds and salts in the presence of a AgOTf (red, bottom) and without AgOTf (blue, top). A 1:1 ratio of AgOTF:metal halide was used. Conditions: 28 μ L toluene- d_8 , 21 μ mol transition metal catalyst, 0.8 mL HTFA, 80 °C, 17 h. Error bars are standard deviations of multiple experiments. COE = cyclooctene; dppe = 1,2-bis(diphenylphosphino) ethane; dppp = 1,3-bis(diphenylphosphino) propane; (NHC)₂ = 1,1'-dimethyl-3,3'-methylenediimidazoline-2,2 '-diylidene. Max TO = 65.

To determine if AgOTf was consistently more active than AgBF₄, the effect of each silver salt with transition metal compounds was investigated. Figure 3.3 shows that

for all species examined the triflate anion gives more TOs. Moreover, results using $Pt(NHC)_2Br_2$ Pd(NHC)_2Br_2, and Au(PPh_3)Cl are statistically identical. When using Au(PPh_3)Cl, the addition of AgOTf and AgBF_4 both improved catalytic TOs by ~3 times.



Figure 3.3. Comparison of triflate anion versus BF_4 anion with various transition metal compounds. A 1:1 ratio of AgX:metal halide was used (X=OTf or BF_4). Conditions: 28 µL toluene- d_8 , 21 transition metal salt, 0.8 mL HTFA, 80 °C, 17 h. COE = cyclooctene; (NHC)₂ = 1,1'-dimethyl-3,3'-methylenediimidazoline-2,2 '-diylidene. Blue highlights the addition of AgOTf. Red highlights the addition of AgBF₄. Green is Au(PPh₃)Cl without Ag salt. Error bars are standard deviations of multiple experiments. Max TO = 65.

Above, we have shown that the combination of metal salts and AgOTf is more efficient at catalyzing H/D exchange benzene and HTFA than metal salts without AgOTf (Figure 3.2) Also, AgOTf has been shown to be more effective than AgBF₄ (Figure 3.3). We were curious if other metal triflate salts (i.e in addition to AgOTf) were also activate for catalyzing H/D exchange between toluene and HTFA. Therefore a variety of triflate salts were examined (Figure 3.4). The most active species were Bi(III), Fe(III), and Al(III) were near quantitative H/D exchange (65 TO). In addition, increasing the toluene concentration (112 μ L toluene-*d*₈) and decreasing the catalyst concentration to 1 μ mol Al(OTf)₃ lead to 2250 TOs after 3 hours at 60 °C. This corresponds to an apparent TOF of 0.2 s⁻¹. Efficient catalysis at lower temperatures highlights the efficacy of Al(OTf)₃ for H/D exchange. The error bars for Fe(OTf)₃ are large due to the broadening of ¹H NMR spectra with paramagnetic species. Mg(OTf)₂ gives lows TOs of H/D exchange because the salt is only marginally soluble in HTFA even at high temperature.



Figure 3.4. H/D exchange of of toluene- d_8 in HTFA with triflate salts. Conditions: 28 µL toluene- d_8 , 21 µmol salt, 0.8 mL HTFA, 80 °C, 17 h. Error bars are standard deviations of multiple experiments. Max TO = 65.
Ison and coworkers discovered that $Cp*Ir(III)(NHC)(OAc)_2$ (NHC = 1,3dimethylimidazol-2-ylidene), was found to undergo protic electrophilic aromatic substitution in HTFA, with no formation of a Ir-Ph bond.⁴³ However, in acetic acid, Cp*Ir(III)(NHC)(OAc)₂ initiated an organometallic C–H activation involving formation of a Ir-Ph bond. Therefore, we studied H/D exchange catalysis between toluene- d_8 and acetic acid (Figure 3.5). Under our screening conditions, (28 μ L toluene- d_{8} , 21 μ mol metal salt, 0.8 mL HOAc (5 mol-% by volume acetic anhydride), 150 °C, 17 h) the control reaction (no salt) was found for H/D exchange in acetic acid. Similar to the HTFA experiments, $Al(OTf)_3$ was the most active catalyst achieving quantitative H/D exchange (TO = 80). The CuOTf)₂ and Fe(OTf)₃ species showed large error bars due to paramagnetic broadening of the ¹H NMR spectra. $Bi(OTf)_3$ and $Pd(PhCN)_2(OTf)_2$ produce moderate 24(4) and 15(2) TO of toluene H/D exchange, respectively. In contrast Zn(OTf)₂, Fe(OTf)₂, Pt(NHC)₂(OTf)₂, Ir(COE)₂Cl + AgOTf, and Rh(COE)₂Cl + AgOTf all showed low activity (<10 TO) in acetic acid. For example, Zn(OTf)₂ in HTFA produced 38(3) TO, whereas in acetic acid it generated 9(5) TO of toluene H/D exchange. We attempted to expand this reactivity to methanol (pKa 15.5).⁴⁴ However, even with Al(OTf)₃, using methanol as a solvent produced no H/D exchange.



Figure 3.5. H/D exchange of toluene- d_8 in acetic acid with metal salts and *in situ* generated transition metal compounds. No TOs were observed for the reaction of toluene- d_8 and HOAc. Conditions: 28 µL toluene- d_8 , 21 µmol metal catalyst, 0.8 mL HOAc (5 mol-% by volume acetic anhydride), 150 °C, 17 h. In case of Pd, Ir, Au, Rh *in situ* generation of triflates by addition of AgOTf stoichiometric to the halide content.

3.3 Mechanistic investigations

Mechanistic investigations were undertaken with toluene- d_8 in HTFA. The rate expression for toluene and silver salt was investigated. Figure 3.6, the effect of toluene- d_8 concentration on H/D exchange TOs, shows a first order dependence on toluene concentration. Figure 3.7, the effect of AgBF₄ concentration on the TOs of H/D exchange, reveals a first order dependence on $AgBF_4$ concentration. Thus the rate expression for H/D exchange between toluene- d_8 and HTFA is rate = [toluene][AgBF_4]. Therefore, we conclude that the silver salt is the catalytically relevant compound in the reaction mixture.



Figure 3.6. The dependence of toluene concentration on TOs of H/D exchange between toluene- d_8 and HTFA. Conditions: 21 µmol AgBF₄, 0.8 mL HTFA, 80 °C, 17 h. Data were acquired from less than 30% of maximum conversion.



Figure 3.7. The dependence of AgBF₄ concentration on TOs of H/D exchange between toluene- d_8 and HTFA. Conditions: 28 µL toluene- d_8 , 0.8 mL HTFA, 80 °C, 17 h.

Computational collaborators, Dr. Ross Fu and Professor William Goddard III at the California Institute of Technology, modeled the H/D exchange reactivity by DFT calculations using the Jaguar 7.6 software package (M06/LACV3P**++//B3LYP/LACVP**) with corrections for the solvent effects by the PBF Poisson-Boltzmann implicit continuum solvation model. A number of simplifications were made to limit the number of reaction pathways. For example, HTFA coordinates to the metal centers and releases OTf. Therefore each metal center possesses a positive charge for each OTf released (Scheme 3.3). In HTFA, the calculations reveal ground states that are metals salts with HTFA ligands.

$$\left[L_m M_n^+ OT f^{n-}\right]$$
 + HTFA \longrightarrow $\left[L_m M_n^+ HTFA\right]$ + OT f^{n-1}

Scheme 3.3. Simplification to enable consistency in calculations.

Computation results are consistent with the experimental data collected (Figure 3.8). These results show that Fe(III) is the most active catalyst followed by Al(III) then Bi(III). The calculated activity for Fe(III), relative to the experimental data, is increased. This relative difference may be due to the variability of Fe(III) spin state. Similar to the experimental results, moderate activity were predicted using Cu(II), Fe(II), and Zn(II).



Figure 3.8. Calculated Δ H of formation for Wheland intermediate based on ground states of metal salts. Fe, Al, Bi, Cu, Fe, and Zn were determined to coordinate 6 HTFA molecules. Ag and Au coordinate 2 HTFA molecules.

3.4 Conclusions

The reactivity of a wide variety of metal salts and transition metal complexes were evaluated for H/D exchange between toluene- d_8 and acids. A variety of silver salts were demonstrated to be efficient catalysts, with the most effective being AgOTf. Indeed a multitude of triflate salts were effective for H/D exchange between toluene- d_8 and HTFA. Increased apparent activity of catalysis correlates with increasing electrophilicity of the catalyst. For example, Al(OTf)₃ was found to be more active than Cu(OTf)₂ for H/D exchange of toluene- d_8 in HTFA. Importantly, many of these salts are utilized for *in situ* generation of electrophilic catalysts. Therefore care must be taken when interpreting results of H/D exchange catalysts between acids and arenes.

Although H/D exchange data can be a useful tool for investigation of C–H activation catalysts, significant care must be taken when interpreting results. For example, we initially believed our rhodium catalysts (in Chapter 2) were active for transition metal mediated C–H activation, through formation of a Rh–Ph bond, in trifluoroacetic acid.⁴⁰ However, by analysis of H/D exchange catalysis between toluene- d_8 and HTFA, it was shown to be protic electrophilic aromatic substitution.³⁹

3.5 General Experimental

3.5.1 General Methodology

All catalytic reactions were performed in screw-cap or J. Young NMR tubes. All reported values are the mean of a minimum of two experiments. All chemicals were obtained by common commercial suppliers and used as received without further purification. Measurement of the NMR spectra were performed on Bruker AC 300-P, Avance III 600, or Varian Inova 500 MHz instruments. The bis-NHC complexes were synthesized according to reported procedures.^{45,46}

3.5.2 General Procedure for H/D exchange

Standard procedure for the H/D exchange reactions. The metal compound was weighed directly into the NMR tube in a N₂-filled glovebox. The NMR tube was brought out of the glovebox, and the indicated amount of toluene- d_8 was quickly added. Silver triflate was rapidly added in the form of 0.8 mL of a freshly prepared diluted solution in HTFA or HOAc (containing 5% acetic anhydride). The diluted solutions were prepared in the glovebox. The NMR tube was sealed and immersed in a hot oil bath for the indicated time. After the mixture was cooled to room temperature, 30 µL of a 1/9 v/v solution of MeNO₂ and HTFA/HOAc, used as a standard for integration, and a capillary tube that contained DMSO- d_6 were added. The reaction was then analyzed by ¹H NMR spectroscopy and the extent of H/D exchange determined by comparing the integrated intensity of the protio toluene or benzene signals to the signal of the MeNO₂ standard (Figure 3.9).



Figure 3.9. Representative ¹H NMR spectrum of H/D exchange of toluene- d_8 in HTFA.

3.5.3 Computational details

All quantum mechanical calculations were carried out using the Jaguar software version 7.6 developed by Schrödinger Inc.⁴⁷ Geometry optimizations were carried out on initial guess structures, and vibrational frequencies were gathered to confirm the optimized geometries as intermediates or transition states and to construct a free energy profile. Solvation energies were calculated using the PBF Poisson-Boltzmann implicit continuum solvation model^{48,49} in Jaguar, with a dielectric constant of 8.55 and a probe radius of 2.451 Å for HTFA.

Geometry optimization and vibrational data were calculated using the B3LYP density functional,⁵⁰⁻⁵² whereas single point gas-phase and solvated energies were calculated using the M06 functional.^{53,54} Calculations involving uncatalyzed H/D exchange of toluene in HTFA used the 6-311G**++ basis set.^{55,56} Geometry optimization and frequency calculations involving metal salts used a modified double- ζ Los Alamos basis set and pseudopotential⁶ that includes *f* functions for transition metals,⁵⁷ and the 6-31G** basis set.⁵⁸ for the other atoms; whereas single point gas-phase and solvated energies used a modified triple- ζ Los Alamos basis set and pseudopotential functions for transition metals,⁵⁷ and the 6-31G** basis set.⁵⁸ for the other atoms; whereas single point gas-phase and solvated energies used a modified triple- ζ Los Alamos basis set and pseudopotential (LACV3P*++) that includes *f* functions and diffuse functions for metals, and the 6-311G**++ basis set.^{59,60} for the other atoms.

The free energy for each molecular species in solution was calculated using the formula

$$G = E_{gas} + \Delta G_{solv} + ZPE + H_{tot} - TS_{tot}$$

where E_{gas} and ΔG_{solv} are the single point gas-phase and solvation energies, respectively, ZPE the zero-point energy, and H_{tot} and S_{tot} the total sum of vibrational, rotational, translational, and electronic enthalpy and entropy at standard conditions, respectively. The energies of uncatalyzed H/D exchange of toluene in HTFA were calculated and ΔG_{s} were reported relative to an energetically minimized assemblage of one toluene and two HTFA molecules.

For metal ions M^{n+} , the relevant species in the equation $M(HTFA)_c^{n+} + benzene \Rightarrow M(HTFA)_{c-1}(TFA)^{(n-1)+} + benzeneH^+$ were calculated, and the metals ranked by ΔG values. To ensure consistency, the coordination number, c, was taken to be 6 for most metals, with octahedral species being calculated; whereas for M = Pt, Pd, Au, and other platinum-group metals c was taken to be 4 and square planar species were calculated. The XYZ coordinates of calculated structures are available in the supporting information through *ACS Catalysis*.⁴¹

3.5.4 References

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4 The Development of Rh(I) Catalysts for the Single-step Production of Styrene from benzene and ethylene

4.1 Introduction to Styrene

The industrial production of vinyl arenes, important commodity chemicals, is practiced on a massive scale worldwide.^{1,2} Styrene, one of the most prominent vinyl arenes, is produced on approximately an 18 million ton scale per year domestically.³ Commercially, styrene has a broad range of applications, the most significant of which is polymerization to give polystyrene and copolymerization of styrene with butadiene to yield styrene-butadiene rubber (Figure 4.1). Other common uses for styrene provide multiple chemical feedstocks after styrene oxidation (Figure 4.2).^{4,5}



Figure 4.1. Repeating chemical structures of polystyrene and styrene-butadiene.⁴



Figure 4.2. Chemical feedstocks produced from the oxidation of styrene.⁵

As discussed in Section 1.4, styrene is currently produced via acid-catalyzed reactions.¹ Benzene is alkylated with ethylene in the presence of an acid catalyst to produce ethylbenzene, which is subsequently dehydrogenated to give styrene (Scheme 4.1). Due to the production of undesired polyalkylated products from the benzene ethylation reaction, a separate transalkylation step is required to enhance the overall yield of ethylbenzene.³ Although zeolites have improved the benzene alkylation step, challenges remain, particularly due to the energy-intensive nature of the dehydrogenation step.⁶⁻⁸



Scheme 4.1. Current routes for the production of styrene from benzene and ethylene.

Currently, 85% of the commercial production of styrene is through direct dehydrogenation of ethylbenzene. Typically, the reaction proceeds over an iron oxide catalyst, with imbedded potassium, with steam at high temperatures.^{2,5} The reaction is reversible, gas phase and endothermic with a Δ H (600°C) = 29.5 kcal/mol (Scheme 4.2). In order to bias the reaction toward product formation, the reaction is commonly run at low pressures to maximize the contribution of entropy, which favors the product side of the reversible reaction.⁵



Scheme 4.2. Reversible and endothermic dehydrogenation of ethylbenzene to styrene.

Furthermore, competing thermal reactions lower yield and produce unwanted side products (Scheme 4.3).⁵. For example, ethylbenzene can be degraded to carbon and hydrogen. Styrene is also not entirely stable under these conditions and can react to form toluene and methane.



Scheme 4.3. Competing reactions that reduce yield and efficacy for ethylbenzene dehydrogenation to styrene. Reactions not balanced.

An alternative method to the current production of styrene by Friedel-Crafts alkylation and subsequent dehydrogenation of ethylbenzene is the direct single-step production of styrene from ethylene and benzene with an oxidant. Transition metal complexes have been shown to catalyze the hydrophenylation of ethylene.⁹⁻²⁵ These catalysts mediate benzene C–H activation and insertion of ethylene into a M–Ph bond. If these catalysts could be designed to undergo β -hydride elimination from the phenethyl intermediate, followed by dissociation of styrene, a catalytic mechanism for the single-step production of styrene is obtained (Scheme 4.4).



Scheme 4.4. Proposed catalytic cycle for the oxidative vinylation of benzene to form styrene. [Ox] = oxidant.

The vinylation of benzene with a transition metal catalyst was first reported in 1969 by Ternashi and coworkers, who discovered that Pd(OAc)₂ and AgOAc in HOAc and benzene produced 59% styrene and 79% *trans*-stilbene, based on Pd(OAc)₂.²⁶ Shue built upon this finding, coupling the Pd(OAc)₂ with Cu(OAc)₂ and O₂ to improve catalysis.²⁷ The Pd(OAc)₂/dibenzoylmethane/H₄PMo₁₁VO₄₀•15H₂O/O₂ system developed by Ishii and coworkers proved to be an efficient catalyst for the production of styrene.²⁸ However, this process also produced significant amounts of byproducts as, relative to palladium, the reaction produced 20 turnovers (TOs) of styrene, 4 TOs *trans*-stilbene, 5 TOs of vinyl acetate and 3 TOs of phenol.

Sanford and coworkers studied the use of ligand systems with $Pd(OAc)_2$ for the oxidative vinylation of benzene in order to enhance product selectivity.²⁹ A ligand screen determined that 3,5-dichloropyridine in a 1:1 ratio with $Pd(OAc)_2$ was the most selective. Using the oxidant $PhCO_3^{t}Bu$, the coupling of benzene with ethylene produced styrene (6.6 TO) in 100% selectivity but in only 33% yield based on oxidant (Scheme 4.5). An

additional complication for this process is the inability to regenerate the oxidant, PhCO₃[']Bu using oxygen.



Scheme 4.5. $Pd(OAc)_2$ based catalyst for the oxidative vinylation of benzene with ethylene.²⁹

Hong and coworkers discovered that rhodium could effectively catalyze the production of styrene. $Rh_4(CO)_{12}$ with ethylene and carbon monoxide produced styrene (Scheme 4.6).³⁰ The reaction produced 472 TON of styrene, however it also produced 809 TON of 3-pentanone, an undesired byproduct. The 3-pentanone formed as a result of the reaction of the liberated dihydrogen with 2 equivalents of ethylene and 1 equivalent of carbon monoxide. In addition to its poor selectivity, the catalysis operated under severe conditions (220 °C) and high pressures (20 atm of carbon monoxide to stabilize the catalyst).



Scheme 4.6. Production of styrene and 3-pentanone by $Rh_4(CO)_{12}$ with benzene, ethylene and carbon monoxide.

Taube, Periana and Matsumoto reported on rhodium catalysis using $Rh(acac)_2Cl(H_2O)$ with $Cu(OAc)_2$ and O_2 as the oxidants.³¹ The catalyst operated at high temperatures (180-220 °C) produced styrene but also the side products vinyl acetate and *trans*-stilbene. The highest ratio achieved of styrene:vinyl acetate was 19:1. However, only 24 TOs of styrene were observed.

Tanaka reported that $Rh(Cl)(CO)(PPh_3)_2$ produces styrene using ultraviolet light.³² Benzene and ethylene were converted into styrene (3 TO), ethylbenzene (1.7 TO), and biphenyl (3.5 TO) using ultraviolet light at room temperature for > 26 h.

The results of oxidative vinylation of benzene with ethylene are summarized in Table 4.1. An important note is that the $(3,5-DCP)Pd(OAc)_2$ with $PhCO_3^{t}Bu$ produces the highest selectivity yet discovered. Whereas the highest TON for catalysis is $Rh_4(CO)_{12}$ with 472 TON of styrene. But, the catalysts shown in Table 4.1 generally suffer from low turnovers, poor selectivity, and/or low yield, which highlights the potential side pathways that can occur during the olefin hydroarylation reaction.

Catalyst	Oxidant	TON ^[a]	Selectivity ^[b]	Yield ^[c]
Pd(OAc) ₂ ^[d]	AgOAc	0.59	44%	12%
Pd(OAc) ₂ ^[e]	Cu(OAc) ₂ /O ₂	19	29%	5%
(DBM)Pd(OAc) ₂ ^[f]	HPA/O2 ^[k]	100	58%	2%
$(3,5-DCP)Pd(OAc)_2^{[g]}$	PhCO ₃ ^t Bu	6.6	100%	33%
$Rh_4(CO)_{12}^{[h]}$	C ₂ H ₄ /CO	472	37%	19%
(acac) ₂ Rh(Cl)(H ₂ O) ^[i]	Cu(OAc) ₂	24	89%	36%

Table 4.1. Comparison of previously reported catalysts for styrene production.

[a] TON = Turnover number for styrene. [b] Selectivity is defined as turnovers styrene/total turnovers (all products), and is given as a percentage. [c] % Yield of styrene reported relative to limiting reagent[d] Ref. ^{26,33}. [e] Ref. ³¹. [f] Ref. ³², [g] Ref. ³⁴, . [h] Ref. ³⁰. [i] Ref. ³¹, acac = acetylacetonate. [j] Ref. ²⁹, DBM = dibenzoylmethane. DCP = 3,5-dichloropyridine. [k] HPA = H₄PMo₁₁VO₄₀ •15 H₂O/O₂.

Scheme 4.7 shows a transition metal catalyzed cycle for the production of styrene with copper(II) salt as the oxidant with commonly observed side reactions shown in red and numbered. Because these side reactions often have similar energetic profiles as the desired reaction in the catalytic cycle, it is difficult to bias the catalyst to solely undergo on-cycle reactions. For example, the bond dissociation energy of ethylene and benzene C-H bonds are 111 kcal/mol and 113 kcal/mol, respectively.³⁵ Therefore the catalyst has to selectively activate benzene C-H bonds but not ethylene C-H bonds. Pathway 1 shows ethylene insertion into the M–X bond followed by β -hydride elimination to give a vinyl– X species. Thus, the formation of vinyl-X, commonly vinyl acetate, partially depends on the comparative rates of ethylene insertion and β -hydride elimination. In contrast pathway 2, benzene oxidation can occur if the rate of ethylene insertion is too slow. Another arene substrate can be activated followed by reductive elimination to form biphenyl. If ethylene activation is competitive with ethylene insertion pathway 3 may happen. Ethylene activation from the putative $LnM(Ph)(\eta^2-C_2H_4)$ complex and C–C bond formation with another equivalent of ethylene leads formation of η^3 -allyl and, ultimately, butenes. Our group has found that the formation of stable η^3 -allyl is a deactivation

pathway for the TpRu(L)(NCMe)Ph (Tp = hydridotris(pyrazolyl)borate, L = CO, PMe₃, P(*N*-pyrrolyl)₃, P(OCH₂)₃CEt, P(O)(OCH₂)₂CMe)) catalysts which form TpRu(L)(η^3 -C₃H₄Me).^{17,24,25,36,37} ENREF 17 The hydrophenylation of ethylene, pathway 4, can occur if the β -hydride elimination step is too slow relative to benzene C–H activation or if the β -hydride elimination is reversible. Pathway 5 highlights the possibility of ethylene polymerization to polyethylene. The rate of ethylene insertion determines the formation of these species. After β -hydride elimination, styrene phenylation pathway 6, generates stilbene if the rate of benzene C–H activation is faster than styrene dissociation. Similarly, styrene vinylation pathway 7, occurs if the coordinated styrene undergoes C–H activation and ethylene insertion. Although this pathway would be useful for the production of divinyl benzenes (*i.e.*, for cross-linked polystyrenes), those are not the targets of our studies.^{38,39} Thus, in light of the many side pathways, the requirements for a selective catalyst are considerable.



Scheme 4.7. Generic catalytic cycle for oxidative vinylation of benzene with ethylene using copper(II) salt as the oxidant. Common side reactions are shown in red and labeled.

Platinum species have been studied for the hydroarylation of ethylene due to the efficient C–H activation of benzene by many Pt(II) complexes.^{10-15,40,41} Indeed, our group has shown that varying the electron density of the ligands on the platinum center dramatically alters the selectivity of the olefin hydroarylation reaction. For example using [(^xbpy)Pt(Ph)THF][BAr'₄] 4,4'-di-*tert*-butyl-2,2'-bipyridine), when (^{*t*}bpy = the hydrophenylation of ethylene favors the production of ethylbenzene, whereas when $(^{NO2}bpy = 4,4'-di-nitro-2,2'-bipyridine)$, styrene formation is favored. While altering the ligand set enables the selective product of alkyl or vinyl arene products, challenges remain for this catalyst motif as the formation of Pt-H intermediates results in catalyst decomposition to inactive Pt(s).^{10,12} Because the formation of Rh(s) from Rh(I) is less favored than that of Pt(s) from Pt(II), we focused on developing rhodium(I) catalysts for this process (Scheme 4.8).⁴²

$$3 \operatorname{Rh}^{+} \longrightarrow \operatorname{Rh}^{3+} + 2 \operatorname{Rh}^{\circ} \qquad \qquad \Delta \operatorname{G}^{298\mathsf{K}} = +10.9 \operatorname{kcal/mol}$$
$$2 \operatorname{PtCl}_{4}^{2-} \longrightarrow \operatorname{PtCl}_{6}^{2-} + \operatorname{Pt}^{\circ} + 2 \operatorname{Cl}^{-} \qquad \qquad \Delta \operatorname{G}^{298\mathsf{K}} = -3.5 \operatorname{kcal/mol}$$

Scheme 4.8. Comparison of Rh(I) versus Pt(II) reduction energies.⁴²

The oxidation step must successfully remove the M–H and regenerate the active catalyst. In an ideal reaction, oxygen or air would be utilized as the oxidant, which would generate H₂O as the byproduct (Scheme 4.9). Alternatively, oxidants such as Cu(II) salts and organic oxidants like dimethylsulfoxide can be used as their reduced forms can be reoxidized by air or oxygen.⁴³⁻⁴⁵ Thus the overall reaction becomes simply the conversion of benzene and ethylene and oxygen to styrene and water, as the oxidant can be regenerated by oxygen.



Scheme 4.9. Single-step production of styrene from benzene and ethylene with oxygen as the oxidant.

We envisioned a Rh catalytic cycle that would proceed through oxidative addition of benzene C–H activation at Rh(I) to give a Rh–Ph , insert ethylene into the Rh–Ph bond, to generate a Rh–Phenethyl intermediate that would undergo β -hydride elimination Copper(II) salts were pursued as oxidants because they are effective for rhodium oxidation.^{46,47} In addition, the resultant reduced copper(I) species can be regenerated easily through oxidation in air.^{43,44} Industrially, copper(I) reoxidation by oxygen has been accomplished for the production of acetaldehyde in the Wacker process.⁴⁸⁻⁵⁰ Importantly, this technology has been operated under two different processes. In the first, the copper(II) salt is regenerated *in situ* by addition of pure oxygen to the reactor system. Purified oxygen is required because the rate of reoxidation of CuCl must be equal to rate of acetaldehyde production.⁴⁸ Alternatively, the reduced Cu(I) is transferred to a separate reactor where air is utilized to reoxidize the Cu(I) to Cu(II). A key determinant of which technique used is the localized cost of pure oxygen versus air at the chemical plant.⁴⁸ As the Wacker process has been well-studied and is commercially successful, we envisioned a similar process for styrene production. Scheme 4.10 compares the Wacker process to the idealized reaction for the production of styrene, which substitute's water for benzene.



Scheme 4.10. Comparison of the Wacker process with an envisioned styrene process. The net reactions are shown in the lower two quadrants.

4.2 **Results and Discussion**

As discussed in Chapter 2, we believed we had developed active catalysts for arene C–H activation. Because a key step for oxidative vinylation of benzene is the C–H activation of benzene, we investigated the most active arene H/D exchange catalysts for the oxidative vinylation of benzene, concomitant with the mechanistic studies of the arene H/D exchange. The most active catalyst was the perfluorodiimine rhodium species.^{51,52} Therefore, collaborating with Benjamin Vaughan in the Gunnoe lab, this catalyst, (FIDAB)Rh(μ -TFA)(η^2 -C₂H₄) (**4.1**) (TFA = trifluoroacetate) (Figure 4.3), was the first screened for single-step styrene production.⁵³ While working closely and discussing the chemistry together, the division of labor was that Mr. Vaughan developed the (FIDAB)Rh(μ -TFA)(η^2 -C₂H₄) catalysis while I pursued the ligand screening catalysis.



Figure 4.3. (FIDAB)Rh(μ -TFA)(η^2 -C₂H₄) (4.1)

To screen **4.1** for the oxidative vinylation of benzene, we used optimized temperature conditions from the H/D exchange reactions (Scheme 4.11). The reaction temperature 150 °C was found to be the most effective temperature for H/D exchange between benzene and HTFA. $Cu(OAc)_2$ was used as the oxidant because common side products of benzene vinylation, phenyl and vinyl acetates, can be observed easily using GC-FID.

In the initial screening, 60(2) TO of styrene was produced as the sole product of the screening reaction, in 100% yield relative to 120 equivalents of Cu(OAc)₂, which is the limiting reagent. This assumes that two equivalents of Cu(II) are consumed per TO of styrene that is produced. The remarkable selectivity of the reaction was confirmed by GC-FID and GC-MS analyses, as none of the likely byproducts, vinyl acetate, phenyl acetate, stilbene and biphenyl, were detected. The complete consumption of oxidant, the limiting reagent, is also of great significance, indicating the efficiency of the catalyst for this reaction. Importantly, the background reaction utilizing the Rh precursor without a DAB ligand, $Rh(\mu$ -TFA)(η^2 -C₂H₄)₂, produced less than 5 TO of styrene which emphasizes the impact of the ligand on catalysis.



Scheme 4.11. Initial screening of $({}^{Fl}DAB)Rh(\mu-TFA)(\eta^2-C_2H_4)$, **4.1**, for the oxidative vinylation of benzene with Cu(OAc)₂. Conditions: 0.001 mol % **4.1** relative to benzene. 120 equivalents of Cu(OAc)₂ relative to **4.1**.

Because catalyst stability in the presence of a large excess of oxidant is necessary for efficient industrial operation, the effect of varying the oxidant concentration was studied (Figure 4.4). Increasing the concentration of $Cu(OAc)_2$ results in increased production of styrene in >95% yield based on oxidant.



Figure 4.4. Effect of copper oxidant concentration on the production of styrene. Reaction conditions: 0.001 mol % **4.1** relative to benzene, 25 psi C_2H_4 , 120 °C, 60, 120, or 240 equivalents of Cu(OAc)₂ relative to **4.1**. Percent yield is reported relative to Cu(II) oxidant, assuming 2 equivalents are required per TO of styrene. Data for two independent reactions are shown for each oxidant amount.

The effect of oxidant identity was investigated (Figure 4.5). As $Cu(OAc)_2$ is only partially soluble in benzene, additional copper(II) salts were also screened to examine the effect of oxidant solubility on the reaction. $Cu(OAc)_2$ (Figure 4.5A) and $Cu(TFA)_2$ (Figure 4.5B) were investigated as the insoluble oxidants, and copper pivalate, $Cu(OPiv)_2$ (Figure 4.5C), and copper 2-ethylhexanoate, $Cu(OHex)_2$ (Figure 4.5D), were utilized as soluble copper(II) oxidants. $Cu(OAc)_2$ appears to produce of styrene steadily until the oxidant is consumed, with an apparent TOF of 2.8 x 10^{-4} s⁻¹ after 4 h. In contrast, $Cu(TFA)_2$ only produces approximately 20 TO of styrene before appearing to decompose. The lack of effective catalysis with $Cu(TFA)_2$ could be the result of HTFA production, as the strong acid may rapidly protonate the incipient Rh-Ph bond, before ethylene can insert, therefore inhibiting catalysis. $Cu(OPiv)_2$ is an effective oxidant, with ~92% yield after 28 h. $Cu(OHex)_2$ is the fastest oxidant with am apparent TOF of 2.8 x 10^{-3} s⁻¹; however, the deviation between trials was greater than for the other oxidants. Therefore, $Cu(OAc)_2$ was used as the oxidant for further studies.



Figure 4.5. Effect of oxidant identity on the production of styrene. A) $Cu(OAc)_2$, B) $Cu(TFA)_2$, C) $Cu(OPiv)_2$, D) $Cu(OHex)_2$. Reaction conditions: 0.001 mol % **4.1** relative to benzene, 25 psi C_2H_4 , 120 equivalents Cu(II) oxidant relative to **4.1**, 150 °C, theoretical maximum TON = 60. Error bars are standard deviations of the 4 data points from two individual experiments analyzed twice.

To further optimize the catalysis, the effect of temperature was studied (Figure 4.6). Similar to the H/D exchange data, the greatest TOs was observed at 150 °C. The optimal temperature range for catalysis is somewhat narrow. At temperatures < 100 °C,

minimal activity is observed, however at 180 °C only 10 TO of styrene were produced, likely a result of rapid catalyst decomposition.



Figure 4.6. TO of styrene as a function of temperature. Reaction conditions: 0.001 mol % **4.1** relative to benzene, 120 equivalents $Cu(OAc)_2$ relative to **4.1**, 25 psi C_2H_4 . Data for two independent reactions are shown for each temperature.

To determine the effect of ethylene concentration on the rate of catalysis,

experiments varying the ethylene pressure were examined. Figure 4.7 shows the apparent TOF (calculated after 4 h) of styrene production versus ethylene pressure. Data after 4 hours was utilized because minimal catalyst decomposition has occurred. The rate of styrene production increased linearly with increasing ethylene pressure. This shows a first order dependence on ethylene pressure. Our group's previous catalysts, based on Ru and Pt, showed an inverse dependence on ethylene pressure.^{15,22} The reaction was not attempted using pressures > 85 psi due to the hazard of using high pressures and temperatures in glass reactors.



Figure 4.7. TOF of styrene production versus ethylene pressure. Reaction conditions: 0.001 mol % **4.1** relative to benzene, 120 equivalents $Cu(OAc)_2$ relative to **4.1**, 150 °C, 4 h. Error bars are standard deviations of the 4 data points from two individual experiments analyzed twice.

To determine the longevity of this catalyst, an experiment was conducted using low catalyst loading with high Cu(OAc)₂ concentration and ethylene pressure in order to obtain the highest TO possible. Using 0.0001 mol % **4.1** and 2400 equivalents of Cu(OAc)₂ with 75 psi of ethylene, 835(18) TOs of styrene were produced after 96 hours (Figure 4.8). To our knowledge, this is the highest reported TO of a catalyst for the oxidative vinylation of benzene. The stability of the catalyst over a long period of time is also promising, although the overall yield of the reaction decreased to 70%. Increasing the reaction time beyond 96 h did not increase TO of styrene. This could be due to catalyst decomposition over time. Another possibility is that the increased concentration of HOAc relative to rhodium has retarded catalysis. HOAc may coordinate to the Rh center preferentially over ethylene or benzene. Further, HOAc could undergo oxidative addition to form Rh(III) which could be inactive for catalysis.



Figure 4.8. TO of styrene versus time for **4.1** with a large excess of copper oxidant. Reaction conditions: 0.0001 mol % 4.1 relative to benzene, 2400 equiv. $Cu(OAc)_2$ relative to **4.1**, 75 psi C₂H₄, 150 °C, theoretical maximum TON = 1200. Data for two independent runs are shown.

The impact of varying the substituents of the diimine ligand on the oxidative vinylation of benzene was investigated. These catalysts were synthesized in a manner analogous to that described in Chapter 2 and Scheme 4.12.

 $\begin{array}{c} \stackrel{F}{\rightarrow} \stackrel{F}{\rightarrow} \stackrel{F}{\leftarrow} \stackrel{F}{\leftarrow$

Fluorine Substituents



In Situ Synthesis



Scheme 4.12. Proligands that were synthesized to evaluate the impact of electron donation, steric profile, and fluorine substituents on Rh(I) catalyst precusors (iPr = isopropyl). On the bottom is shown the general synthesis of *in situ* generated catalyst precursors from the coordination of DAB ligands with $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$. When the numbers 4.2 - 4.13 are used in this chapter they refer to the proligands complexed rhodium species as shown in on the bottom.

The screening conditions were designed based upon the optimized catalysis with **4.1**. Therefore the temperature was set to 150 °C, the ethylene pressure was 40 psi, and the reaction was analyzed after 24 hours. After analyzing the oxidative vinylation of benzene with ethylene using **4.1**, the catalysis appears to show an induction period. Figure 4.6 shows this clearly, after 4 hours ~5 TOs are produced before increasing to ~20 and ~50 after 8 and 12 hours, respectively. Therefore we hypothesized that for slower catalysts a 24 hour reaction would attenuate the consequences of induction periods.

4.6



Figure 4.9. TO of styrene after 24 h for each catalyst. Reaction conditions: 0.001 mol % Rh (relative to benzene), 40 psi ethylene, 240 equiv. $Cu(OAc)_2$ relative to Rh, 150 °C. The theoretical maximum TO is 120. Error bars are standard deviations of three reactions.

The effect of fluorine substituents on the aryl ring on catalysis is significant and indicates that the positions, rather than the quantity, of the fluorine substituents are particularly impactful. The two catalysts that achieve quantitative production of styrene, **4.2** and **4.4**, both have fluorine substituents in the 2- and 6-positions on the aryl ring. In addition, the catalysis improves with increasing substitution of the 2- and 6-positions. Comparing **4.3** (2,4-diFl), **4.4** (2,6-diFl) and **4.5** (3,5-diFl) is informative as these catalysts each have 4 fluorine substituents but differentiate in position (Figure 4.10); the positional effect is revealed by 65(5), 120(4) TO and 36(4) TO of styrene, respectively. Thus, **4.3** is more effective than **4.5**, but less effective than **4.4**.



Figure 4.10. The impact of fluorine position on catalytic oxidative vinylation of benzene with ethylene to styrene.

This positional substitution effect was also observed with Pt catalysts for arene activation.⁵⁴ Sanford and coworkers discovered that the position of chlorines on diimine ligands effect the rate of benzene C–H activation. Thus for the oxidative vinylation of benzene the rate of arene C–H activation could be increased similarly. Another tentative hypothesis for this reactivity is that the fluorine substituents in the 2- and 6-positions blocks catalyst deactivation through C–H activation of the ligand in the 2- and 6-positions. Additional experimental studies are required to confirm the mechanistic details.

An original hypothesis for the effectiveness of **4.1** as a catalyst was that the electron-withdrawing ^{FI}DAB ligand could stabilize the Rh(I) active catalyst by suppressing the formation of Rh(III) under the oxidizing conditions. This is important because Rh(III) may be inactive for arene C–H activation. In addition, the ligand could facilitate rapid ethylene insertion into Rh–Ph bond and efficient exchange between styrene and ethylene. Therefore, other electron poor ligands were investigated. Complex **4.7** contains trifluoromethyl groups in the 3- and 5- positions of the aryl ring, complexes **4.8** and **4.9** contain nitro substituents in the 4-position of the aryl ring (Figure 4.11). Under the conditions tested **4.7**, **4.8**, and **4.9** produced 97(4), 78(2), and 78(3) TO,

respectively. Relative to the catalyst with the unsubstituted phenyl DAB ligand, **4.10**, with TO of 53(6), these species all exhibit increased efficacy, similar to the H/D exchange findings. Thus, strong electron-withdrawing substituents increase catalyst efficacy for oxidative vinylation.



Figure 4.11. Comparison of electron-withdrawing substituents on the catalytic oxidative vinylation of benzene with ethylene to styrene.

Increasing the steric bulk by adding alkyl substituents to the phenyl ring has a negative impact on the efficacy of catalysis. Increased steric bulk in the 2- and 6-positions inhibits catalysis. Complexes **4.12** (2,4,6-trimethyl) and **4.13** (2,4-diisopropyl) produce 27(3) and 5(2) TO after 24 h, respectively. A possible reason is that the steric bulk hinders coordination of ethylene and/or benzene, and therefore retards catalysis. However, the comparison of **4.8** and **4.13** provides evidence against this hypothesis. Both species contain isopropyl groups in the 2- and 6- positions; however, **4.8** also contains a nitro group in the 4-position. Substituents on the 4-aryl position are unlikely to have a steric effect on the rhodium center. Importantly, **4.8** produces 78(2) TO while **4.13** produce 5(2) TO of styrene. Further evidence against the hypothesis that ethylene and/or benzene coordination is inhibited by sterically bulky ligands is provided by comparing the results from **4.8** and **4.9**, which produce 78(2) and 78(3) TO of styrene, respectively.

after 24 h. Both species contain a 4-nitro group but **4.8** has isopropyl groups in the 2- and 6-positions of the aryl ring. Thus, the isopropyl groups appear to exert little influence on the rate of ethylene or benzene coordination. However, examining the catalysis over 48 h revealed some interesting observations (Figure 4.12). Indeed, the isopropyl groups of complex **4.8** seem to enhance the initial catalytic rates. After 48 hours, complex **4.8** achieves 100% consumption of oxidant whereas complex **4.9** yields 72%.



Figure 4.12. A comparison of **4.8** and **4.9** for the production of styrene over time. Reaction conditions: 0.001 mol % Rh (relative to benzene), 40 psi ethylene, 240 equiv. $Cu(OAc)_2$ relative to Rh, 150 °C. Error bars are standard deviations of three trials; for some samples the error bars small and hidden by the shape

To determine if the aryl groups are necessary for catalysis, the ligand screen was extended to include dimethylglyoxime (**4.14**), 2,2'-bipyridine (**4.15**) and bisoxazoline (**4.16**) (Figure 4.13). Oxidative vinylation of benzene investigated, over 24 h at 150 °C, and revealed 2(1), 7(1), and 22(1) for **4.14**, **4.14** and **4.15**, respectively.


Figure 4.13. Diffinite ligands, without aryl groups coordinated to nitrogen, coordinated to Rh and screened for the oxidative vinylation of benzene. On the top is shown the general synthesis of *in situ* generated catalyst precursors from the coordination of ligands with $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$. When the numbers 4.14 – 4.16 are used in this chapter they refer to the complexed rhodium species as shown in on the bottom. Reaction conditions: 0.001 mol % Rh (relative to benzene), 40 psig ethylene, 240 eq. Cu(OAc)₂, 150 °C. Parentheses are standard deviations of three reactions.

Although more detailed kinetic and mechanistic studies are needed, studies show that in general electron-deficient ligands are the more proficient catalysts under our conditions screened. Alkyl substituents, in general, decrease catalyst effectiveness. Further, the position of the electron-withdrawing fluorine substituents has a dramatic impact on catalyst efficacy. In addition, catalysis is enhanced by ligands with aryl groups on the diimine. These results highlight the importance of achieving the right steric and electronic environment for catalysis.

4.3 Conclusion

 $(^{FI}DAB)Rh(\mu-TFA)(\eta^2-C_2H_4)$ (4.1) was an effective catalyst for the H/D exchange between benzene and HTFA. Since arene C–H activation is an important step in the oxidative vinylation of benzene, we hypothesized that complex 4.1 might be successful the production of styrene. The initial screening of 4.1 for the oxidative vinylation of

benzene was successful, revealing 100% selectivity for the production of styrene. Furthermore, increasing the oxidant concentration led to an increase in the TO of styrene and proved that the catalyst was stable in the presence of excess oxidant, as greater than 95% selectivity was obtained. In addition, although soluble copper species proved to exhibit increased initial rates of catalysis, those reactions did not reach completion even over extended times. The optimal temperature for the oxidative vinylation of benzene with ethylene is 150 °C. Increased reaction temperatures, specifically 180 °C, can decompose the catalyst and result in the formation of the undesired byproducts phenyl acetate and biphenyl. Previous examples for the hydrophenylation of ethylene with Pt and Ru were found to have an inverse dependence on the concentration of ethylene. Interestingly, the reaction was shown to have a first order dependence on ethylene concentration. This is exciting because industrially the production of ethylbenzene occurs under high ethylene pressures (> 200 psi ethylene).⁵⁵ Moreover, experimental conditions were discovered that produced the highest reported TO of styrene for a transition metal homogenous catalyst, 835(18). Under our conditions, a brief ligand screen seemingly determined that fluorine substituents in the 2- and 6-positions of the aryl ring provide efficient catalysis. In particular, electron-deficient ligands were found to enhance catalysis. Studies revealed that catalysis with ligands other than diazobutadiene ligand motif can be observed; however, catalytic efficacy is reduced. Under the specific conditions screened less than 5 TOs of styrene were discovered when using $[Rh(\mu -$ TFA) $(\eta^2$ -C₂H₄)₂]₂. Thus, complex **4.1** is the most active and selective catalyst yet designed for the single-step production of styrene. By utilizing 4.1, we have been able to

develop a process to produce styrene in one step using an air-regenerable oxidant, a potential improvement on the standard industrial process (Scheme 4.13).



Scheme 4.13. Comparison of the current industrial route to styrene and the single step production described.

4.4 Experimental Methods

4.4.1 General Information

All manipulations were performed under an atmosphere of dry nitrogen using standard Schlenk or high vacuum techniques and/or in a Vac Atmospheres Dri-Lab glovebox equipped with a Dri-Train MO-41 purifier. Dry, oxygen-free solvents were employed throughout. THF was dried by passage through columns of activated alumina, followed by distillation from sodium benzophenone ketyl. Pentane was dried over sodium benzophenone ketyl. Deuterated solvents were purchased from Cambridge Isotope Labs, degassed, and dried over 4Å molecular sieves. NMR spectra were recorded on a Varian Inova 300 MHz NMR spectrometer (¹⁹F, 282.21 MHz operating frequency), Bruker Avance III 600 MHz NMR spectrometer (¹⁴H, 600.13 MHz operating frequency), or a Bruker Avance III 800 MHz NMR spectrometer (¹³C, 201.27 MHz operating frequency)

and are reported with reference to residual solvent resonances. GC/MS was performed using a Shimadzu GCMS-QP2010 Plus system with a 30 m x 0.25 mm SHRXI-5MS column with 0.25 μ m film thickness using electron impact (EI) ionization. GC/FID was performed using a Shimadzu GC-2014 system with a 30 m x 90.25 mm HP5 column with 0.25 μ m film thickness. Styrene production was quantified using linear regression analysis of gas chromatograms of standard samples of authentic product. A plot of peak area ratios versus molar ratios gave a regression line. For the GC/FID system, the slope and correlation coefficient of the regression line were 1.34 and 0.99, respectively. FID response factors for other products were determined in a similar fashion, using authentic standards of products. Ethylene was purchased in gas cylinders from GTS-Welco and used as received. All other reagents were purchased from commercial sources and used as received.

4.4.2 Ligand synthesis

Most of the diimine ligands (diazbutadienes, or DABs) were synthesized following a modified literature procedure:⁵⁶ To a round-bottom flask, 2.1 equivalents of the aniline, 1 equivalent of 2,3-butanedione, 0.1 equivalents of *p*-toluenesulfonic acid and 4 equivalents of trimethylorthoformate were combined in 10 mL of anhydrous methanol under air. The reaction mixture was stirred for 8 hours accompanied by the precipitation of a yellow solid. The solid was collected by filtration, washed with 5 mL of cold methanol, and dried under vacuum. The identity of the DABs was confirmed by comparison to reported NMR data for 3,5-diMeDAB = N,N'-bis-(3,5-dimethylphenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene),⁵⁸ 2,6-dippDAB = N,N'-bis-(2,6-diisopropylphenyl)-2,3-dimethyl-1,4-diaza-

1,3-butadiene),⁵⁸ 2,6-diClDAB = N,N'-bis-(2,6-dichlorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene),⁵⁹ 3,5-diCF₃DAB = N,N'-bis-(3,5di(trifluoromethyl)phenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene),⁶⁰ 2,6-diFlDAB = N,N'-bis-(2,6-difluorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene),⁶¹ (2,4-diFlDAB = N,N'-bis-(2,4-difluorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene) and (4-FlDAB = N,N'-bis-(4-fluorophenyl)-2,3-dimethyl-1,4diaza-1,3-butadiene),⁶² (^{Fl}DAB = N,N'-bis-(pentafluorophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene),⁵⁶ The ligands (2,6-dip-4-nitroDAB = N,N'-bis-(2,6-diisopropyl,4nitrophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene) and (4-nitroDAB = N,N'-bis-(4nitrophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene) were prepared according to literature procedures,⁶³ and 4-nitroDAB was confirmed to reported NMR data.⁶⁴

4.4.3 Synthesis of [(FIDAB)Rh(µ-TFA)]₂.

To a stirring solution of $[Rh(\eta^2-C_2H_4)_2(\mu-TFA)]_2$ (200 mg, 0.368 mmol) in THF (25 mL), ^{FI}DAB (310 mg, 0.735 mmol) was added, and the mixture was stirred for 10 minutes. The solvent was removed *in vacuo*, and the purple solid was washed with pentane (c.a. 80 mL) and dried to afford 4.1 as a purple powder (330 mg, 0.501 mmol, 68%). Upon prolonged drying *in vacuo*, the ethylene is removed to form $[(^{FI}DAB)Rh(\mu-TFA)]_2$ (Scheme 4.14), characterization data for which is as follows. ¹H NMR (800 MHz, DMF- d_7): δ -0.6 (s, 6H, DAB-CH₃). ¹³C NMR (800 MHz, DMF- d_7): δ 163.8 (s, DAB-C=N), 142.0 (d, ³ $J_{CF} = 8$ Hz, C₆F₅-*ortho* C), 140.8 (d, ³ $J_{CF} = 12$ Hz, C₆F₅-*ortho* C), 139.6 (t, ³ $J_{CF} = 13$ Hz, C₆F₅-*meta* C), 139.0 (t, ³ $J_{CF} = 15$ Hz C₆F₅-*meta* C), 137.8 (t, ³ $J_{CF} = 13$ Hz, C₆F₅-*ipso* C), 115.8 (q, ¹ $J_{CF} = 293$ Hz, CO₂CF₃), 20.9 (s, DAB-CH₃), 13.7 (q, ³ $J_{CF} = 23$ Hz, CO₂CF₃). ¹⁹F NMR (300 MHz, DMSO- d_6): δ -74.0 (s, TFA), -151.9 (dd, J = 24 Hz, 6 Hz, C₆F₅ *para* F), -162.3 (t, J = 23 Hz, C₆F₅ *meta* F), -

163.4 (td, J = 23 Hz, 6 Hz, C₆F₅ ortho F). Anal. Calcd for C₃₆H₁₂F₂₆N₄O₄Rh₂: C, 34.20; H, 0.96; N, 4.43. Found: C, 33.61; H, 1.05; N, 4.14. NMR spectrum shown in chapter 2. Upon pressurizing with ethylene, complex 4.1 can be regenerated (Scheme 4.14), *in situ* characterization data are as follows: ¹H NMR (800 MHz, DMF-d₇): δ 5.9 (s, 4H, C₂H₄), 3.5 (s, 6H, DAB-CH₃).



Scheme 4.14. Synthesis of $(^{Fl}DAB)Rh(TFA)(\eta^2-C_2H_4)$ (4.1).

4.4.4 Catalytic Oxidative Hydrophenylation of Ethylene with (FIDAB)Rh(TFA)(η^2 -C₂H₄) (4.1).

A representative catalytic reaction is described. A stock solution containing 4.1 (0.015 g, 0.023 mmol), decane (44 μ L, 0.23 mmol), and benzene (200 mL) was prepared in a volumetric flask. Fisher-Porter reactors were charged with stock solution (20 mL) and copper 2-ethylhexanoate (0.095 g, 0.27 mmol). The vessels were sealed, pressurized with ethylene (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled every 4 h for the first 12 h, then every subsequent 12 h. At each time point, the reactors were cooled to room temperature, sampled, recharged with ethylene, and reheated. Aliquots of the reaction mixture were analyzed by GC/FID using relative peak areas versus an internal standard (decane).

4.4.5 Catalyst Loading Experiments with (FIDAB)Rh(TFA)(η^2 -C₂H₄) (4.1).

Three separate stock solutions were prepared in 50 mL volumetric flasks, each containing 4.1 (0.05 mol %, 0.025 mol %, or 0.001 mol % relative to benzene), decane (10 equiv.

relative to 4.1), and benzene (50 mL). Fisher-Porter reactors (2 reactors per loading) were charged with stock solution (20 mL) and $Cu(OAc)_2$ (60 equiv. relative to 4.1). The vessels were sealed, charged with ethylene (25 psig), and subsequently stirred and heated to 120 °C. The reaction was sampled every 4 h for the first 12 h, then every subsequent 12 h. At each time point, the reactors were cooled to room temperature, sampled, recharged with ethylene, and reheated. Aliquots of the reaction mixture were analyzed by GC/FID using relative peak areas versus an internal standard (decane).

4.4.6 Experiments with 0.0001 mol % of complex 1 (relative to benzene) with (FIDAB)Rh(TFA)(η^2 -C₂H₄) (4.1).

A 0.001 mol % stock solution containing **4.1** (0.002 g, 0.003 mmol), decane (6 μ L, 0.03 mmol), and benzene (25 mL) was prepared in a volumetric flask. A 0.0001 mol % stock solution was prepared by transferring 5 mL of 0.001 mol % stock solution to a 50 mL volumetric flask and diluting to volume with benzene. Fisher-Porter reactors were charged with 0.0001 mol % stock solution (20 mL) and Cu(OAc)₂ (0.100 g, 0.55 mmol). The vessels were sealed, pressurized with ethylene (75 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled every 24 h. At each time point, the reactors were cooled to room temperature, sampled, recharged with ethylene, and reheated. Aliquots of the reaction mixture were analyzed by GC/FID using relative peak areas versus an internal standard (decane).

4.4.7 Oxidant Screening Experiments with (^{FI}DAB)Rh(TFA)(η^2 -C₂H₄) (4.1).

A stock solution containing **4.1** (0.001 mol % relative to benzene), decane (10 equiv. relative to **4.1**), and benzene (200 mL) was prepared in a volumetric flask. Fisher-

Porter reactors (2 per oxidant) were charged with stock solution (20 mL) and oxidant (120 equiv. relative to **4.1**). Oxidants screened included copper(II) pivalate, copper(II) 2-ethylhexanoate, copper(II) trifluoroacetate, and copper(II) acetate. The vessels were sealed, charged with ethylene (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled at 3, 8, 12, 24, and 28 h. At each time point, the reactors were cooled to room temperature, sampled, recharged with ethylene, and reheated. Aliquots of the reaction mixture were analyzed by GC/FID using relative peak areas versus an internal standard (decane).

4.4.8 Oxidant Concentration Experiments with (^{Fl}DAB)Rh(TFA)(η^2 -C₂H₄) (4.1).

A stock solution containing **4.1** (0.001 mol % relative to benzene), decane (10 equiv. relative to **4.1**), and benzene (200 mL) was prepared in a volumetric flask. Fisher-Porter reactors (2 per oxidant amount) were charged with stock solution (20 mL) and Cu(OAc)₂ (60, 120, or 240 equiv. relative to **4.1**). The vessels were sealed, charged with ethylene (25 psig), and subsequently stirred and heated to 120 °C. The reaction was sampled every 4 h for the first 12 h, then every subsequent 12 h. At each time point, the reactors were cooled to room temperature, sampled, recharged with ethylene, and reheated. Aliquots of the reaction mixture were analyzed by GC/FID using relative peak areas versus an internal standard (decane).

4.4.9 Temperature Variation Experiments with $(^{Fl}DAB)Rh(TFA)(\eta^2-C_2H_4)$ (4.1).

A stock solution containing **4.1** (0.001 mol % relative to benzene), decane (10 equiv. relative to **4.1**), and benzene (200 mL) was prepared in a volumetric flask. Fisher-

Porter reactors were charged with stock solution (20 mL) and $Cu(OAc)_2$ (120 equiv. relative to **4.1**). The vessels were sealed, charged with ethylene (25 psig), and subsequently stirred and heated to 90, 120, 150, or 180 °C (2 reactors per temperature). The reaction was sampled every 4 h for the first 12 h, then every subsequent 12 h. At each time point, the reactors were cooled to room temperature, sampled, recharged with ethylene, and reheated. Aliquots of the reaction mixture were analyzed by GC/FID using relative peak areas versus an internal standard (decane).

4.4.10 Ethylene Pressure Experiments with (^{Fl}DAB)Rh(TFA)(η^2 -C₂H₄) (4.1).

A stock solution containing **4.1** (0.001 mol % relative to benzene), decane (10 equiv. relative to **4.1**), and benzene (200 mL) was prepared in a volumetric flask. Fisher-Porter reactors were charged with stock solution (20 mL) and Cu(OAc)₂ (120 equiv. relative to **4.1**). The vessels were sealed, charged with ethylene (15, 25, 50, or 100 psig, 2 reactors at each pressure), and subsequently stirred and heated to 150 °C. The reaction was sampled every 4 h for the first 12 h, then every subsequent 12 h. At each time point, the reactors were cooled to room temperature, sampled, recharged with ethylene, and reheated. Aliquots of the reaction mixture were analyzed by GC/FID using relative peak areas versus an internal standard (decane).

4.4.11 General procedure for complex synthesis with 4.1.

Under nitrogen, the diimine ligand (2 equiv, 414.5 μ mol) in THF (10 ml) was added to a stirring solution of [Rh(μ -TFA)(η^2 -C₂H₄)₂]₂ (1 equiv, 207 μ mol) in THF (15 mL). The solution immediately became deep purple to black. After 1 hour the solvent was removed *in vacuo*, and the resulting solid was washed with *n*-pentane (20 mL) and then dried under vacuum to yield the corresponding *in situ* rhodium catalyst.^{65 65}

4.4.12 Catalytic Oxidative Hydrophenylation of ethylene ligand screen.

A representative catalytic reaction is described. A stock solution containing **4.10** (0.011 g, 0.023 mmol of rhodium), hexamethylbenzene (0.075 mg, 0.46 mmol), and benzene (200 mL) was prepared in a volumetric flask. Fisher-Porter reactors were charged with stock solution (10 mL) and CuOAc₂ (0.050 g, 0.28 mmol). The vessels were sealed, pressurized with ethylene (40 psig), and subsequently stirred and heated to 120, 150, and 180 °C. The reaction was sampled after 24 hours. If more time points were investigated the reaction was sampled every 4 h for the first 12 h, then subsequent 12 h, and then every 24 h subsequently. At each time point, the reactors were cooled to room temperature, sampled, recharged with propylene, and reheated. Aliquots of the reaction (<100 μ L) mixture were analyzed by GC/FID using relative peak areas versus an internal standard (hexamethylbenzene).

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5 Rhodium Species for the Conversion of Arenes and α-Olefins to Anti-Markovnikov Vinyl and Allyl Arenes

5.1 Introduction to Anti-Markovnikov Alkyl Arenes

Alkyl arenes are the precursors for a wide range of materials for plastics, elastomers, detergents, fuels and fine chemicals, and are produced on a scale of approximately 30 million tons annually (Table 5.1).¹⁻⁴ Globally, the largest alkylation process is the alkylation of benzene with ethylene to produce ethylbenzene, which is synthesized on a 20 million ton scale annually.⁵ The majority of ethylbenzene is then dehydrogenated to produce styrene.^{6,7} Through the addition of benzene to propylene, the second most prominent alkyl arene, cumene, is produced on a 7.5 million ton scale annually and is subsequently oxidized to produce phenol and acetone.^{8,9} Similarly, two equivalents of propylene and benzene are used to produce *p*-diisopropylbenzene on a 100,000 ton scale annually.¹ The oxidation of *p*-diisopropylbenzene yields hydroquinone, which is used in the rubber industry, dyes and pigments, and as a precursor to agricultural chemicals.10 Benzene is also alkylated with C10-C18 olefins to produce long chain alkylbenzenes on a 900,000 ton scale annually.¹ These longer chain alkylbenzenes are predominately sulfonated at the *para* position of the arene to be used as surfactants.² Alkylphenols, which are used as detergents, lubricants, and in flavor industries,^{11,12} are produced on a 300,000 ton scale annually by a similar process through the alkylation of phenol with C_8 - C_{20} olefins.

Arene	Olefin	Catalyst (s)	Alkylated Product	Production, 10^6 t/a
benzene	ethylene	AlCl ₃ , zeolites, HF	ethylbenzene	20
benzene	propylene	solid acids, zeolites, HF	cumene	7.5
benzene	C_{10} - $C_{18} \alpha$ - olefins	H_2SO_4 , HF, AlCl ₃ , solid acids	alkylbenzenes	0.9
benzene	propylene	zeolites	<i>p</i> -diisopropylbenzene	0.1
phenol	C ₈ -C ₂₀ olefins	solid acids	alkylphenols	0.3

Table 5.1. Industrial examples of alkylation processes.¹

Each of these industrial alkylation processes utilize acid-based catalysts that operate through a mechanism similar to that shown in Scheme 5.1, which uses HF as a representative acid catalyst. These reactions operate through the generation of a cationic alkyl species that subsequently reacts with the electron-rich arene to produce a Wheland intermediate. Upon deprotonation of the Wheland intermediate, the alkylbenzene is produced and the acid catalyst is regenerated.



Scheme 5.1. The acid-based alkylation of benzene with 1-butene for the production of 2-phenylbutane.

Generating the cationic intermediate by reaction of acid with the olefin is achieved by two methods in industry. The more prevalent technique operates via the protonation of an olefin with an acid as shown in Scheme 5.1. Alternatively, alkylchlorides are reacted with with $AlCl_3$ produces cationic alkyl substrates (Scheme 5.2). Because each method employs the same mechanism of action, these reactions produce very similar ratios of branched products (2-phenylalkyl, 3-phenylalkyl etc) with only trace quantities of *n*-alkylbenzene (1-phenylalkyl).



Scheme 5.2. The production of alkylbenzenes from benzene and alkylchlorides.

The cationic alkyl intermediate determines the selectivity of the reaction as product formation is influenced by cationic stability of primary < secondary < tertiary.^{4,13} This cationic effect greatly limits the product selectivity. For example, under certain conditions, secondary alkylbenzene products are observed from reactions with tertiary alkyl halides. A representative example of this reactivity is observed for the alkylation of benzene with 2-chloro-2,3-dimethylbutane using AlCl₃, as the major product of the reaction is 2,2-dimethyl-3-phenylbutane while 2-methyl-3-methyl-3-phenylbutane is the minor product (Scheme 5.3).¹ This occurs as a result of isomerization of 2-methyl-3-methyl-3-phenylbutane and the formation of a more stable carbocation. Thus, the possible products for acid-based alkylation reactions are often dependent upon the formation of the most stable carbocation intermediate, and opportunities for catalyst controlled selectivity are minimal with acid.



Scheme 5.3. The alkylation of benzene with 2-chloro-2,3-dimethylbutane produces 2,2-dimethyl-3-phenylbutane as the major product.

The work in this chapter is focused on the production of straight-chain alkenylbenzenes, which cannot be produced through the aforementioned acid-catalyzed alkylation methods. Therefore a more detailed history of the production of linear alkylbenzenes is helpful. Until the early 1940s, the majority of the detergents and surfactants were derived from animal and vegetable fats.¹⁴ However, with the development of synthetic alkylbenzene sulfonates, which offered superior performance, natural fats were phased out and these alkylbenzene derivatives became the basis of the detergent industry.^{2,15}

The first of these alkylbenzene based detergents were generated through Friedel-Crafts alkylation of benzene with propylene tetramer – a mixture of C_{12} olefins (Figure 5.1).¹⁴ This mixture of olefins, upon carbocation rearrangement, led to highly branched alkylbenzenes also known as BABs (Figure 5.2).¹ Subsequent sulfonation of the benzene ring is achieved through reaction of the BAB with oleum or gaseous sulfur trioxide.² Today, the majority of the sulfonation is done with sulfur trioxide primarily due to increased reaction rates and in order to reduce the amount of toxic sulfuric acid waste. Following sulfonation, the alkylbenzene sulfonates are neutralized by washing with aqueous NaOH or Na_2CO_3 solutions. The sodium alkylbenzene sulfonates are then formulated into commercial products (Scheme 5.4).^{2,3,14}



Figure 5.1. Two examples of the structures of propylene tetramers ($C_{12}H_{24}$).



Figure 5.2. An example of a BAB, 4-phenyl-4,6,8-trimethylnonane.



Scheme 5.4. Sulfonation and neutralization of a branched alkylbenzene.

Although highly branched alkylbenzene sulfonates are effective detergents, environmental concerns developed because of their slow biodegradation.^{2,14,16} In the late 1950s, Germany experienced several abnormally dry summers, which restricted water flow. As a result, large quantities of foam from BAB-based detergents began appearing.^{15,17} Further, the branched alkylbenzene sulfonates were found to pass through sewage plants unperturbed. Accordingly, in the interest of public health, regulations led toward efforts to improve the biodegradability of these detergents.^{2,15} Because the highly branched nature of the alkyl chain of these compounds rendered them resistant to aerobic

degradation,¹⁶ the chemical industry developed "linear" alkylbenzenes or LABs (Figure 5.3), as these were found to have improved biodegradability.



Figure 5.3. An example of a LAB, 2-dodecylbenzene.

The production of LABs operates through the same acid-based processes as BABs; however, α -olefins are used instead of significantly branched olefins. Consequently, the generation of these LABs was dependent on the development of methods to produce α -olefins. Initially, linear olefins were produced through the mono-chlororination of *n*-alkanes.^{18,19} The resulting chloroalkane was then used directly with AlCl₃ or dehydrochlorinated to form α -olefins. Today, the most common methodologies to yield α -olefins are the oligomerization of ethylene and the dehydrogenation of linear alkanes.^{14,20,21}

However, even using α -olefins, the production of 1-phenylbenzenes cannot be generated from acid-based alkylation reactions (Table 5.2). Indeed a variety of different "linear" alkylbenzenes are produced; of which the exact production formation depends partially on the acid utilized .²² Even utilizing shape selective zeolite the production of 1-phenylbenzenes is not possible.²³

Phenyldodecane,	Catalyst (Temperature)			
% mass fraction	HF (16 °C)	AlCl ₃ (30 °C)	H ₂ SO ₄ (10 °C)	
1-Phenyl	0	0	0	
2-Phenyl	20	32	41	
3-Phenyl	17	22	20	
4-Phenyl	16	16	13	
5-Phenyl	23	15	13	
6-Phenyl	24	15	13	

Table 5.2. Formation of phenyldodecanes from 1-dodecene with benzene using a variety of acids.²²

The conversion of detergents from BABs to LABs has been beneficial for the environment (Scheme 5.5). However, the acid-based methodology cannot make the 1-phenyl substituted alkanes, or as the Gunnoe group has named them, super linear alkylbenzenes (SLABs). The generation of 1-phenylalkanes could potentially be advantageous. For example, 1-phenyldodecane was found to have increased detersive power in low concentrations relative to the branched products.²⁴ Additionally, SLABs achieve the linearity of the alkyl chain that is typically found in natural soaps and detergent precursors such as stearic acid and lauric acid.²⁵



BAB: 1940s chemical

LAB: current chemical

SLAB: future chemical

Scheme 5.5. The progression of detergent substrates with a view to the future.

The current method to synthesize 1-phenylalkane compounds is through Friedel-Crafts acylation followed by reduction (Scheme 5.6). However, the generation of functionalized substrates then Friedel-Crafts acylation followed by reduction is not economically viable on the multi-million ton scale necessary for petrochemical processes. Developing a process that is selective for anti-Markovnikov alkylbenzenes using petrochemical feedstocks, such as benzene or toluene, with readily available α -olefins such as propylene and 1-pentene, is highly desirable.



Scheme 5.6. Friedel-Crafts acylation followed by reduction to yield *n*-alkylbenzenes.

As current acid-based methods are subject to carbocation rearrangement and unable to produce SLABs, a new strategy is required. A transition metal-mediated catalyst for hydrophenylation of olefins that operates through C–H activation of the arene followed by insertion of the olefin into the M–Ph bond could enable production of straight chain alkylbenzenes.^{26,27} This strategy is possible because the olefin insertion step can control which product, linear or branched, is formed. The ratio of linear to branched (L:B) species would be partially dependent upon the rate of 2,1-insertion versus 1,2-insertion (Scheme 5.7). Product selectivity could also be reliant on Curtin-Hammett conditions; for example, after the olefin insertion, the relative rates of arene C–H activation for product formation (Scheme 5.8). Notably, these methods to control selectivity are not available through acid-based mechanisms.



Scheme 5.7. The production of linear or branched alkylbenzene is partially dependent on the rate of 2,1- versus 1,2-insertion.



Scheme 5.8. Reaction coordinate showing Curtin-Hammett conditions could control the linear to branched selectivity through arene C–H activation. In this example, $\Delta\Delta G_{\downarrow}^{\ddagger} > \Delta G$ and $\Delta G_{1}^{\ddagger} > \Delta G_{2}^{\ddagger}$.

Selectivity, albeit moderate, for linear alkylbenzenes has been observed using transition metal complexes.²⁶ However, the most selective catalyst yet discovered for the conversion of benzene and propylene to n-propylbenzene and cumene gives a ratio of

1.6:1. Selected examples of transition metal mediated hydrophenylation of propylene are shown in Scheme 5.9. Our group has developed a [(^{tBu}bpy)Pt(Ph)THF][BAr'₄] catalyst $(^{tBu}bpy = 4.4'-di-tert-butyl-2.2'-bipyridine, Ar'_4 = 3.5-bis(trifluoromethyl)phenyl)$ for propylene hydrophenylation that produces 33.5 TON of *n*-propylbenzene and cumene in a 1:2.9 ratio.^{28,29} Goldberg and coworkers developed a Pt catalyst for propylene hydrophenylation, $[(dmpp)Pt(SMe_2)Ph]$ (dmpp = 3,5-dimethyl-2-(2-pyridyl)pyrrolide), which improved the L:B ratio to 1:1.³⁰ For Goldberg's catalyst, the ratio of linear to branched products can be increased by using sterically hindered olefins. For example, the 1:1 L:B ratio with benzene and propylene can be increased to 5.7:1 with benzene neohexene. Higher L:B selectivity for propylene hydrophenylation was achieved by Periana, Goddard, and coworkers, using two similar iridium complexes, trans- $[(acac)_2 Ir(Ph)(py)]$ and *trans*- $[(trop)_2 Ir(Ph)(py)]$ (trop = $\kappa^2 - O, O$ -tropolonato), which both give L:B ratios of 1.6:1 with a max TON of 13.31-33 Further, our group's TpRu(CO)(NCMe)Ph complex catalyzes the hydrophenylation of propylene with a L:B ratio of 1.6:1 with 14 TON.³⁴



Scheme 5.9. Selected examples of the transition metal catalysts for the hydrophenylation of propylene.²⁸⁻³³

Hartwig and coworkers demonstrated a nickel bis-NHC (NHC = (1,3-bis(2,6-disopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene)) complex for the stoichiometric production of anti-Markovnikov alkylbenzenes.³⁵ Using benzene and 1-octene produces *n*-octylbenzene and 2-phenyloctane in a 19:1 L:B ratio (Scheme 5.10). This is the most selective reported process for anti-Markovnikov alkylation using non-Michael acceptors. However, the reaction is stoichiometric with respect to the nickel complex.



Scheme 5.10. In situ formation of a nickel complex for the production of anti-Markovnikov *n*-octylbenzene and 2-octylbenzene. (COD = 1,5-cyclooctadiene).

Ruthenium carboxylates have been shown to mediate hydroarylation of unactivated olefins to produce anti-Markovnikov alkylarenes.³⁶ But, the reaction is

limited to substrates with directing groups, such as pyridine, to aid the C–H activation. However, an important aspect of this chemistry was the demonstration that ruthenium carboxylates can be effective for the C–H activation step of olefin hydroarylation.

Another interesting development in the field of anti-Markovnikov alkylation was demonstrated by Goldman, Brookhart and coworkers.³⁷ *N*-alkylbenzenes were synthesized through alkyl group cross-metathesis reactions from alkanes and alkylbenzenes. This combines dehydrogenation, olefin metathesis, and hydrogenation by using two catalysts in one pot. The iridium catalyst promotes dehydrogenation, while the tungsten catalyst mediates olefin metathesis, and then the iridium catalyst hydrogenates the new olefin species. For example, ethylbenzene and *n*-octane can be converted to *n*-octylbenzene as well as several other hydrocarbons in the C_{10} - C_{14} range such as 1-phenylheptane and tetradecane (Scheme 5.11). The formation of undesired side products has so far limited the practicality of this methodology.



Scheme 5.11. Alkyl group cross-metathesis reaction of *n*-octane with ethylbenzene to produce 1-phenyloctane as the major product.

5.2 **Results and Discussion**

Chapter 4 focused on a variety of rhodium complexes that achieve single-step styrene production from benzene and ethylene through a transition metal mediated mechanism. We envisioned that using longer chain olefins may enable the production of *n*-vinyl benzenes. These vinyl benzenes could then be hydrogenated to produce *n*alkylbenzenes or used as precursors for other reactions. Therefore, using the catalysts from Chapter 4, we attempted the oxidative vinylation of benzene with propylene. The most selective catalyst, for the single-step production of styrene from ethylene and benzene, $(^{Fl}DAB)Rh(TFA)(\eta^2-C_2H_4)$ (5.1) was evaluated, at 0.001 mol% with 240 equivalents of Cu(OAc)₂ (relative to 5.1) at 150 °C, to determine the L:B ratio (Scheme 5.12). Interestingly, four products were observed after 48 hours at 150 °C for a total of 60(4) TO: *cis*-β-methylstyrene 3.7(1), allylbenzene 27(2), *trans*-β-methylstyrene 23(1), and α -methylstryene 6(2). Parenthesis indicates the standard deviations from at least three different experiments. To determine the L:B ratio, the sum of the TO of "linear" products, cis- β -methylstyrene, allylbenzene, and *trans*- β -methylstyrene, was divided by the TO of the branched product, α -methylstryene. The L:B was found to be approximately 9:1.



Scheme 5.12. Oxidative vinylation of benzene with propylene using (^{FI}DAB)Rh(μ -TFA)(η^2 -C₂H₄) (5.1).

This initial result was exciting because the L:B ratio is higher than any previously reported method of catalysis, starting with benzene and α -olefin and proceeding through hydroarylation, for the production of anti-Markovnikov alkylbenzenes. A likely catalytic cycle is shown in Scheme 5.13. The first step is benzene C–H activation, followed by olefin insertion into the M–Ph bond. β -hydride elimination from the M–Phenethyl intermediate produces M–hydride and coordinated vinyl arene. Dissociation of the vinyl arene and subsequent oxidation of the metal center regenerates the catalyst. The catalytic cycle shows the production of *trans*- β -methylstyrene; however, if β -hydride elimination occurs from the C–H bond on the methyl group, allylbenzene will be produced. We hypothesized that changing the steric environment of the ligand may influence the ratio of 2,1-insertion versus 1,2-insertion and subsequently change the L:B ratio, in a manner similar to Goldberg's Pt catalysts.³⁰



Scheme 5.13. General catalytic cycle for the production of vinyl benzene.

Consequently, a variety of catalysts were evaluated for the oxidative coupling of propylene and benzene with Cu(OAc)₂ (Scheme 5.14). The catalysts were investigated under the following conditions: 0.001 mol % Rh, 25 psig propylene, 10 mL of benzene, with 240 equivalents Cu(OAc)₂ (relative to Rh). (4-NO₂DAB)Rh(TFA)(η^2 -C₂H₄) (5.2) and (PhDAB)Rh(TFA)(η^2 -C₂H₄) (5.3) were both generated *in situ* as discussed in Chapters 2 and 4.(*i*PrNNN)Rh(TFA) (5.4) was synthesized in 70% yield by combining the *i*PrNNN ligand with [Rh(μ -TFA)(η^2 -C₂H₄)₂]₂ in refluxing toluene, followed by *in vacuo* removal of the solvent and subsequent washing of the purple solid with pentane (Figure 5.4 and Figure 5.5). Dr. Kathleen Taylor kindly provided the (PNPcy₂)Rh(Cl) (5.5) species for me to test.



Scheme 5.14. A selection of catalysts tested for the oxidative coupling of benzene and propylene.



Figure 5.4.¹H NMR spectrum of (*i*PrNNN)Rh(TFA) in C₆D₆.



Figure 5.5. ¹⁹F NMR spectrum of (*i*PrNNN)Rh(TFA) in C_6D_6 .

Using (4-NO₂DAB)Rh(TFA)(η^2 -C₂H₄) (**5.2**) produced approximately 60 TO of alkenyl benzenes after 48 hours at both 150 °C and 180 °C (Figure 5.6), and a L:B of less than 4:1 at both temperatures was achieved (Figure 5.7). No activity was observed at 120 °C. Further, at 180 °C 10(3) and 6(1) TO of biphenyl and phenyl acetate, respectively, were observed after 48 hours. Due to the low L:B ratio this catalyst was not pursued further.



Figure 5.6. TO of alkenyl products from the reaction of benzene and propylene with $(4-NO_2DAB)Rh(TFA)(\eta^2-C_2H_4)$ (**5.2**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars.



Figure 5.7. L:B ratio of alkenyl products from the reaction of benzene and propylene with $(4-NO_2DAB)Rh(TFA)(\eta^2-C_2H_4)$ (**5.2**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh).

Error bars are standard deviations of three individual experiments that were each analyzed twice.

Interestingly, (PhDAB)Rh(TFA)(η^2 -C₂H₄) (**5.3**) showed an increase in TO (Figure 5.8) and L:B ratio (Figure 5.9) relative to the nitro containing ligand. With the PhDAB catalyst (**5.3**), 88(2) TO were obtained with a L:B ratio of 7:1 while the nitro DAB (**5.2**) gave 60(10) TO and a L:B of 3.8:1, after 48 hours at 180 °C. Catalysis was observed at all studied temperatures for **5.3**; however, at 120 °C, large deviations in the L:B ratios were observed. Interestingly, (PhDAB)Rh(TFA)(η^2 -C₂H₄) (**5.3**) gave statistically identical results as (^{FI}DAB)Rh(TFA)(η^2 -C₂H₄) (**5.1**) at 150 °C after 48 hours, in both TO and L:B. Moreover, as usual at 180 °C the production of phenyl acetate [10(5)] and biphenyl [7(3)] was seen.



Figure 5.8. TO of alkenyl products from the reaction of benzene and propylene with (PhDAB)Rh(TFA)(η^2 -C₂H₄) (**5.3**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars.



Figure 5.9. L:B ratio of alkenyl products from the reaction of benzene and propylene with (PhDAB)Rh(TFA)(η^2 -C₂H₄) (**5.3**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars.

In order to evaluate if tridentate ligands could give active catalysts (*i*PrNNN)Rh(TFA) was utilized. At the conditions tested (0.001 mol % Rh, 25 psig C₃H₆, and 240 equivalents Cu(OAc)₂ relative to Rh) the catalyst produced 71(10) TO of alkenyl benzenes (Figure 5.10) with a L:B ratio of 9.7:1 (Figure 5.11), after 24 hours. Although this catalyst produces more TO [105(2)] after 24 hours at 180 °C versus (PhDAB)Rh(TFA)(η^2 -C₂H₄) (**5.3**) [88(2)], the initial rate is slower; 34(4) TOs versus 60(3) TOs after 8 hours. The production of phenyl acetate [6(1)] and biphenyl [7(2)] is observed at 180 °C. This catalyst highlighted the possibility of tridentate ligands as successful ligands.


Figure 5.10. TO of alkenyl products from the reaction of benzene and propylene with (*i*PrNNN)Rh(TFA) (5.4) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars.



Figure 5.11. L:B ratio of alkenyl products from the reaction of benzene and propylene with (*i*PrNNN)Rh(TFA) (**5.4**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C_3H_6 , 240 equivalents $Cu(OAc)_2$ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments

that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars.

(PNPcy₂)Rh(Cl) (**5.5**) was utilized as a catalyst because the ligand motif is substantially different from the dimine based systems. Further, this complex would evaluate if catalysts without the Rh-TFA moiety could achieve oxidative vinylation. Under the screening conditions at 150 °C after 48 hours, the production of 87(3) TO of alkenyl products was observed (Figure 5.12). Further, the L:B ratio of the alkenyl products was fairly constant at 9:1 for 150 °C and 7:1 for 180 °C (Figure 5.13). These results are exciting because they highlight the capability of catalyst precursors with Rh– Cl bonds for this chemistry. Importantly, the least expensive rhodium salts are Rh–Cl based complexes.



Figure 5.12. TO of alkenyl products from the reaction of benzene and propylene with (PNPcy₂)Rh(Cl) (**5.5**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C_3H_6 , 240 equivalents Cu(OAc)₂, (relative to Rh) theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars.



Figure 5.13. L:B ratio of alkenyl products from the reaction of benzene and propylene with (PNPcy₂)Rh(Cl) (**5.5**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C_3H_6 , 240 equivalents $Cu(OAc)_2$ (relative to Rh). Error bars are standard deviations of three individual experiments that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars. 120 °C removed for clarity and lack of TO.

These catalysts, (^{Fl}DAB)Rh(μ -TFA)(η^2 -C₂H₄), (^{4-NO2}DAB)Rh(μ -TFA)(η^2 -C₂H₄), (^{Ph}DAB)Rh(μ -TFA)(η^2 -C₂H₄), (*i*PrNNN)Rh(TFA), and (PNPcy₂)Rh(Cl) are compared after 24 hours in Table 5.3. Each catalyst produces greater than 40 and 7:1 TO and L:B ratio, respectively; these are significant improvements on literature precedent. An interesting note is that catalysis efficacy holds across bidentate and tridentate ligand systems as well as Rh–TFA and Rh–Cl complexes.

ТО Catalyst L:B $(^{Fl}DAB)Rh(\mu-TFA)(\eta^2-C_2H_4)$ 60(4)9:1 $(^{4-NO2}DAB)Rh(\mu-TFA)(\eta^2-C_2H_4)$ 51(5) 5:1 $(^{Ph}DAB)Rh(\mu-TFA)(\eta^2-C_2H_4)$ 40(2)7.8:1 (*i*PrNNN)Rh(TFA) 61(6) 9.8:1 $(PNPcy_2)Rh(Cl)$ 60(5)9.5:1

propylene. Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents

Table 5.3. Comparison of rhodium catalysts for oxidative coupling of benzene and

 $\frac{(PFNNN)Rh(1FA)}{(PNPcy_2)Rh(Cl)} = \frac{61(6)}{60(5)} = \frac{9.8:1}{9.5:1}$ Successful catalysis with such a wide range of rhodium complexes led to the investigation of the rhodium precursors. Therefore catalysis with the precursor, [Rh(µ-TFA)(η²-C₂H₄)]₂ (**5.6**), was investigated. The oxidative vinylation of benzene with ethylene using [Rh(µ-TFA)(η²-C₂H₄)]₂ led to less than 5 TO after 24 hours. Although we assumed that its reactivity with propylene would be comparable, as shown in Figure 5.14, after 24 h the TO of alkenyl benzenes dramatically increase from 3(1) at 24 hours to 98(10) after 48 hours at 150 °C with a L:B ratio of 9.5:1 (Figure 5.15). Thus, there is a subtle induction period for catalysis using [Rh(µ-TFA)(η²-C₂H₄)]₂. One possibility is the formation of a Rh–OAc species which, relative to Rh–TFA, could have greatly enhanced rates of catalysis. The Rh–OAc would be generated after one successful catalytic cycle

when using $Cu(OAc)_2$ as the oxidant.

Cu(OAc)₂ (relative to Rh), after 24 hours.



Figure 5.14. TO of alkylated products from the reaction of benzene and propylene with $[Rh(\mu-TFA)(\eta^2-C_2H_4)]_2$ (**5.6**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice.



Figure 5.15. L:B ratio of alkylated products from the reaction of benzene and propylene with $[Rh(\mu-TFA)(\eta^2-C_2H_4)]_2$ (**5.6**) at different temperatures. Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh). Error bars are standard deviations of three individual experiments that were each analyzed twice.

In order to test this hypothesis, $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$ (5.7) was synthesized and screened under the same reaction conditions [0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh)]. The data in Figure 5.16 reveal that initial rate of catalysis for $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$ (5.7) is dramatically higher relative to catalysis with $[Rh(\mu-TFA)(\eta^2-C_2H_4)]_2$ (5.6) . For example, at 150 °C after 24 hours, with 5.7 59(6) TO are observed with a L:B ratio of 8:1 versus 3(1) TO and a 6:1 L:B ratio for 5.6. The increased catalytic activity highlights that formation of a Rh–OAc bond is crucial for effective catalysis. Although the initial rate is slightly faster at 180 °C for 5.7, relative to 150 °C, after 72 hours the formation of 9(1) TO of biphenyl land 10(1) PhOAc was observed. At 150 °C these side products were not observed.



Figure 5.16. TO of alkylated products from the reaction of benzene and propylene with $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$ (**5.7**). Reaction conditions: 0.001 mol % Rh, 25 psig C₃H₆, 240 equivalents Cu(OAc)₂ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice



Figure 5.17. L:B of alkylated products from the reaction of benzene and propylene with $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$ (5.7). Reaction conditions: 0.001 mol % Rh, 25 psig C_3H_6 , 240 equivalents $Cu(OAc)_2$ (relative to Rh). Error bars are standard deviations of three individual experiments that were each analyzed twice. The L:B for 120 °C is not shown due to lack of product formation.

To determine if other complexes containing Rh–OAc bonds are active for oxidative vinylation of benzene with propylene, catalysis with commercially available Rh₂(OAc)₄ (**5.8**) was probed. While all effective catalysts tested previously were Rh(I), the use of Rh₂(OAc)₄ (**5.8**) would enable the efficacy of a Rh(II) species to be analyzed, potentially opening a new avenue for catalyst design. Rh₂(OAc)₄ is not soluble in benzene at room temperature even at these low concentrations (0.001 mol % relative to benzene). However, catalysis was observed at 150 °C and 180 °C (Figure 5.18). The L:B ratio of 8.3:1 after 48 hours is statistically identical at both temperatures (Figure 5.19). However, at 180 °C the formation of 14(4) TO of phenyl acetate and 3(1) TO of biphenyl is observed as unwanted side products. Therefore, due to the lack of Rh₂(OAc)₄ (**5.8**) solubility in benzene and decreased catalytic activity relative to [Rh(μ -OAc)(η^2 -C₂H₄)]₂ (**5.7**), at 150 °C, **5.7** was selected as the catalyst for more investigation.



Figure 5.18. TO of alkenylbenzene products from the reaction of benzene and propylene with Rh_2OAc_4 . Reaction conditions: 0.001 mol % Rh, 25 psig C_3H_6 , 240 equivalents $Cu(OAc)_2$ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars.



Figure 5.19. L:B ratio of alkenylbenzene products from the reaction of benzene and propylene with Rh_2OAc_4 . Reaction conditions: 0.001 mol % Rh, 25 psig C_3H_6 , 240 equivalents $Cu(OAc)_2$ (relative to Rh), theoretical maximum TON = 120. Error bars are standard deviations of three individual experiments that were each analyzed twice. For data points with no obvious error bars, the size of the point covers the error bars.

Next, we sought to investigate the impact of the concentration of $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$ on catalysis. Increasing the rhodium concentration 5- and 10-fold, relative to benzene, (0.005 and 0.01 mol %) resulted in very similar catalytic reaction profiles (Figure 5.20). Furthermore, the L:B ratios are statistically identical for each of the three concentrations after 48 and 72 h (Figure 5.21). This is a positive development for possible industrial application because it allows for higher space-time-yields. In addition, a higher conversion of arene substrate to functionalized product is observed.



Figure 5.20. Effect of rhodium loading (relative to benzene) on catalytic conversion of benzene and propylene using $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$ as catalyst. Reaction conditions: 240 equivalents Cu(OAc)₂ (relative to Rh), 25 psig C₃H₆, 150 °C. Error bars represent standard deviations of at least three independent experiments each analyzed in duplicate.



Figure 5.21. Effect of rhodium loading (relative to benzene) on the L:B ratio of the catalytic conversion of benzene and propylene using $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$ as catalyst. Reaction conditions: 240 equivalents $Cu(OAc)_2$ (relative to Rh), 25 psig C_3H_6 , 150 °C. Error bars represent standard deviations of at least three independent experiments each analyzed in duplicate.

The effect of Cu(II) oxidant concentration was then evaluated. Increasing the concentration of oxidant led to an overall increase in TO of alkenyl benzenes (Figure 5.22). This is important as it allows for increased yield of product relative to benzene. Assuming two copper equivalents per TO of alkenyl benzene the maximum TO are 30, 60, and 120 for 60, 120, and 240 equivalents of copper, respectively. However, an interesting observation of this catalysis is that when using Cu(OAc)2, approximately a third of the copper is not productive for alkenyl arene generation even after extended time periods. After 72 hours, the TO for each copper loading are 18(1), 47(3), and 80(4) for 60, 120, and 240 equivalents of copper, respectively. The reason for this lack of reactivity is unclear and will be investigated in future studies.



Oxidant Loading versus TO using $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$

Figure 5.22. Effect of oxidant concentration on conversion of benzene and propylene using $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$ as catalyst. Reaction conditions: 0.01 mol % Rh (relative to benzene), 60, 120, or 240 equivalents Cu(OAc)₂ (relative to Rh), 150 °C, 25 psig C₃H₆. Error bars represent standard deviations of at least three independent experiments analyzed in duplicate. For data points with no obvious error bars, the size of the point covers the error bars.

The impact of copper oxidant identity was investigated by using CuO, CuCl₂, Cu(OAc)₂, and Cu(OPiv)₂ (OPiv = pivalate). Using 240 equivalents of CuO or CuCl₂, relative to Rh, did not result in the formation of vinyl or allyl benzene products over 48 hours at either 150 °C or 180 °C. In contrast, catalysis was observed with Cu(OAc)₂ and Cu(OPiv)₂, as shown in Figure 5.23. Higher TO were observed for Cu(OPiv)₂ at every time point, relative to Cu(OAc)₂. This is most likely due to the increased solubility of Cu(OPiv)₂ relative to Cu(OAc)₂. The total TOs of vinyl and allyl arenes are approximately 100 and 80 for Cu(OPiv)₂ to 6:1 with Cu(OAc)₂, respectively. However, the L:B ratio decreases from 8:1 with Cu(OAc)₂ to 6:1 with Cu(OPiv)₂ (Figure 5.24). This trend is consistent for all time points studied. These results highlight the importance of generating a Rh carboxylate species for effective catalysis. Transition-metal carboxylates

are known to be effective for C–H activation.^{36,38} Indeed, Jones and coworkers found that Rh–OAc formation was key for efficient toluene C–H activation from Cp*RhCl₂.³⁹ Therefore, we believe that one important role of the copper carboxylates is to generate Rh–OAc or related Rh carboxylates that mediates arene C–H activation.



Comparison of $Cu(OAc)_2$ and $Cu(OPiv)_2$ for TO of Alkenyl Arenes using $[Rh(\mu-OAc)(\eta^2-C_2H_4)]_2$

Figure 5.23. Effect of CuX₂ identity on conversion of benzene and propylene using $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$ as catalyst. Reaction conditions: 0.01 mol % Rh, 240 equivalents CuX₂ (relative to Rh), 25 psig C₃H₆. Error bars represent standard deviations of at least three independent experiments analyzed in duplicate. For data points with no obvious error bars, the size of the point covers the error bars.



Figure 5.24. Effect of CuX₂ identity on the L:B ratio for the conversion of benzene and propylene using $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$ as catalyst. Reaction conditions: 0.01 mol % Rh, 240 equivalents CuX₂ (relative to Rh), 25 psig C₃H₆. Error bars represent standard deviations of at least three independent experiments analyzed in duplicate. For data points with no obvious error bars, the size of the point covers the error bars.

Conditions were varied to determine if high TO (>500) were possible. Due to issues with stirring the reactors using high copper concentrations, it was necessary to decrease the rhodium concentration. Using 0.0001 mol % Rh, 2400 equivalents $Cu(OAc)_2$ (relative to Rh) and 25 psig C_3H_6 yielded 551(76) TO over 96 hours (Figure 5.25). Further the L:B ratio of approximately 8:1 is constant throughout the 96 h reaction (Figure 5.26). The theoretical maximum TO is 1200 and therefore the yield is approximately 46%, based on $Cu(OAc)_2$. A possible reason for this low yield could be due to inhibition of catalysis by acetic acid. C–H activation of benzene across the Rh– OAc bond produces Rh–Ph and HOAc.



Figure 5.25. Effect of high oxidant and low rhodium concentration for functionalized benzene production using $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Reaction conditions: 0.0001 mol % Rh, 2400 equivalents Cu(OAc)₂ (relative to Rh), 25 psig C₃H₆. Error bars represent standard deviations of three independent runs analyzed in duplicate.



Figure 5.26. L:B ratio for the reaction with high oxidant and low rhodium concentration for functionalized benzene production using $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Reaction conditions: 0.0001 mol % Rh, 2400 equivalents Cu(OAc)₂ (relative to Rh), 25 psig C₃H₆. Error bars represent standard deviations of three independent runs analyzed in duplicate.

Because $Cu(OPiv)_2$ is soluble in benzene and the rate is faster than $Cu(OAc)_2$, $Cu(OPiv)_2$ was also investigated for a high TO experiment. Using 0.0001 mol % [Rh(μ -OAc)(η^2 -C₂H₄)]₂, 2400 equivalents Cu(OPiv)₂ (relative to Rh), and 25 psig C₃H₆, 1015 TO of alkenyl products were observed after 48 h (Figure 5.27). Since the majority of the copper was used, another 1200 equivalents of Cu(OPiv)₂ was added to the reaction. This increased the TO by approximately 400 TO to ~1470 TO after an additional 48 h. Therefore, the catalyst has not decomposed after 48 hours.



Figure 5.27. Effect of high oxidant and low rhodium loading on functionalized benzene production using $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$ (1) as catalyst. Reaction conditions: 0.0001 mol % Rh, 2400 equivalents Cu(OPiv))₂ (relative to Rh), 25 psig C₃H₆. Following the sampling after the 48 h time point, an additional 1200 equivalents Cu(OPiv))₂ (relative to Rh) was added. Data for two independent runs are shown.

To expand the substrate scope, a range of α -olefins was tested. In order to help identify and quantify product formation, the products of reaction mixtures were

hydrogenated. The hydrogenation of the reaction mixture was achieved by using 5% Pt on carbon under hydrogen pressure in an ethanolic solution (see page 227 for details).

Goldberg and coworkers have shown that for their [PtPh(pypyr)(SMe₂)] (pypyr = (pyridyl)pyrrolide), using the sterically hindered olefin neohexene, the L:B ratio dramatically increased to 85:15 from the 1:1 ratio observed for propylene.³⁰ Therefore, we utilized neohexene and discovered that the arene vinyl product was produced with 100% selectivity (Scheme 5.14). No allyl product was formed because there is no hydrogen to undergo hydride elimination. However, neohexene undergoes a coupling reaction to produce 27(6) TO of 2,2,4,6,6-pentamethylheptane, after hydrogenation (Figure 5.28).



Scheme 5.15. Oxidative vinylation of benzene with neoxhexene produced, after hydrogentation, (3,3-dimethylbutyl)benzene.



Figure 5.28. Example GC/MS trace of oxidative coupling of benzene with neohexene after hydrogenation. X-axis is the retention time in minutes. Y-axis is the relative intensity of peaks. Hexamethylbenzene was used as the internal standard.

Isobutylene was tested as another sterically hindered α -olefin (Scheme 5.16). The oxidative addition of benzene with isobutylene produced both the allyl and vinyl products in 100% linear selectivity; after 72 hours at 150 °C, 100(2) TO of isobutylbenzene were produced (Figure 5.29).



Scheme 5.16. Production of isobutylbenzene from the oxidative coupling of benzene and isobutylene via formation of the allyl and vinyl species.



Figure 5.29. Example GC/MS trace showing the allyl and vinyl species from the coupling of isobutylene with benzene before hydrogenation. X-axis is the retention time in minutes. Y-axis is relative intensity of peaks. Hexamethylbenzene was used as the internal standard.

Expanding the substrate scope to longer chain α -olefins is important because these can isomerize the terminal olefin to an internal olefin and therefore change the L:B ratios. Catalysis was investigated with 1-pentene and benzene to determine if we could generate and in what ratios, *n*-pentylbenzene, 2-pentylbenzene, and 3-pentylbenzne. Using 0.001 mol % [Rh(μ -OAc)(η^2 -C₂H₄)₂]₂ relative to benzene, 2000 equivalents 1-pentene and 240 equivalents of Cu(OAc)₂ (both relative to Rh), at 150 °C over 100 h produced a number of different products (Figure 5.30). To help aid in analysis and quantification, the reaction mixture was hydrogenated (Figure 5.31). After hydrogenation, 98(14) TO of *n*pentylbenzene and 6(2) TO of 2-pentylbenzene were observed giving a L:B of 16(1):1 for the pentylbenzenes. However, 6(1) TO of PhOAc and 20(4) TO of biphenyl were also observed.



Figure 5.30. GC/MS trace from the oxidative coupling of 1-pentene with benzene to produce alkenyl benzenes before hydrogenation. X-axis is the retention time in minutes. Y-axis is relative intensity of peaks. Hexamethylbenzene was used as the internal standard.



Figure 5.31. GC/MS trace from the oxidative coupling of 1-pentene with benzene to produce alkenyl benzenes after hydrogenation. The peaks correspond to the labeled product. Phenol was produced as a by-product of the hydrogenation process. X-axis is the retention time in minutes. Y-axis is relative intensity of peaks. Hexamethylbenzene was used as the internal standard.

Interestingly, increasing the rhodium concentration by 10 fold led to increased TO of pentylbenzenes and less biphenyl and phenyl acetate formation. Using the conditions in Scheme 5.17, produced 110(10) TO of *n*-pentylbenzene with 12(3) TO of 2-

pentylbenzene after 72 h at 150 °C. Thus, conversion of benzene and 1-pentene is observed in 100% yield. This gives a L:B of ~8:1; importantly, there was minimal production of 3-pentylbenzene (< 2 TO). This indicates that minimal olefin isomerization is occurring. Additionally, negligible formation of PhOAc and biphenyl is observed.



Scheme 5.17. The oxidative coupling of 1-pentene and benzene to produce *n*-pentylbenzene and 2-pentylbenzene after hydrogenation.

To determine the effect of internal olefins on the L:B ratio, Junqi Chen investigated 2-pentene as the olefin and subsequent olefin isomerization experiments. Using 0.01 mol % $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$ relative to benzene, 2000 equivalents 2pentene and 240 equivalents of Cu(OAc)₂ (both relative to Rh), at 150 °C over 72 hours yielded 22(4) TO of *n*-pentylbenzene, 48(6) TO of 2-pentylbenzene and 27(5) TO of 3pentylbenzene after hydrogenation. Interestingly, the production of *n*-pentylbenzene is statistically identical to that of 3-pentylbenzene. Accordingly, isomerization of 1-pentene to 2-pentene was investigated with $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Catalysis without Cu(OAc)₂ yielded rapid isomerization of 1-pentene to 2-pentene. Initially the olefin was 99.5% 1pentene, but after 48 hours the percent of 1-pentene remaining is 13.4% while the remaining olefin was converted to 2-pentene (Table 5.4). In contrast, with 240 equivalents of Cu(OAc)₂ relative to Rh, isomerization was dramatically slowed. After 72 h, in addition to production 108(9) TO of *n*-pentylbenzene with 11(3) TO of 2-pentylbenzene, 77.6% of the remaining olefin is 1-pentene (Table 5.5). Furthermore, we investigated the isomerization of 2-pentene to determine if isomerization to 1-pentene is possible with [Rh(μ -OAc)(η^2 -C₂H₄)₂]₂ (Table 5.6). As expected, the percentage of 1-pentene stays almost constant, approximately 1%, throughout the reaction over 72 h. This is concomitant with the production of *n*-pentylbenzene [22(4) TO], 2-pentylbenzene [48(6) TO], and 3-pentylbenzene [27(5) TO]. Thus, [Rh(μ -OAc)(η^2 -C₂H₄)₂]₂ appears to react more rapidly with 1-pentene than 2-pentene.

Table 5.4. Isomerization of 1-pentene to 2-pentene with $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Reaction conditions: 0.01 mol % Rh, 2000 equivalents of 1-pentene, 150 °C. Quantification achieved through GC/FID. Error represents standard deviations of at least three independent experiments.

1 I entene 15					
			Total	% 1-	% 2-
Time (h)	1-pentene	2-pentene	Olefin	pentene	pentene
0	1856 (67)	9.4 (2)	1865 (66)	99.5	0.5
48	258 (17)	1669 (80)	1927 (66)	13.4	86.6
72	229 (13)	1645 (50)	1874 (39)	12.2	87.8

1-Pentene Isomerization without Cu(OAc)₂

Table 5.5. Isomerization of 1-pentene with 240 equivalents of Cu(OAc)₂ using $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Reaction conditions: 0.01 mol % Rh, 2000 equivalents of 1-pentene, 150 °C. Quantification achieved through GC/FID. Error represents standard deviations of at least three independent experiments.

1-Pentene Isomerization with 240 equivalents of $Cu(OAc)_2$

			% 1-		
Time (h)	1-pentene	2-pentene	Total Olefin	pentene	% 2-pentene
0	1885 (65)	8 (0.6)	1893 (64)	99.6	0.4
48	1461 (44)	280 (31)	1741 (19)	83.91	16.1

72 1246 (37) 360 (38) 1605 (19) 77.6 22.4

Table 5.6. Isomerization of 2-pentene with 240 equivalents of Cu(OAc)₂ using $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Reaction conditions: 0.01 mol % Rh, 2000 equivalents of 1-pentene, 150 °C. Quantification achieved through GC/FID. Error represents standard deviations of at least three independent experiments.

Time (h)	1-pentene	2-pentene	Total Olefin	% 1-pentene	% 2-pentene
0	19.4	2066	2085.4	0.93	99.07
48	23.975	1653.75	1677.725	1.43	98.57
72	25.25	1562.25	1587.5	1.59	98.41

2-Pentene Isomerization with 240 equivalents of Cu(OAc)₂

The scope of the reaction was then examined with respect to the identity of the arene. With acid-based arene alkylation, the electronic properties of the arene have a significant impact on the efficacy and selectivity of catalysis. Highly electronwithdrawing substituents like nitro groups inhibit catalysis completely.¹ In Friedel-Crafts alkylation, the electrons of the arene donate to the carbocation to form a Wheland intermediate. Thus, if the arene is too electron-poor, the reaction can be retarded. Another pertinent example is that of chlorobenzene, which can be alkylated with acid-based mechanisms; however, the rate is approximately 10 times slower than the alkylation of benzene.¹ The selectivity for acid-based mechanism follows electrophilic aromatic substitution directing groups. For example, using AlCl₃ with chlorobenzene and propylene in nitromethane at 25 °C the product distribution of *ortho:meta:para* (o:m:p) is approximately ~11:1:8 (Scheme 5.18).^{40,41} However, utilizing 0.01 mol % [Rh(µ- $OAc)(\eta^2-C_2H_4)_2]_2$ (relative to chlorobenzene), 10 mL chlorobenzene, 240 equivalents Cu(OAc)₂, 150 °C, and 25 psig C₃H₆ over 48 hours, after hydrogenation, gave 116(3) TO (97% yield) of alkyl chlorobenzene with a L:B ratio of 10:1 and o:m:p ratio of 1:11:7

(Figure 5.32). These results illustrate the contrast between acid-based catalysis and our new Rh catalyzed method. For chlorobenzene, after 48 hours of catalysis 116(3) TO of product are attained, a slight improvement, relative to the 79(4) TO obtained when using benzene as the arene substrate. Further, the rhodium catalysis produces a *o:m:p* ratio of 1:11:7 versus *o:m:p* ratio of ~11:1:8 for AlCl₃. Therefore, for chlorobenzene, using $[[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2]$ provides alternative selectivity to traditional acid-based alkylation.



Scheme 5.18. Comparison of acid-based and rhodium catalyzed coupling of chlorobenzene with propylene to produce alkyl and alkenyl chlorobenzene. Only the *para* production is shown for the rhodium catalyzed oxidative vinylation to enhance clarity. Reaction conditions: 0.01 mol % [Rh(μ -OAc)(η^2 -C₂H₄)₂]₂(relative to chlorobenzene), 240 equivalents Cu(OAc)₂ (relative to Rh), 150 °C, and 25 psig C₃H₆ after 48 hours.



Figure 5.32. GC/MS trace of the oxidative coupling of chlorobenzene and propylene with $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Reaction conditions: 0.01 mol % Rh (relative to chlorobenzene), 240 equivalents Cu(OAc)₂ (relative to Rh), 150 °C, and 25 psig C₃H₆ after 48 hours, following hydrogenation. A = *meta*-isopropyl-chlorobenzene. B = *para*-isopropyl-chlorobenzene. C = *ortho-n*-propyl-chlorobenzene. X-axis is the retention time in minutes. Y-axis is relative intensity of peaks. Hexamethylbenzene was used as the internal standard.

Although electron withdrawing substituents slow acid-based catalysis, electron donating groups enhance the rate of alkylation. Polyalkylated arenes are often obtained as a result, which must then undergo a separate transalkylation step to enhance the yield of the desired mono-substituted product.^{5,42} For example, the alkylation of ethylbenzene is approximately 2-3 times faster than alkylation of benzene.⁴³ Using AlCl₃ as a catalyst, toluene alkylation with propylene (AlCl₃ in nitromethane at 25 °C) produces an *o:m:p* ratio of 3:1:2.6. Utilizing [Rh(μ -OAc)(η^2 -C₂H₄)]₂, the reaction of toluene and propylene gave 86(17) TO (72% yield) of *alkyl toluenes* with a L:B ratio of 9.4:1, and an *o:m:p* ratio of 1:8.9:9.3 (Figure 5.33).



Figure 5.33. GC/MS trace of the oxidative coupling of toluene and propylene with $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Reaction conditions: 0.01 mol % Rh (relative to toluene), 240 equivalents Cu(OAc)₂ (relative to Rh), 150 °C, and 25 psig C₃H₆ after 48 hours, following hydrogenation. A = *meta*-isopropyl-toluene. B = *para*-isopropyl-toluene. X-axis is the retention time in minutes. Y-axis is relative intensity of peaks. Hexamethylbenzene was used as the internal standard.

In order to further examine the selectivity of arene substrates, anisole was tested. Utilizing 0.01 mol % $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$ (relative to anisole), 240 equivalents $Cu(OAc)_2$, 150 °C, and 25 psig C_3H_6 over 48 hours, after hydrogenation, gave 92(7) TO (77% yield) of *alkyl anisoles* with a L:B of 7.8:1 and an *o:m:p* ratio of 1:2.4:6.4 (Figure 5.35). The anisole results are particularly intriguing because the *para*-alkenyl products are estragole (allyl) and anethole (vinyl), which are common materials in the flavors and fragrance industries (Figure 5.34). Estragole is currently produced through distillation of basil oils.⁴⁴



Figure 5.34. Anethole and Estragole. Common chemicals found in the flavor and fragrances industries.



Figure 5.35. GC/MS trace of the oxidative coupling of anisole and propylene with $[Rh(\mu-OAc)(\eta^2-C_2H_4)_2]_2$. Reaction conditions: 0.01 mol % Rh (relative to anisole), 240 equivalents Cu(OAc)₂ (relative to Rh), 150 °C, and 25 psig C₃H₆ over 48 hours, after hydrogenation. A = *para*-isopropyl-anisole. B = *ortho-n*-propyl-anisole. C = *meta-n*-propyl-anisole. X-axis is the retention time in minutes. Y-axis is relative intensity of peaks. Hexamethylbenzene was used as the internal standard.

A comparison of acid-based and rhodium catalyzed arene alkylations is shown in Table 5.7. Interestingly, for the rhodium based catalysis, the TO are fairly consistent between arene substrates and the *o:m:p* ratio favors *meta* and *para* functionalization. This *o:m:p* ratio is presumably determined by the regioselectivity of the arene C–H activation step.⁴⁵ Furthermore, the acid-based chemistry does not produce vinyl or allyl species. The generation of vinyl or allyl species is valuable because of the diverse reactions that are possible with olefins. Therefore, our rhodium based catalysis offer opportunities to generate substrates that are difficult and/or laborious to synthesize from basic chemical

feedstocks.

Table 5.7. Comparison of arene alkylation using AlCl₃ as the primary catalyst versus [Rh(μ -OAc)(η^2 -C₂H₄)₂]₂. L:B ratios and total TO of alkylated products determined after hydrogenation of unsaturated products. Unless otherwise noted, reaction conditions are: 0.01 mol % Rh relative to arene, 25 psig gaseous olefin or 2000 equivalents of liquid olefin, 150 °C, 48 h, 240 equivalents Cu(OAc)₂ relative to Rh.

Catalyst	Arene	Coupling Partner	o:m:p	L:B	TON	Product
AlCl ₃ ^[*]	toluene	propylene	3:1:2.6	>98% B	n.r.	
5.7	toluene	propylene	1:8.9:9.3	9.4:1	86(17)	
AlCl ₃ ^[£]	chlorobenzene	2-chloropropane	6.4:1:5.1	100% B	n.r.	CI CI
5.7	chlorobenzene	propylene	1:11:7	10:1	116(3)	
$AlCl_3^{[\pi]}$	anisole	2-chloropropane	62:4:34	100% B	n.r.	OMe OMe
5.7	anisole	propylene	1:2.4:6.4	7.8:1	92(7)	
AlCl ₃ ^[†]	benzene	propylene	n/a	100% B	95	
5.7	benzene	propylene	n/a	8:1	80(4)	
AlCl ₃ ^[†]	benzene	1-hexene	n/a	100% B	67	R R
5.7	benzene	1-pentene ^[§]	n/a	8:1	122(10)	
5.7	benzene	neohexene ^[§]	n/a	100% L	30(8)	
5.7	benzene	isobutylene ^[§]	n/a	100% L	100(2)	
AlCl ₃ ^[*]	benzene	isobutylene	n/a	100% B	n.r.	$\bigcirc \leftarrow$

n.r. = not reported ^[*] Data and conditions are from reference ⁴⁰. ^[‡] Data and conditions are from reference ⁴⁶. ^[π] Data and conditions are from reference ⁴⁷. ^[†] Data and conditions are from reference ⁴¹. ^[§] 72 h. ^[*] Data and conditions are from reference ⁴¹.

5.3 Conclusion

Efficient and selective technologies to synthesize *n*-alkylarenes are highly desired. For example 1-phenylalkanes would be particularly valuable in the detergent industry as these exhibit highly detersive powers in low concentrations. Therefore, the development of simple commercially available rhodium salts for the production of anti-Markovnikov vinyl and allyl species from arenes and α -olefins is highly significant (Scheme 5.19). This is partially due to the increased options for further chemistry that vinyl and allyl species allow. Important results from these studies include: the relatively equivalent TO and L:B ratios when increasing the rhodium concentration, a positive development due to increased space-time yields. The higher TO with increasing copper oxidant is useful from a commercial standpoint. Further, TO numbers of greater than 1400 were observed. Continued catalysis was observed by the addition of more copper oxidant indicating that catalyst decomposition is not significant after 48 h. However, catalyst decomposition is still not fully understood. Importantly, this rhodium catalyst system successfully operates with a range of olefins and arenes. This new methodology has allowed for the production of substrates which are difficult to synthesize from simple petrochemical chemicals, such as anethole and estragole. To our knowledge, there are no previous examples of catalytic conversion of simple arenes and α -olefins, such as propylene, 1-pentene, 1-hexene, etc., to alkyl or vinyl/allyl products with high selectivity for the anti-Markovnikov products. Moreover, the simplicity and the similarity to the Wacker process make this an intriguing prospect for further study, due to its possible ability to be scaled and used commercially.



Scheme 5.19. Comparison of the current industrial route to LAB and the singlestep production of SLABs described herein.

5.4 Experimental Methods

5.4.1 General Information.

All manipulations were performed under an atmosphere of dry nitrogen using standard Schlenk or high vacuum techniques and/or in a glovebox. Glovebox purity was maintained by periodic nitrogen purges and was monitored by an oxygen analyzer ($O_2 < 15$ ppm for all reactions). Dry, oxygen-free solvents were employed throughout and stored over 4Å molecular sieves. Benzene and toluene were dried by passage through columns of activated alumina. Pentane was dried over sodium benzophenone ketyl. GC/MS was performed using a Shimadzu GCMS-QP2010 Plus system with a 30 m x 0.25 mm SHRXI-5MS column with 0.25 μ m film thickness using electron impact (EI) ionization. GC/FID was performed using a Shimadzu GC-2014 system with a 30 m x 90.25 mm HP5 column with 0.25 μ m film thickness. TFA-*d*₁was used as received. Argon was purchased from GTS Welco and used as purchased. ¹H spectra were recorded on a Varian Inova 500 MHz spectrometer; all ¹H spectra are referenced against residual proton signals (¹H NMR). ¹⁹F NMR (operating frequency 564 MHz) spectra were obtained on a

Varian Mercury 600 MHz spectrometer and referenced against an external standard of hexafluorobenzene (δ –164.9).

Phenyl acetate, 3-pentylbenzene, 2-pentylbenzene, n-pentylbenzene, cumene, npropylbenzene, α -methylstyrene, *trans*- β -methylstyrene, and biphenyl production were quantified using linear regression analysis of gas chromatograms of standard samples of authentic product. A plot of peak area ratios versus molar ratios gave a regression line. For the GC/FID instrument, the slope and correlation coefficient of the regression lines were 2.51 and 0.97 (phenyl acetate), 1.78 and 0.98 (3-pentylbenzene), 1.82 and 0.98 (2pentylbenzene), 2.09 and 0.98 (n-pentylbenzene), 0.68 and 0.99 (cumene), 0.73 and 0.99 (n-propylbenzene), 0.74 and 0.99 (α -methylstyrene), 0.72 and 0.99 (*trans*- β methylstyrene), 1.55 and 0.98 (biphenyl), 2.78 and 0.99 (1-pentene), 2.9 and 0.99 (2pentene), respectively. Quantification of allyl benzene was estimated using the slope and correlation coefficient of the regression lines for cumene. Quantification of cis-βmethylstyrene was estimated using the slope and correlation coefficient of the regression lines for *trans*- β -methylstyrene. For the GC/MS instrument, the slope and correlation coefficient of the regression lines were 0.63 and 0.99 (4-ethylanisole), 0.56 and 0.99 (4ethylchlorobenzene), 0.29 and 0.99 (3-ethylchlorobenzene), 0.55 and 0.99 (npropylbenzene), and 0.55 and 0.99 (*n*-pentylbenzene). Quantification of 2-propylanisole, 3-propylanisole, 4-propylanisole, and 4-isopropylanisole was estimated using the slope and correlation coefficient of the regression lines for 4-ethylanisole. Quantification of 2propylchlorobenzene, 3-propylchlorobenzene, 4-propylchlorobenzene, 3isopropylchlorobenzene, and 4-isopropylchlorobenzene was estimated using the slope

and correlation coefficient of the regression lines for 3-ethylchlorobenzene and 4ethylchlorobenzene. Quantification of 2-propyltoluene, 3-propyltoluene, 4-propyltoluene, 3-isopropyltoluene, 4-isopropyltoluene, and isobutyl benzene was estimated using the slope and correlation coefficient of the regression lines for cumene. Quantification of 3,3dimethylbutylbenzene was estimated using the slope and correlation coefficient of the regression lines for *n*-pentylbenzene. Identification of peaks due to linear versus branched products was determined by studying the mass fragmentation patterns. Branched products have substantially larger peak 15 m/z units less than the molecular ion peak relative to linear products. Linear products reveal loss of alkyl chain up to the allylic position. For example, in the alkylation of toluene with propylene reveal this difference. Both have a molecular ion peak of 134 m/z but differ in the base peak of 119 (branched) and 105 (linear) m/z, respectively (Scheme 5.20).



Scheme 5.20. Example of the different fragmentation patterns for the linear versus branched products.

Propylene and isobutylene were purchased in gas cylinders from GTS-Welco and used as received. All other reagents were purchased from commercial sources and used as received. $[Rh(\eta^2-C_2H_4)_2(\mu-TFA)]_2$ was made following the literature procedure using AgTFA instead of AgPF₆.⁴⁸ [Rh(η^2 -C₂H₄)₂(μ -OAc)]₂ was prepared according to literature procedures.⁴⁹

5.4.2 Ligand Synthesis.

Most of the diimine ligands (diazbutadienes, or DABs) were synthesized following a modified literature procedure ⁵⁰: To a round-bottom flask, 2.1 equivalents of the aniline, 1 equivalent of 2,3-butanedione, 0.1 equivalents of *p*-toluenesulfonic acid and 4 equivalents of trimethylorthoformate were combined in 10 mL of anhydrous methanol under air. The reaction mixture was stirred for 8 hours accompanied by the precipitation of a yellow solid. The solid was collected by filtration, washed with 5 mL of cold methanol, and dried under vacuum. The identity of the DABs was confirmed by comparison to reported NMR data for PhDAB = N,N'-bis-(2,3-dimethyl-1,4-diaza-1,3-butadiene).⁵¹ 4-nitroDAB = N,N'-bis-(4-nitrophenyl)-2,3-dimethyl-1,4-diaza-1,3-butadiene) was prepared according to literature procedures,⁵² and 4-nitroDAB synthesis was confirmed to reported NMR data.⁵³ The (*i*PrNNN) ligand was synthesized according to literature procedures.⁵⁴

5.4.3 In Situ Generated Catalysts.

Under nitrogen, the diimine ligand (2 equivalents, 414.5 µmol) in THF (10 ml) was added to a stirring solution of $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$ (1 equivalent, 207 µmol) in THF (15 mL). The solution immediately became deep purple to black. After 1 hour the solvent was removed *in vacuo*, and the resulting solid was washed with *n*-pentane (20 mL) and then dried under vacuum to yield the corresponding *in situ* rhodium catalyst.

5.4.4 Synthesis of (*i*PrNNN)Rh(TFA) (5.4).

Under nitrogen, the ligand (1 equivalent, 208 μ mol) in toluene (10 ml) was added to a stirring solution of [Rh(μ -TFA)(η^2 -C₂H₄)₂]₂ (1 equivalent, 208 μ mol) in toluene (15 mL). The solution was refluxed overnight and became deep purple to black. After 15 hours the solvent was removed *in vacuo*, and the resulting solid was washed with *n*-pentane (20 mL) and then dried under vacuum to yield the catalyst in 101 mg (70% yield) of catalyst. ¹H NMR (497 MHz, THF-*d*₈): δ 7.73 (t, ³*J*_{HH}= 8 Hz, 1H, pyridine *para*), 7.27 – 7.18 (overlapping, 6H, 2 x phenyl *meta* + phenyl *para*), 6.69 (d, ³*J*_{HH} = 8 Hz, 2H, pyridine *meta*), 3.40 – 3.18 (m, 4H, isopropyl CH), 1.43 (d, ³*J*_{HH} = 7 Hz, 12H, 2 x isopropyl CH₃), 1.12 (s, 6H, 2 x methyl), 1.03 (d, ³*J*_{HH} = 7 Hz, 12H, 2 x isopropyl CH₃). ¹⁹F NMR (564 MHz, benzene-*d*₆): δ -74.15 (s).

5.4.5 Catalytic Oxidative Hydrophenylation of Propylene.

A representative catalytic reaction is described. A stock solution containing **5.7** (0.01 g, 0.023 mmol, 0.001 mol % of rhodium), hexamethylbenzene (0.075 mg, 0.46 mmol), and benzene (200 mL) was prepared in a volumetric flask. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and CuOAc₂ (0.050 g, 0.28 mmol). The vessels were sealed, pressurized with propylene (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled every 4 h for the first 12 h, then at the 24 h time point, and then every 24 h subsequently. At each time point, the reactors were cooled to room temperature, sampled, recharged with propylene, and reheated. Aliquots of the reaction (<100 μ L) mixture were analyzed by GC/FID using relative peak areas versus the internal standard (hexamethylbenzene).

5.4.6 Hydrogenation General Procedure.

To a glass Fischer-Porter reactor, an aliquot of reaction sample was mixed in a 1:1 V:V mix with absolute ethanol, approximately 50 mg of 5% Pt on carbon and a stir bar were added. The reactor was then pressured with hydrogen and released (3 x 70 psi)

before being placed under 150 psig of hydrogen while stirring for 17 hours. The reaction was then degassed, and the mixture was analyzed by GC/MS or GC/FID.

5.4.7 Temperature Variation Experiments.

A stock solution containing **5.7** (0.001 mol % relative to benzene), hexamethylbenzene (20 equivalents relative to Rh), and benzene (200 mL) was prepared in a volumetric flask. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and Cu(OAc)₂ (240 equivalents relative to **5.7**). The vessels were sealed, charged with propylene (25 psig), and subsequently stirred and heated to 120, 150 or 180 °C. The reaction was sampled every 4 h for the first 12 h, then at the 24 h time point, and then every 24 h after that. At each time point, the reactors were cooled to room temperature, sampled, recharged with propylene, and reheated. Aliquots of the reaction (<100 \Box L) mixture were analyzed by GC/FID using relative peak areas versus an internal standard (hexamethylbenzene).

5.4.8 Rhodium Loading Experiments.

Three stock solutions containing **5.7** (0.001 mol % relative to benzene, 0.005 mol % relative to benzene, or 0.01 mol % relative to benzene), hexamethylbenzene (20 equivalents relative to Rh), and benzene (200 mL) was prepared in volumetric flasks. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and Cu(OAc)₂ (240 equivalents relative to **5.7**). The vessels were sealed, charged with propylene (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled every 4 h for the first 12 h, then at the 24 h time point, and then every 24 h subsequently. At each time point, the reactors were cooled to room temperature, sampled, recharged with

propylene, and reheated. Aliquots of the reaction ($< 100 \ \mu$ L) mixture were analyzed by GC/FID using relative peak areas versus an internal standard (hexamethylbenzene).

5.4.9 High Turnover Experiment.

A stock solution containing **5.7** (0.0001 mol % relative to benzene), hexamethylbenzene (20 equivalents relative to **5.7**), and benzene (200 mL) was prepared in a volumetric flask. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and Cu(OAc)₂ (2400 equivalents relative to **5.7**). The vessels were sealed, charged with propylene (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled at 6h, 18h, 24h, 36h, 48h, 72h and 92h. At each time point, the reactors were cooled to room temperature, sampled, recharged with propylene, and reheated. Aliquots of the reaction (<100 µL) mixture were analyzed by GC/FID using relative peak areas versus the internal standard (hexamethylbenzene).

5.4.10 Oxidant Loading Experiments.

A stock solution containing **5.7** (0.001 mol % relative to benzene), hexamethylbenzene (20 equivalents relative to Rh), and benzene (200 mL) was prepared in a volumetric flask. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and Cu(OAc)₂ (60, 120 or 240 equivalents relative to **5.7**). The vessels were sealed, charged with propylene (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled every 4 h for the first 12 h, then at the 24 h time point, and then every 24 h subsequently. At each time point, the reactors were cooled to room temperature, sampled, recharged with propylene, and reheated. Aliquots of the reaction (<100 µL) mixture were analyzed by GC/FID using relative peak areas versus the internal standard (hexamethylbenzene).

5.4.11 Oxidant Identity Experiments.

A stock solution containing **5.7** (0.001 mol % relative to benzene), hexamethylbenzene (20 equivalents relative to **5.7**), and benzene (200 mL) was prepared in a volumetric flask. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and oxidant (240 equiv relative to **5.7**). Oxidants tested include copper(II) pivalate, copper(II) oxide, copper(II) chloride, and copper(II) acetate. The vessels were sealed, charged with propylene (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled every 4 h for the first 12 h, then at the 24 h time point, and then every 24 h subsequently. At each time point, the reactors were cooled to room temperature, sampled, recharged with propylene, and reheated. Aliquots of the reaction (<100 μ L) mixture were analyzed by GC/FID using relative peak areas versus the internal standard (hexamethylbenzene).

5.4.12 Olefin Identity Experiments.

A stock solution containing **5.7** (0.01 mol % relative to benzene), hexamethylbenzene (20 equivalents relative to **5.7**), and benzene (200 mL) was prepared in a volumetric flask. When using liquid olefins, 2000 equivalents (relative to **5.7**) of olefin were added to the stock solution. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and oxidant (240 equivalents relative to **5.7**). The vessels were sealed, charged with olefin if necessary (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled after 24h, 48h, and 72h. At each time point, the reactors were cooled to room temperature, sampled, recharged with propylene, and reheated. Aliquots of the reaction (<100 μ L) mixture were analyzed by GC/MS using relative peak areas versus the internal standard (hexamethylbenzene). Using neohexane
30(8) TO of 100% linear product (3,3-dimethylbutyl)benzene and 27(6) TO of the olefin coupled product 2,2,4,6,6-pentamethylheptane was observed after 72 hours.

5.4.13 Isomerization of 1-Pentene.

A stock solution containing **5.7** (0.01 mol % relative to benzene), hexamethylbenzene (20 equivalents relative to **5.7**), and benzene (200 mL) was prepared in a volumetric flask. Either -pentene or 2-pentene (2000 equivalents relative to **5.7**) was added to the stock solution. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and, if required, Cu(OAc)₂ (240 equivalents relative to **5.7**) was added. An initial sample (100 μ L) was taken before heating (t = 0) and analyzed by by GC/FID to determine the ratio of 1-pentene and 2-pentene. The vessels were sealed, stirred and heated to 150 °C. The reaction was sampled at 48 h and 72 h. At each time point, the reactors were cooled to room temperature, and reheated. Aliquots of the reaction (< 100 μ L) mixture were analyzed by GC/FID using relative peak areas versus the internal standard (hexamethylbenzene). The total concentration of pentenes decreases over time due to the high volatility.

5.4.14 Arene Identity Experiments.

A stock solution containing **5.7** (0.01 mol % relative to arene), hexamethylbenzene (20 equivalents relative to Rh), and arene (100 mL) was prepared in a volumetric flask. Glass Fisher-Porter reactors were charged with stock solution (10 mL) and oxidant (240 equiv relative to **5.7**). The vessels were sealed, charged with propylene (25 psig), and subsequently stirred and heated to 150 °C. The reaction was sampled after 24h, 48h, and 72h. At each time point, the reactors were cooled to room temperature, sampled, recharged with propylene, and reheated. Aliquots of the reaction (<100 uL) mixture were

analyzed by GC/MS using relative peak areas versus the internal standard (hexamethylbenzene).

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6 Summary and Future Research Directions

Due to the limitations of current, acid-based industrial methods, novel selective and efficient catalysts for the functionalization of petrochemical substrates are highly desirable.¹⁻⁶ In particular, a non-acid based methodology for the coupling of olefins and arenes, offer a potential route to new catalytic methodologies.^{7,8} The transition metal mediated hydroarylation of olefins offers many improvements over traditional methods including: selectivity for monoalkylation, production of *n*-alkylbenzenes, and single-step synthesis of vinyl or allyl species. The Gunnoe group has demonstrated a series of TpRu(L)(NCMe)Ph ($Tp = hydridotris(pyrazolyl)borate, L = CO, PMe_3, P(N-pyrrolyl)_3,$ P(OCH₂)₃CEt, P(O)(OCH₂)₂CMe) are active catalysts for olefin hydroarylation.⁹⁻¹³ Further studies showed that $[HC(pz^5)_3)Ru(P(OCH_2)_3CEt)(NCMe)Ph][BAr'_4] (HC(pz^5)_3 =$ tris(5-methyl-pyrazolyl)-methane, Ar' = 3.5-bis(trifluoromethyl)phenyl) species was a more active catalyst ¹⁴. These Ru catalyst motifs has been expanded to Fe which has been moderately successful.¹⁵ In addition, the Gunnoe group has also developed a number of Pt species, based on bipyridine and dipyridylmethane motifs, are active catalysts for olefin hydroarylation with a range of arenes and olefin substrates.¹⁶⁻²¹ Both the Ru and Pt complexes operate through a transition metal mediated C-H activation followed by olefin insertion into the M-Ph bond. However, the deactivation pathway for the Pt catalysts is irreversible β -hydride elimination, from the M-Phenethyl intermediate, generating unstable M-H species which decompose to yield Pt(s). Consequently, because Rh is less

likely to form the elemental solid relative to Pt, rhodium species were investigated for C– H activation and subsequent hydroarylation of ethylene.²²

6.1 Summary

6.1.1 Summary of H/D exchange data

In Chapter 2, a variety of Rh(I) diimine species were found to be active for the H/D exchange of benzene with trifluoroacetic acid- d_1 .²³ Initially, the systems also appeared to be active for transition metal mediated C-H activation of benzene. However, mechanistic investigations using toluene for H/D exchange, to determine the ortho:meta:para ratio, revealed that the reaction operated through electrophilic protic substitution.²⁴ Indeed the rhodium complexes were found to have increased the acidity of the solvent which therefore increased the rate of H/D exchange. Further evidence for this mechanism was provided by the lack of H/D exchange reactivity with weaker acids and non-aromatic substrates. These results prompted the study of a wide range of transition metal salts and complexes as well as main group salts for H/D exchange between arenes and acids, as discussed in Chapter 3.²⁵ This was also warranted due to the large literature precedent of enhanced H/D exchange through the in situ addition of halide extracting agents. Experiments revealed that the common salts containing BF₄ and OTf were exceptionally active for the H/D exchange of toluene and trifluoroacetic acid- d_1 through electrophilic protic substitution. In addition, the meta/ortho selectivity correlates with the TO of benzene H/D exchange. These results highlight the importance of mechanistic studies and control reactions in reporting catalytic results.

6.1.2 Summary of Oxidative Vinylation of Arenes with α-Olefins

Chapter 4 highlights the development of (^{FI}DAB)Rh(TFA)(η^2 -C₂H₄) as the most active and selective catalyst for the single-step production of styrene.²⁶ This catalyst produces the highest TO (>800) of styrene with the highest selectivity (>95%) and almost complete consumption of the limiting reagent, the oxidant. Importantly, the copper oxidants are air recyclable, offering the tentative possibility for the net reaction of benzene, ethylene, and ½ oxygen yielding styrene and water (Scheme 6.1). Initial studies indicate that varying the diimine system can dramatically change the rate of styrene production. Results indicate that electron-deficient ligand systems increase the efficacy of catalysis. Specifically, blocking the 2,6-positions of the aryl ring with fluorine substituents appears to be the key for the most efficient catalysis.

$$+ 1/2 O_2 + C_6 H_6 + H_2 O$$

Scheme 6.1. Net reaction for the oxidative vinylation of benzene with ethylene to yield styrene and water.

Chapter 5 demonstrates the extension of this catalysis to α -olefins. A wide variety of complexes were shown to be active for the oxidative coupling of benzene and propylene to yield *cis*- β -methylstyrene, allylbenzene, *trans*- β -methylstyrene, and α methylstryene. Importantly, the catalytic L:B ratio was consistently >8:1 which is, to our knowledge, the highest reported ratio for this reaction. Crucially, simple and commercially available Rh(I) salts, containing an carboxylates, were found to be active for this chemistry. The oxidative vinylation of propylene with [Rh(μ -OAc)(η^2 -C₂H₄)]₂ was demonstrated to yield greater than 1400 TO with L:B ratios >8:1. Further, this catalysis showed no decrease in TO or L:B ratio when increasing the Rh concentration; tentatively allowing for increased conversions of arene to functionalized products. Further, a variety of alpha-olefins could be oxidatively coupled with benzene, giving product distributions with high L:B ratios. Notably, in the case of sterically hindered alpha-olefins, 100% linear products were obtained. Importantly, catalysis was shown to be active for both electron-deficient and electron-rich arenes while simultaneously yielding *ortho:meta:para* selectivity opposite to that obtained by acid-based mechanisms. The simplicity and broad substrate scope of this catalysis is encouraging and permits the extension of this research into a variety of potential future directions.

6.2 Future Directions

Biaryl-containing complexes are of significant industrial interest due to the high prevalence of biaryl units in pharmaceuticals and agricultural compounds (Scheme 6.2).^{27,28} Although biphenyl is not particularly useful as a product, our ability to synthesize it illustrates the significant achievement of coupling two non-functionalized arenes.²⁹ The most common methods of generating biaryl units are through Mizoroki–Heck, Negishi, Stille, and Suzuki–Miyaura couplings, which generally require pre-functionalized substrates.^{30,31} Moreover, the cross-coupling of two arenes, by avoiding the preparation of haloaromatics, is highly sought after by the pharmaceutical industry.³²



Scheme 6.2. Selected pharmaceutical and agricultural compounds with biaryl units. 27

As shown in Chapter 2, $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$ with $Cu(OAc)_2$ in benzene can produce 2 TO of biphenyl and approximately 1 TO of PhOAc at 180 °C over 4 hours (Scheme 6.3). The hypothesis is that the PhOAc formation is a result of $Cu(OAc)_2$ radical decomposition, whereas the formation of biphenyl is the result of two arene C–H bond activations. Although low TOs were observed, the simplicity of this system could be useful for future study.



Scheme 6.3. Production of PhOAc and biphenyl from as $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$ and $Cu(OAc)_2$ in benzene.

Therefore, a screen of reaction conditions utilizing toluene as the arene substrate with $[Rh(\mu-TFA)(\eta^2-C_2H_4)_2]_2$ and $Cu(OAc)_2$ should be undertaken. Toluene is a useful model substrate because it allows for the observation of the *ortho:meta:para* coupling reactions. The first reactions should focus on increasing the TO of biaryl formation by varying temperature, oxidant loading, and rhodium concentration. Subsequently, ligand systems should be introduced to try and influence the *ortho:meta:para* coupling ratios (Scheme 6.4). The *ortho:meta:para* ratio of toluene oxidative vinylation with propylene was observed to be 1:8.9:9.3. Therefore, the system should follow a similar ratio pattern for the formation of biaryl species. In addition, since the reaction should operate through carboxylate-assisted C–H activation, electron rich and poor arenes should be available for coupling, which is also similar to the oxidative vinylation of anisole and chlorobenzene. This may allow for the production of industrially relevant intermediates.

$$(Rh) \longrightarrow (Rh) + (Ph) +$$

Scheme 6.4. Toluene coupling to give ratios of the *ortho:meta:para* coupling, not all possible permutations shown for clarity.

Another interesting future research direction to evolve from this project is the direct production of PhOAc from benzene and Cu(OAc)₂ as new methods to generate phenol selectively are highly sought after in the petrochemical industry; due to the cost of the cumene-phenol process and the need to develop increased markets for acetone.^{5,33,34} The literature precedent for the direct hydroxylation of benzene to phenol often requires the use of hydrogen peroxide as the oxidant.³⁵⁻³⁷ A possible method for phenol production is the hydrolysis of phenyl acetate to phenol and acetic acid, which could then be recycled with oxygen and copper to regenerate the Cu(OAc)₂ (Scheme 6.5). This methodology is similar to the gas phase production of fluorobenzene from CuF₂ and benzene.³⁸ Important reactions to investigate would be to determine the impact of oxygen on the formation of PhOAc.



Scheme 6.5. Generation of PhOAc from $Cu(OAc)_2$ and benzene catalyzed by the oxygen regeneration of $Cu(OAc)_2$.

6.2.1 Future Research Opportunities for the Oxidative Vinylation of Arenes

The oxidative coupling of ethylene and benzene demonstrated in Chapter 4 highlights the efficacy of $(^{Fl}DAB)Rh(TFA)(\eta^2-C_2H_4)$ for the production of styrene. Although the selectivity for styrene is exceptional (>95%), the overall yield of styrene, relative to benzene, is low. Under the conditions tested, we convert less than 1% of benzene to styrene. Therefore, techniques to improve the yield would be highly beneficial. One potential method to optimize the yield relative to benzene is to develop a system that is stable and active in the presence of oxygen, which could regenerate the $Cu(OAc)_2$ in situ, subsequently increasing the oxidant loading and possible TO. Sadly for all the rhodium complexed diimines studied, the catalysts deactivate rapidly in the presence of oxygen. However, there are a number of NHC Rh complexes that are stable under an oxygen atmosphere.^{39,40} Further, similar NHC rhodium species have been found to be active catalysts for the hydroformylation of olefins.⁴¹ These species should be tested for oxidative vinylation of benzene with α -olefins under an oxygen atmosphere. A second option for increasing the yield with respective to benzene conversion is to run the catalysis in other solvents. Solvents which do not contain arene C–H bonds must be used because those bonds would be susceptible to activation by the catalyst. Additionally, the use of solvents with high boiling points (> 145 $^{\circ}$ C) would enable the styrene to be

distilled from the reaction mixture. An example of such a solvent is sulfolane which has a boiling point of 285 °C and is currently utilized industrially to separate arenes from hydrocarbons.^{42,43} Other potential, intriguing solvents are ionic liquids. For example, ionic liquids have been developed for efficient palladium C–C bond coupling reactions.⁴⁴ These solvents are highly tunable to specific reactions and have high boiling points with opportunities to increase the miscibility of substrates and oxidants; relative to neat arene.^{45,46}

To further improve this method of oxidative vinylation of benzene with ethylene, the rate of catalysis must be increased. This can be achieved by increasing the ethylene pressure and by utilizing soluble copper species.²⁶ However, by changing the copper oxidant, and subsequently the carboxylate moiety, the rate of C–H activation can be influenced. Ison and coworkers recently showed that the rate of carboxylate-assisted C–H activation with Cp*Ir(III) increased with increasing electron density of the carboxylate (Figure 6.1).⁴⁷ This trend was supported by computational findings in which formimidates replaced the carboxylates. The Δ G of C–H activation for formimidate and N-methylformimidate led to barriers of 23.4 and 21.7 kcal/mol, respectively, versus 28.2 kcal/mol for acetate. Therefore, a similar range of formimidates and carboxylates should be evaluated to determine if the rate of oxidative vinylation can be increased.



Figure 6.1. Carboxylates and formimidates with their calculated ΔG of assisted C–H activation.⁴⁷

As discussed in Chapter 1, the majority of industrial chemical processes utilize heterogeneous catalysts.^{48,49} Therefore, attempts to tether these low valent rhodium species on solid supports would be valuable as this would allow for easier separation of the catalyst from the product mixture. The immobilization of homogenous catalysts on supports is a growing field.^{50,51} <u>ENREF 50</u> These supports are often based on carbon, alumina, and silica. Messerle and coworkers have successfully immobilized Rh(I) species to carbon black, graphene, and glassy carbon electrodes (Scheme 6.6).⁵²⁻⁵⁴ Recently a number of Rh(I) species have been successfully immobilized on polymers.⁵⁵ Another possibility is to put homogenous catalysts into metal organic frameworks (MOFs).^{56,57}



Scheme 6.6. The immobilization of homogenous Rh(I) catalyst onto carbon supports. Carbon source is either a glassy carbon electrode, carbon black, or graphene. Mes = mesityl.⁵²

Immobilization is a covalent bond to the support formed through the reduction of the diazonium moiety. Most ligand systems that contain a NH₂ group can be coordinated to a carbon support using this methodology, as long as they are stable to the acidic conditions. Therefore, the most active ligands for our oxidative vinylation chemistry should be modified to include an NH₂ group. Examples of potential ligand systems are shown in Figure 6.2.



Figure 6.2. Ligands containing NH_2 groups that could be complexed to immobilized carbon supports.

Future research directions for the oxidative coupling of benzene and α -olefins for the production of vinyl and allyl species are similar those discussed above: designing catalysts for *in situ* oxygen regeneration and using new solvents, oxidants with different carboxylate moieties, and immobilized catalysts. However, research into the generation of linear products has opportunities for multiple new research avenues. One example is the possible coupling of butadiene and benzene to produce (E)-buta-1,3-dien-1ylbenzene. This would offer the chemical industry a new polymer precursor. Another new research avenue is based off a side product observed. During the coupling of benzene and neohexene we observed 27(6) TO of 2,2,4,6,6-pentamethylheptane, after hydrogenation (Scheme 6.7). An important industrial process is the acid-based coupling of olefins. For example the coupling of butenes with isobutane to yield isooctanes for motor fuels.⁵⁸ Importantly in our reaction, analysis of the GC-MS traces revealed that before hydrogenation, the product generated was an olefinic species, believed to be 2,2,6,6-tetramethyl-4-methyleneheptane. This would enable acid based alkylation of the 2,2,6,6-tetramethyl-4-methyleneheptane which would generate highly branched alkanes which are desired for aviation fuels.^{59,60} Therefore understanding the conditions that lead to olefin coupling is important to either minimize side product formation or to identify useful olefin-coupled products.



Scheme 6.7. Formation of the side product 2,2,4,6,6-pentamethylheptane from the oxidative coupling of neohexene and subsequent hydrogenation.

The work presented in this Dissertation provides an important foundation for C–H activation and functionalization catalysis. Specifically, the discovery of these Rh complexes for the oxidative vinylation of arenes with α -olefins is a promising avenue of research. Significant potential exists for the extension of this work toward commercialization of desirable products for the petrochemical, surfactant, and pharmaceutical industries.

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