Ruthenium-Diazafluorenide Complexes for Catalysis of Oxa-Michael Addition Reactions

by

Celia Gendron-Herndon

A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department
University of Toronto

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Celia Gendron-Herndon

Master of Science
Department of Chemistry
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Abstract
Recent studies in the field of organometallic catalysis have explored metal-ligand cooperativity in the catalysis of oxa-Michael addition reactions. The ligand-based reactivity of ruthenium-diazafluorenide complexes for the activation of small molecules has previously been reported in our group. This thesis presents an exploration into the catalytic potential of these complexes for oxa-Michael addition reactions. Herein, we reveal an efficient ruthenium-diazafluorenide system which catalyzes the hydroalkoxylation of α,β-unsaturated nitriles, followed by an analysis of the reactivity, conditions, and substrate scope of the catalyst system.
Acknowledgments

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<table>
<thead>
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<tbody>
<tr>
<td>PNN</td>
<td>2-di-tert-butylphosphinomethyl-6-diethylaminomethylpyridine</td>
</tr>
<tr>
<td>NHC</td>
<td>n-heterocyclic carbene</td>
</tr>
<tr>
<td>eq</td>
<td>equivalents</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>o/n</td>
<td>overnight</td>
</tr>
<tr>
<td>iPrOH</td>
<td>isopropanol</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>GC/MS</td>
<td>gas chromatography/mass spectroscopy</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>Mesitylnacnac</td>
<td>mesityl β-diketiminate</td>
</tr>
<tr>
<td>v/v</td>
<td>volume to volume</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
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Chapter 1

1 Introduction

1.1 Catalysis

Catalysts allow reactions to take place by lowering the activation energy of a reaction. Chemists have extensively developed the field of catalysis from simply facilitating reactions to the development of complex catalysts which precisely control the outcome of the catalyzed reaction. Several considerations come into play when studying catalysis of a reaction. The efficiency of a catalyst is dependent upon the amount of catalyst needed per moles of substrate produced. This is referred to as the turnover number of the catalyst, which allows for assessment of the utility of a catalyst. Another important factor is the recyclability of the catalyst, as well as its robustness—a catalyst is more desirable if it can be re-used for further reactions and does not degrade quickly. The ideal catalyst operates quickly and in good or quantitative yields. Ambient temperature and pressure conditions are ideal, and a reaction time of less than a day is desirable. Another consideration for catalysis of these types of reactions is the stereospecificity of the product influenced by the catalyst. Tolerance of functional groups is also an important factor in the use of catalysts for organic synthesis. For example, the tolerance of protecting groups or heavily substituted substrates is desirable when synthesizing natural products. Michael additions are essential in the synthesis of pharmaceutical materials and organic synthesis reactions.

1.2 Oxa-Michael Addition Reactions

Michael addition reactions involve the addition of a nucleophile to a conjugated system. This type of reaction has been extensively studied; the products of Michael addition reactions are greatly varied and exceedingly useful in organic synthesis reactions. Oxa-Michael addition reactions are a class of Michael addition involving the addition of an alcohol to a Michael acceptor (Scheme 1-1).¹ Recent advancements have been made in the formation of complex molecules with an oxa-Michael addition reaction embedded in domino reactions. The addition of an oxa-Michael donor to a conjugate acceptor forms a reactive intermediate, which can then further react. An example of this is the oxa-Michael addition of a phenolic donor to an alkynal to form 4H-chromenes, which are useful because of the strong cytotoxicity of these molecules against cancer cells.²
In comparison to the plethora of oxa-Michael additions to more reactive substrates, the addition of alcohols to α,β-unsaturated nitriles is a much less developed field, due in part to the low reactivity of these substrates. Challenges such as low stereoselectivity, low functional group tolerance, and reversibility of reaction are existent in this field. As such, there is little research in the way of catalysis of this reaction in good yield, with all of these problems addressed.

### 1.3 Known Catalysts

Oxa-Michael addition reactions are catalyzed by a variety of bases.\(^3\) Acid-catalyzed oxa-Michael additions to unsaturated ketones have also been reported.\(^4\) Alkyl phosphine catalysts have also been developed for this reaction (Scheme 1-2).\(^5\)

Many recent efforts have been made in organometallic catalysis to generate useful oxa-Michael addition products. The majority of these studies focus on the addition of alcohols to α,β-unsaturated ketones, but there are a few organometallic catalysts active towards acrylonitrile and other nitriles. Due to the lowered reactivity of α,β-unsaturated nitriles towards conventional nucleophiles, catalytic studies on this reaction are limited.\(^6\)

A copper-NHC catalyst put forth by Gunnoe et al catalyzes additions of amines and alcohols to acrylonitrile, as well as oxa- and aza-Michael additions to α,β-unsaturated ketones (Figure 1-1).\(^7\) These reactions take place in good yields, but occur slowly, with no nitrile substrate scope and limited alcohol substrate scope.
Zargarian et al. have developed a nickel pincer-type complex which catalyzes oxa- and aza-Michael additions to acrylonitrile (Figure 1-2). This catalyst is quite reactive in regards to aza-Michael additions, but falls somewhat short on oxa-Michael additions, garnering few turnovers and little reactivity with nitriles other than acrylonitrile. This system is most effective for the oxa-Michael addition of phenols to acrylonitrile. A nitrile coordination mechanism has been put forth regarding the previously mentioned this complex, in which the nitrile is postulated to coordinate to the nickel center.

Base-catalyzed reactions have been reported for the addition of primary alcohols to acrylonitrile, though at high catalyst loadings and no nitrile substrate scope. Trialkylphosphine catalysts are known, but the addition of alcohols to acrylonitrile necessitate high temperatures and catalyst loadings, and have poor reaction yields. Triphenylphosphine is reported to catalyze the addition of a variety of alcohols to acrylonitrile. A few remarkable ruthenium organometallic catalysts are reported. Yi et al. report a ruthenium-acetamido complex which catalyzes the addition of various alcohols to substituted nitriles in good yields. The proposed mechanism for this reaction involves the coordination of the nitrile moiety to the ruthenium center, and subsequent deprotonation of the alcohol and oxa-Michael addition to the activated nitrile substrate (Scheme 1-3).
Scheme 1-3: Proposed catalyst mechanism of oxa-Michael addition to acrylonitrile catalyzed by ruthenium-acetamido complex.

Nitrile coordination is a commonly proposed motif in ruthenium-mediated reactions. This is supported by olefin isomerization of unsaturated substrates. A β,γ-unsaturated nitrile, in this case 3-pentenenitrile, will react under catalytic conditions to give the same oxa-Michael addition product observed for its α,β-unsaturated counterpart, 2-pentenenitrile (Scheme 1-4). This phenomenon was observed for the ruthenium-acetamido catalyst.

Scheme 1-4: Formation of a single olefin isomerization product from 2- and 3-pentenenitrile

A recent report of a ruthenium-PNN catalyst has garnered attention for activity towards acrylonitrile and substituted nitriles, and especially for intramolecular oxa-Michael addition reactions. Like the ruthenium-acetamido complex mentioned above, this catalyst also generates the same addition product for 2-pentenenitrile and 3-pentenenitrile, a result which is supported by X-ray crystallographic evidence. The proposed catalytic mechanism claims a metal-ligand cooperative pathway, in which the nitrile substrate not only N-coordinates to the ruthenium center, but also adds to the sidearm of the aromatic ligand, facilitating addition of the alcohol to the substrate (Scheme 1-5).
This catalytic system bears resemblances to the ruthenium-diazafluorenide complexes researched in our group.

### 1.4 Metal-Diazafluorenide Complexes

Recent developments in organometallic chemistry have seen complexes in which the ligand system participates in chemical reactions. Ruthenium-diazafluorenide complexes are one such species. Due to the proximity of the unquenched Lewis acidity of the ruthenium center and the basic diazafluorenide ligand, these complexes exhibit reactivity akin to that of frustrated Lewis pairs and other zwitterionic complexes. Long range heterolytic cleavage of dihydrogen has been reported with the ruthenium-diazafluorenide complex shown below (Scheme 1-6).
A different type of reactivity has also been reported in which the “actor” diazafluorenide ligand is responsible for primary reactivity and the metal center acts as a “spectator”. Formal insertion of CO$_2$ has been reported with metal-diazafluorenide complexes, in which the metal center serves only to tune the reactivity of the ligand (Scheme 1-7).\textsuperscript{12}

Various metal-diazafluorenide and metal-free diazafluorenide analogs have also been reported in our group, further illustrating the remarkable reactivity of diazafluorenide (Scheme 1-8).

In addition to small-molecule activation, the metal-diazafluorenide system has potential for reactivity in other reactions. As previously mentioned, similar metal-ligand cooperative organometallic catalysts have been shown to be active for oxa-Michael addition reactions.\textsuperscript{10} The metal-ligand cooperativity of the 1 begs the question; could this system exhibit reactivity toward $\alpha$,$\beta$-unsaturated nitriles, in the same way that the previously mentioned ruthenium-PNN system does?

In this thesis, we outline an efficient ruthenium diazafluorenide catalyst 1 for the facilitation of oxa-Michael addition reactions in low catalyst loading and fast conversion. These reactions exhibit one hundred percent atom economy. The mechanism of this catalyst is investigated. The similarity between the ruthenium-diazafluorenide catalyst and other oxa-Michael addition reaction catalysts bears scrutiny because of the similarities between the reported catalysts. A vital aspect in
comparison is the metal-ligand cooperative reactivity of 1. The metal-diazafluorenide complex 1 in oxa-Michael addition reactions should act cooperatively with the ruthenium metal center in a fashion analogous to the ruthenium-PNN catalyst mentioned above, or reactivity could be limited to the diazafluorenide ligand, as has also been reported for this complex. Reactivity could also be confined to the metal center. The major goals of this project are to test the reactivity of various metal-diazafluorenide complexes towards catalysis of oxa-Michael addition reactions to α,β-unsaturated nitriles, and in doing so elucidate the reaction mechanism of this system. In addition to this, we explore the sensitivity and substrate scope of the catalyst. This information will expand the usefulness of metal-diazafluorenide complexes, and help explain the similarities and differences between this system and other organometallic oxa-Michael addition catalysts.
Chapter 2

2 Results and Discussion

2.1 Analytical Method Development

The ruthenium-diazafluorenide catalysts were first tested for reactivity using reported methods. This was done in order to have a good baseline for comparison to other reactions. Initial reactivity was analyzed using GC/MS. Anti-Markovnikov oxa-Michael adduct formation was observed (Scheme 2-1). The addition of isopropanol was observed only on the β position of acrylonitrile. Product formation confirms that 1 catalyzes this reaction.

Scheme 2-1: Initial reaction for testing of reactivity

These preliminary reactions were run in tetrahydrofuran and isopropanol, then the entire reaction mixture was analyzed using GC/MS. This method proved unsuitable for quantitative analysis, however, because both substrates and the solvent have similar elution times. NMR spectroscopic analysis was therefore chosen as an effective method of quantitation and reaction monitoring. The catalyst was first dissolved in the alcohol substrate, followed by addition of the nitrile. The reactions were run in neat alcohol in order to simplify analysis of the NMR spectra.

Both ruthenium-containing catalysts 1 and 2 catalyze the oxa-Michael addition of isopropanol to acrylonitrile in similar yields and at similar reaction rates (Scheme 2-2). The reaction goes to completion within 30 minutes at 40°C using either species. For further catalytic reactions, catalyst 1 was chosen in order to simplify the procedure and also due to its higher solubility in isopropanol.

Scheme 2-2: Preliminary reaction conditions

2.2 Catalyst Lifetime

The stability and lifetime of catalyst 1 under catalytic conditions was tested through two sequential additions of acrylonitrile substrate. After conversion of the first aliquot of acrylonitrile in approximately 30 minutes, a second aliquot was added to the reaction mixture and the reaction
was monitored for a further 30 minutes. The reaction in neat isopropanol goes to near-completion in approximately 15 minutes with 0.1 mole percent catalyst loading (Scheme 2-3). The lifetime of this catalyst was tested under the same conditions. 35 minutes after addition of the substrate, a second equivalent of acrylonitrile was added to the reaction, then further monitored. The second addition reaction also went to near-completion after 30 minutes, indicating that the catalyst reactivity is not limited to 0.1 mole percent catalyst loading.

Figure 2-1 shows the monitoring of the consumption of acrylonitrile by $^1$H NMR spectroscopy. Thirty minutes after the first addition of acrylonitrile to the reaction vessel, the acrylonitrile substrate is almost completely consumed (Figure 2-1: $t = 10 - 30$ min). The NMR spectra labeled as $t = 45$ and 60 minutes correspond to 15 and 30 minutes, respectively, after the addition of a second volume of acrylonitrile to the reaction vessel and show that the size of these peaks continues to decrease relative to the internal standard peak (Figure 2-1: $t = 45 - 60$ min). This result indicates that the catalyst continues to be active beyond 0.1 mole percent catalyst loading.
Further reactions involving catalyst 1 were done at 40°C and 0.5 mole percent catalyst loading in order to speed up reaction time.

![Figure 2-1: 1H NMR spectrum (400 MHz, CDCl₃, 25 °C) of the reaction of catalyst 1 and acrylonitrile in neat isopropanol showing the changes in the acrylonitrile peaks after the first addition of substrate (t = 10 - 30 min) and after the second addition of substrate (t = 45 - 60 min).](image-url)

2.3 Base-Catalyzed oxa-Michael Addition Reactions

Test reactions were run on different diazafluorenide-containing complexes (Scheme 2-4). A zinc-diazafluorenide analogue 4 was tested for catalytic activity under identical reaction conditions to those used for initial screening of complexes 1 and 2, with no success. A rhodium-diazafluorenide complex 3 was also tested for reactivity. Due to the electron-rich metal center, 3 should be the more basic complex compared to the ruthenium-diazafluorenide analogues.¹² No product formation was observed with this 3, either.

![Scheme 2-4: Catalyst Screening Conditions](image-url)
Several examples of base-catalyzed oxa-Michael addition reactions are known.\(^3\) Diazafluorenide has nucleophilic reactivity and has the potential to act as a base. These results eliminate the possibility of a simple base-catalyzed reaction, since the most basic metal-diazafluorenide analogue \(3\) demonstrates no reactivity towards oxa-Michael addition. The methyl-diazafluorenide system \(5\), which exhibits similar reactivity to \(1\) and \(3\) in \(\text{CO}_2\) activation reactions, does not exhibit reactivity under these conditions. This indicates that there is more reactivity at play than the basic character of the diazafluorenide ligand. It is likely that the ruthenium center plays a part in the catalysis of this reaction, since no reactivity was observed with metal-free diazafluorenide analogues or diazafluorenide analogues coordinated to other metals.

### 2.4 Triphenylphosphine-Catalyzed oxa-Michael Addition Reactions

Triphenylphosphine has also been reported to catalyze Oxa-Michael addition reactions (Scheme 2-5).\(^5\) This poses an issue because of the triphenylphosphine moieties present on \(1\). These moieties may be dissociating and simply catalyzing this reaction, as opposed to product formation stemming from organometallic catalysis by the ruthenium-diazafluorenide system. A control reaction was run in order to test this theory. Catalyst \(1\) was run under the conditions indicated below, but at half the catalyst loading, since there are two triphenylphosphine groups on \(1\) with catalytic potential (Scheme 2-6). The rate of reaction of \(1\) is much faster than that of triphenylphosphine alone under the same reaction conditions. Whereas the triphenylphosphine-catalyzed reaction gives 68% yield over 6 hours at reflux conditions, \(1\) catalyzes this reaction to quantitative yield in less than one hour. It is therefore reasonable to conclude that this reaction is not simply catalyzed by triphenylphosphine, and that there is reactivity based on the catalyst itself, which is more than the sum of its parts.
2.5 Nitrile Substrate Scope

Substituted nitriles were tested for reactivity (Scheme 2-7). Substituted nitriles are known to be much less reactive, whereas acrylonitrile displays more reactivity. Reactions with crotonitrile, cinnamonic acid, and fumaric acid did not show the expected addition product within 60 minutes at 40°C (Figure 2-3). The reaction mixtures were further monitored overnight in hopes of observing product formation with no success. 2-chloroacrylonitrile was also tested in hopes that a 2-substituted olefin would be more susceptible to addition (Figure 2-3). No addition product was observed for this reaction.

Substrates containing electron-donating and electron-withdrawing groups were investigated with zero reactivity in either case.

2.6 Olefin Isomerization

The previously mentioned study of the ruthenium-PNN oxa-Michael addition catalyst has reported olefin isomerization of the substrate, in which a β,γ-unsaturated nitrile such as 3-pentenenitrile, shown below, isomerizes to an α,β-unsaturated nitrile before undergoing addition (Scheme 1-4, Scheme 1-5). This type of reactivity was tested with 3-pentenenitrile and 1 (Scheme 2-8). No product was observed.
The absolute lack of \(\alpha,\beta\)-unsaturated nitrile substrate scope suggests that substituted acrylonitrile substrates are unreactive with this catalyst.

### 2.7 Alcohol Substrate Scope

Alcohol substrate scope was strongly pursued due to the lack of substituted \(\alpha,\beta\)-unsaturated nitrile scope (Scheme 2-9). The reaction proceeds efficiently with isopropanol as a substrate. Ethanol and methanol were then tested under identical conditions. Product formation was observed, but the reaction proceeded slowly and in low yields; 32% and 46.5% for methanol and ethanol, respectively (Table 2-1). When these reactions were left overnight, no further product formation was observed. The acidity of ethanol and methanol may be responsible for these results. The pK\(_a\) of these primary alcohols is roughly 16, whereas the pK\(_a\) of isopropanol is 16.5, making it about five times less acidic than ethanol and methanol. There is evidence of catalyst poisoning of 1 by methoxide, which is a likely culprit for the low yield of the methanol addition reaction.

With the high reaction yield of the isopropanol substrate in mind, the reactivity of other secondary alcohols was also investigated. Catalytic reactions were performed with 2-butanol, cyclopentanol, and cycloheptanol. Efficient product formation was observed with 2-butanol, and similar results were observed with cycloheptanol (Table 3-1). The reaction of cyclopentanol proceeded more slowly. Secondary alcohols are the most reactive under these conditions. Bulkier alcohols were also screened for reactivity. The same conditions were applied to tert-butanol and phenol screening reactions. No product formation was observed. Starting material peaks were observed in NMR. (Table 3-1).
Table 2-1: Yields of alcohol substrate screening

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
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<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>32%</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>46.5%</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Quantitative</td>
</tr>
<tr>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Quantitative</td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>27%</td>
</tr>
<tr>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Quantitative</td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>No Product</td>
</tr>
<tr>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>No product</td>
</tr>
</tbody>
</table>

2.8 Co-Solvent Reactions

Similar ruthenium-based catalyst systems showed increased reactivity with some alcohol substrates when the substrate is mixed with another alcohol as a co-solvent.¹⁰ Since primary alcohols did not display good reactivity in neat reactions, co-solvent reactions were run with primary alcohols, isopropanol, and catalyst 1 in an attempt to increase reaction yields (Scheme 2-10). A series of trial reactions were performed with methanol and ethanol with a co-solvent. Reactions were done in various alcohol substrate to isopropanol solvent ratios. The first trials were done with 50/50, 25/75, and 75/25 v/v ratios of ethanol to isopropanol. The highest percent yield
of the ethanol addition reactions was observed with a 50/50 ratio of ethanol to isopropanol co-solvent (Table 2-2).

![Scheme 2-10: Ethanol Co-Solvent Reactions](image)

Table 2-2: Ethanol Co-Solvent Reaction Products

<table>
<thead>
<tr>
<th>Ratio iPrOH/ EtOH v/v</th>
<th>Ethanol adduct yield</th>
<th>Isopropanol adduct yield</th>
</tr>
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<tr>
<td>25/75</td>
<td>0.5%</td>
<td>No product observed</td>
</tr>
<tr>
<td>50/50</td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td>75/25</td>
<td>13%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

A small amount of isopropanol adduct was observed for some reactions. This is most noticeable when the reaction is done with a 75% excess of isopropanol to the substrate (Table 2-2).

Co-solvent catalytic tests were also run with various alcohols and isopropanol. The same conditions as above were used to test the reactivity of methanol, cyclopentanol, and cycloheptanol (Scheme 2-11).

![Scheme 2-11: Co-Solvent Reactions](image)

Table 2-3: Co-solvent reaction products

<table>
<thead>
<tr>
<th>Desired Product</th>
<th>Yield</th>
<th>Isopropanol adduct yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Desired Product" /></td>
<td>32%</td>
<td>No product observed</td>
</tr>
<tr>
<td><img src="image" alt="Desired Product" /></td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td><img src="image" alt="Desired Product" /></td>
<td>29%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Adducts from both alcohol substrates were observed in significant yields for these co-solvent reactions (Table 2-3).

Table 2-4: Comparison of neat reaction yields to co-solvent reaction yields

<table>
<thead>
<tr>
<th>Alcohol Substrate</th>
<th>Yield Neat</th>
<th>Yield in Co-Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>Ethanol</td>
<td>46.5%</td>
<td>15%</td>
</tr>
<tr>
<td>Cyclopentanol</td>
<td>27%</td>
<td>29%</td>
</tr>
<tr>
<td>Cycloheptanol</td>
<td>Quantitative</td>
<td>13%</td>
</tr>
</tbody>
</table>

The co-solvent reactions did not increase the yield of product, though product formation was observed for each primary alcohol. When methanol was reacted under these co-solvent conditions, the percent yield did not increase or decrease compared to reactions run neat in methanol. The yield was nearly identical in both conditions (Table 2-4). In the ethanol co-solvent reaction, percent yield was much lower than that of the neat reaction. The percent yield was significantly decreased in the case of cycloheptanol compared to a neat reaction. The reactivity of cyclopentanol was slightly higher in a co-solvent, but the change in yield is not significant. The percent yield changes drastically in this case, and is not a simple effect of dilution of substrate. These results are in contrast to data found with the ruthenium PNN system, which observed increased yield in co-solvent reactions.\(^\text{10}\)

For alcohol substrates with low yield in a neat reaction, the percent yield is slightly increased with the use of isopropanol as a co-solvent, but the effect is not significant. In cases where the alcohol substrate is more reactive in neat conditions, the reactivity is actually lessened with a co-solvent. The co-solvent does not increase yield and in some cases significantly decreases the yield of desired product, and forms undesirable isopropanol adduct. Under these conditions, isopropanol in many cases acts as a competing solvent, as opposed to being a co-solvent.
2.9 Stoichiometric Reactions

The reaction pathway of catalyst 1 is unknown. In an attempt to gain insight into the mechanism, the reactivity of each substrate with the catalyst was explored. One equivalent of substrate was added to an equivalent of catalyst 1 and monitored by NMR spectroscopy (Scheme 2-12).

No change was observed upon addition of isopropanol to catalyst 1. In contrast, addition of acrylonitrile to 1 caused the disappearance of the acrylonitrile peaks in the $^1$H-NMR spectrum, along with a shift in the ruthenium-hydride triplet peak of the catalyst. This change indicates a reaction between acrylonitrile and 1. In order to further elucidate this reaction pathway, 5 equivalents of acrylonitrile were added to a solution of 1 and the reaction was monitored by $^1$H- and $^{31}$P-NMR spectroscopy. Within ten minutes of addition, the formation of a second set of catalyst peaks was seen in the $^1$H-NMR spectrum. This new set of peaks reflects a new species with similar peaks to those of the initial catalyst, but with a slight shift up-field by approximately 0.13 ppm (Figure 2-4). These shifts are congruent with the changes previously observed in the initial addition of one equivalent of acrylonitrile to 1.
The most notable change is that of the ruthenium-hydride peak. The appearance of a new triplet at approximately -12.56 ppm in $^1$H-NMR is seen ten minutes after the addition of acrylonitrile (Figure 2-5). Growth of this peak is observed over 24 hours, indicating the formation of a major species. A third triplet peak is also observed in the same region at approximately -12.52 ppm (Figure 2-5). It does not grow over time and may be a minor decomposition product. The hydride peaks disappear over time, which could be an indication that 1 reacts in a way that depletes the hydride. However, a general decrease in peak size is universally observed in NMR, indicating precipitation of the catalyst.
Figure 2-5: Hydride region of the $^1$H NMR spectrum (600MHz, C$_6$D$_6$, rt) of catalyst 1 in the presence of 5 eq of acrylonitrile before addition (red), at 10 min (yellow), 70 min (light green), 130 min (dark green), overnight (blue), after two days (indigo), and after three days (purple) Note that the NMR spectrum taken at t=0 is from a different NMR sample (300 MHz, C$_6$D$_6$, rt), hence the slight difference in NMR peak shape.

Changes observed in $^{31}$P-NMR peaks further confirms formation of a different catalyst species (Figure 2-6). The doublet appearance of the new peak in $^{31}$P-NMR indicates phosphorus-hydride
coupling is still present, and confirms that the hydride is still coordinated to the ruthenium center.

Figure 2-6: $^{31}$P-NMR spectrum (242 MHz, C$_6$D$_6$, rt) of catalyst 1 in the presence of 5 equiv. of acrylonitrile before addition (red), at 10 min (yellow), 70 min (green), 130 min (blue), and after 18 hours (purple). Note that the NMR spectrum taken at t=0 is from a different NMR sample (121 MHz, C$_6$D$_6$, rt), hence the slight difference in NMR peak shape.

After 18 hours, the sample was composed primarily of the unknown species. A set of new peaks were observed at approximately 2.99-3.55 ppm and continued to grow over time (Figure 2-8). These manifested as a series of doublet of doublets. The composition of this new species is unknown. It is possible that acrylonitrile undergoes a different type of reaction with 1.

Literature investigations of the reactivity between metals and acrylonitrile provide insight into the potential interaction between acrylonitrile and the ruthenium catalyst. These interactions between acrylonitrile and metal centers have been reported. The reaction between acrylonitrile and metal-hydrogen bonds is known for several metal complexes, such as insertion of acrylonitrile into palladium-hydride and palladium-methyl bonds, in which acrylonitrile n-coordinates to the metal center before undergoing insertion into a metal-hydride bond.$^{13}$
Reactions of acrylonitrile with ruthenium catalysts are known, especially in the realm of polymerization or dimerization of acrylonitrile. Tail-to-tail dimerization of acrylonitrile by low-valent ruthenium complexes has been reported. The reaction in neat acrylonitrile under pressure of H₂ yields dicyanobutyl tail-to-tail dimers. The proposed mechanism for this reaction details the insertion of acrylonitrile into a ruthenium-hydride bond, and the subsequent insertion of an other equivalent of acrylonitrile to yield the dimer. This type of reactivity could be replicated by 1 and acrylonitrile in the absence of an alcohol substrate. The dinitrogen ligand could be displaced in favor of acrylonitrile, and the nitrile could then insert into the ruthenium-hydride bond on 1. However, the continued presence of phosphorus-hydride coupling in 3¹P-NMR and the continued presence of the ruthenium-hydride peak in ¹H-NMR do not suggest this type of reactivity.

It is useful to explore the coordination modes of acrylonitrile to ruthenium in the pursuit of a deeper understanding of the interaction between acrylonitrile and 1. Acrylonitrile has the potential to coordinate to ruthenium in two ways; through σ-coordination of the nitrile, or through the η²-coordination of the olefin. The ¹H-NMR shifts of acrylonitrile have been studied upon coordination to metal centers. In general, upon η²-coordination of an olefin to a metal in the +2 oxidation state, significant upfield shifts are observed in NMR. Contrastingly, less dramatic shifts are observed for the σ-coordination of acrylonitrile to a metal center. If the upfield shifts of NMR peaks hold true for this complex, the growth of peaks significantly farther upfield at approximately 3 ppm could indicate displacement of the dinitrogen ligand and η²-coordination of acrylonitrile to the ruthenium center of 1 (Figure 2-7).

The coordination of acrylonitrile to ruthenium complexes has been previously studied. NMR spectroscopic data of a ruthenium-acrylonitrile complex indicates that η²-coordinated acrylonitrile to ruthenium gives rise to several sets of doublets of doublets at 2.76, 2.86, and 3.11 ppm in C₆D₆. In the ¹H-NMR spectrum of 1 and acrylonitrile, peaks with a similar doublet of doublet splitting pattern arise at approximately 2.94, 3.0, and 3.07 ppm (Figure 2-8). The similarity of these peaks to the reported peaks of η²-coordinated acrylonitrile to ruthenium suggests that this same type of coordination is taking place between acrylonitrile and 1 (Figure 2-7).
Diazafuorenide could also be responsible for the change in NMR signals over time. Figure 2-8 shows the disappearance of the 9-position hydrogen peak at approximately 6.44 ppm. Disappearance of this peak is observed 18 hours after addition. These changes in NMR may be due to the slow degradation of 1 over time, since the other catalyst peaks also diminish over time. It could also be indicative of a slow reaction taking place between 1 and acrylonitrile. Catalyst 1 is active towards the activation of small molecules such as CO$_2$.$^{12}$ However, if an interaction between diazafluorenide and acrylonitrile was taking place, there would be an observable change in $^{31}$P-NMR peaks (Figure 2-6). The formation of a new peak would be present as an effect of the insertion. The two triphenylphosphine moieties would no longer be equivalent and the shift would change drastically in $^{31}$P-NMR. This data combined with the newfound peaks in the 3 ppm range in $^1$H-NMR is more suggestive of the interaction between acrylonitrile and ruthenium, instead of interaction between acrylonitrile and diazafluorenide.
Figure 2-8: Region of the $^1$H NMR spectrum (600MHz, C$_6$D$_6$, rt) showing NMR effects on 1 in the presence of 5 eq of acrylonitrile before addition (red), at 10 min (yellow), 70 min (light green), 130 min (dark green), 18h (blue), after two days (indigo), and after three days (purple). Isopropanol was added 2 days after the addition of acrylonitrile to 1. Note that the NMR spectrum taken at t=0 is from a different NMR sample (300 MHz, C$_6$D$_6$, rt), hence the slight difference in NMR peak shape.

Though a conclusion cannot be made from this data alone, it aids in the development of further tests for 1. In order to confirm hypotheses, further investigation is needed. A thorough NMR study of this reaction would provide valuable insight into the reactivity of 1 with acrylonitrile. Efforts are also underway to obtain a crystal structure of the newly formed ruthenium complex and discover more details about this reaction.

The reactivity of the sample containing 5 equivalents of acrylonitrile was investigated by adding 5 equivalents of isopropanol and monitoring the reaction. No oxa-Michael addition product peaks were observed in the sample, even when left over several days. Free diazafluorene signals were observed in NMR, indicating that isopropanol likely protonates the diazafluorenide ligand, prompting catalyst decay and precipitation out of solution, which would explain the lessening of signals over time (Figure 2-8). This confirms that acrylonitrile reacts with 1 in a side reaction which deactivates the catalyst. The catalyst is quite active under standard reaction conditions in
which the catalyst is first dissolved in the alcohol substrate, but 1 exhibits no catalytic activity for oxa-Michael addition reactions when added to acrylonitrile without an alcohol substrate present.

2.10 Simultaneous Addition

The NMR spectroscopy study indicates that over time, acrylonitrile reacts with the catalyst, changing the composition of 1 and rendering it unreactive when isopropanol is added. With this data in mind, the reactivity of the catalyst was investigated upon simultaneous addition of both substrates. Up to this point, catalytic reactions were run by first dissolving the catalyst in the alcohol substrate, followed by the addition of the nitrile substrate. Simultaneous addition eliminates the possibility of side reactions occurring between the substrates and the catalyst. Since lower yields were observed with ethanol and methanol as solvents, these alcohol substrates were tested. The reactions were run in an excess of acrylonitrile. A mixture of acrylonitrile and alcohol was heated, then added to the catalyst and monitored (Scheme 2-13).

\[ \text{Scheme 2-13: Reactions in Acrylonitrile} \]

\[ \text{Table 2-5: Yield of reactions in acrylonitrile} \]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Volume Acrylonitrile</th>
<th>Yield</th>
<th>Yield in 1mL alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>0.50mL</td>
<td>92%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>0.75mL</td>
<td>Quantitative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0mL</td>
<td>Quantitative</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.50mL</td>
<td>99%</td>
<td>46.5%</td>
</tr>
<tr>
<td></td>
<td>0.75mL</td>
<td>Quantitative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0mL</td>
<td>97%</td>
<td></td>
</tr>
</tbody>
</table>
As shown in Table 2-5, simultaneous addition of substrates is vastly more successful for methanol and ethanol substrates. When these reactions were run by first dissolving 1 in methanol or ethanol, the yields were less than 50 percent. This method yields full or nearly full conversion within one hour.

Stoichiometric investigations indicate that the catalyst undergoes a slower side reaction when reacted with acrylonitrile in the absence of an alcohol substrate. Adding both substrates simultaneously in an excess of acrylonitrile is the most efficient method for achieving good yields with methanol and ethanol. The oxa-Michael addition reaction occurs quickly, before the slower side reaction observed in the NMR spectroscopy study occurs between acrylonitrile and 1. It is possible that the higher reactivity of ethanol and methanol deactivate the catalyst when it is first dissolved in alcohol substrate with no nitrile substrate present. The unfavorable interactions do not take place when both substrates are added simultaneously to 1.

### 2.11 Other Alcohol Substrates

The discovery of the more effective simultaneous addition method opens avenues to other alcohol substrates with limited reactivity or other practical concerns. For example, bulkier alcohols are typically not liquid at screening temperatures, and therefore the standard reaction conditions cannot be applied. Catechol, which is a solid at screening temperatures, was tested for reactivity by first dissolving it in acrylonitrile, then adding the mixture of substrates to the catalyst (Scheme 2-14). Unfortunately, no product was observed for the catechol reaction. The possibility remains, however, that this method may be more effective for other alcohol substrates, especially other primary alcohols.

![Scheme 2-14: Catechol Screening Reaction](image)

### 2.12 Conclusion

In the past, ruthenium-diazafluorenide catalyst 1 has exhibited ligand-based reactivity. It has been shown, however, that this is not the case for the catalysis of oxa-Michael addition reactions. Catalyst screening has revealed that the ruthenium metal center, along with diazafluorenide, is essential for the catalysis of this reaction. Metal-ligand cooperativity has been previously reported
for this catalyst, and it is likely that both the Lewis acidic ruthenium center and the carbanionic diazafluorenide ligand are cooperatively catalyzing this reaction.

Catalyst 1 is active for specific substrates in specific conditions. Though the reaction proceeds quickly with acrylonitrile, no activity was observed with 2- and 3-substituted nitriles. Olefin isomerization has been observed with other organometallic catalysts for this reaction, but attempts to replicate these results with 1 were unsuccessful. Screening with various alcohol substrates was more successful, however, especially with secondary alcohols. The initial reaction yields for primary alcohols were low. This prompted a foray into co-solvent reactions, which previously have been reported to help increase yield. Screening alcohols in the presence of isopropanol as a co-solvent did not significantly increase yield, and in some cases dramatically decrease desired product yield, instead forming undesired isopropanol adduct.

The interactions between substrate and catalyst were probed by NMR monitoring. Though there appears to be no reaction between isopropanol and 1, acrylonitrile does undergo a side reaction with the catalyst, as evidenced by new peaks in NMR. Further investigation revealed the formation of a new species with peaks separate from 1, as well as the formation of several new peaks. In the absence of alcohol substrate, acrylonitrile undergoes a side reaction with 1, changing the composition of the catalyst and rendering it unreactive towards alcohol substrates.

The reactivity of the catalyst upon simultaneous addition was explored. Using this method, the yield of methanol and ethanol were optimized. Quantitative yield was obtained for both primary alcohol substrates, which under previous conditions were poorly reactive. The unfavorable reaction between primary alcohols and catalyst is mitigated by the excess of acrylonitrile and the simultaneous addition of substrates. This method optimization can potentially lead to wider alcohol substrate scope.

There are several avenues left to be explored within this catalytic system. Though 1 carries out oxa-Michael addition in good yield in under one hour at near-ambient conditions, the nitrile scope is limited to acrylonitrile. Investigating the reaction pathway of 1 would be helpful in expanding the substrate scope. Given the low reactivity of this system toward substituted nitriles, knowledge of the catalyst function would allow for changes to the system which could potentially support substituted nitriles. Though bulkier and more electron-donating alcohols are not especially reactive, secondary alcohols have moderate success with this system. A variety of functionalized
secondary alcohols have a possibility of reacting to form desirable substrates. There remains much investigation to be done on this system, which could be optimized for better substrate scope.
Chapter 3
Experimental

3 Experimental Methods

3.1 Preparation of Substrates

Isopropanol, tert-butanol, 2-butanol, cyclopentanol, and cycloheptanol were dried over calcium hydride overnight, then distilled under vacuum. Catechol was recrystallized out of dry toluene, producing fluffy white crystals, which were dried in vacuo. Phenol was recrystallized out of dry hexanes. White needle-like crystals were dried in vacuo. Ethanol and methanol were dried over magnesium activated with I₂ under inert conditions, then distilled under vacuum. Acrylonitrile and other nitriles were degassed and dried over 3Å molecular sieves. Tetrahydrofuran was dried over sodium overnight, then distilled under vacuum. Deuterated benzene was dried over 3Å molecular sieves.

3.2 Catalyst Syntheses

Synthesis of 1

Followed previously published protocol (Scheme 3-1).¹¹

Synthesis of 2

A solution of sodium hydride in tetrahydrofuran was added dropwise to a stirring solution of diazafluorene in tetrahydrofuran and stirred at room temperature overnight in a glove box.
atmosphere. The solution of diazafluorenide was then added through a filter pipette to a stirring solution of RuHCl(PPh$_3$)$_3$(CO) in tetrahydrofuran and stirred at room temperature overnight in a glove box atmosphere. Solvent was evaporated in vacuo, then dissolved in toluene and filtered. Solvent was then evaporated in vacuo, and the residue was then redissolved in tetrahydrofuran and 3 times the volume of pentane. Pure product was collected by vacuum filtration (Scheme 3-1).

$^1$H-NMR (C$_6$D$_6$, 300 MHz, 25°C) δ 7.96 (d, $J = 6$ Hz, 2H), δ 7.73 (d, $J = 9$ Hz, 2H), δ 7.62 (d, $J = 6$ Hz, 2H), δ 7.36 (m, 15H), δ 7.04 (m, 2H), δ 6.84 (m, 15H), δ 6.69 (dd, $J = 6$ Hz, $J = 6$ Hz, 2H), δ 6.47 (s, 1H), δ 6.20 (dd, $J = 6$ Hz, $J = 3$ Hz, 2H), δ -11.54 (t, $J = 18$ Hz, $J = 21$ Hz, 1H) $^{31}$P-NMR (C$_6$D$_6$, 121 MHz, 25°C) δ 48.55 (s)

Synthesis of rhodium-COD-diazafluorenide complex 3

Followed previously published protocol.$^{12}$

Synthesis of zinc-mesitylnacnac-diazafluorenide species 4

A (0.1 M in hexanes) solution of diethylzinc was added dropwise in a nitrogen environment to a stirring solution in dry toluene of one equivalent of diazafluorene, then stirred overnight at room temperature. Volatiles were removed in vacuo and the solid was redissolved in toluene. To this stirring solution was added one equivalent of mesitylnacnac. This solution was stirred at room temperature in a nitrogen environment for two days. Volatiles were removed in vacuo to yield 4. Recrystallization to yield pure product was carried out in a layered mixture of THF and hexanes.

$^1$H-NMR (C$_6$D$_6$, 400 MHz, 25°C) δ 7.88 (d, $J = 8$ Hz, 4H), δ 7.82 (d, $J = 8$ Hz, 4H), δ 6.90 (dd, $J = 4$ Hz, $J = 4$ Hz, 2H), δ 6.41 (s, 4H), δ 6.27 (s, 1H), δ 5.0 (s, 1H), δ 2.22 (s, 12H), δ 1.78 (s, 6H), δ 1.70 (s, 6H)

Synthesis of 5

Followed previously published protocol.$^{12}$

3.3 Gas Chromatography Method

An aliquot of reaction mixture was diluted to approximately 100 ppm, then filtered through Fisherbrand G6 glass fiber filter paper into an Agilent Teflon-capped vial. Gas
chromatography/mass spectroscopy data was obtained on an Agilent instrument. The product was identified by NIST library.

### 3.4 General Screening Procedure

One milliliter of isopropanol was added to the catalyst, followed by fifty microliters of dry mesitylene. The solution was heated to 40 degrees Celsius in an aluminum block fitted to an IKA stirring and heating plate equipped with an electronic thermocouple. The solution was allowed to come to temperature, then nitrile substrate was added by a Hamilton GASTIGHT #1810 microsyringe. A twenty-five microliter aliquot of reaction mixture was taken, then syringed into a 5-milliliter NMR tube and dissolved in deuterated chloroform. The solution was monitored by NMR. NMR spectra were taken on Varian Mercury 300 MHz or 400 MHz NMR spectrometers.

The same procedure was used for co-solvent screening reactions, but a volume of co-solvent was added to the solution of 1 in isopropanol.

The same procedure was used for recyclability reactions, but a second amount of acrylonitrile was added after 30 minutes, then monitored using the same method.

NMR data for 3-methoxypropionitrile

$^1$H-NMR (CDCl$_3$, 300 MHz, 25°C) $\delta$ 3.60 (t, $J = 6$ Hz, $J = 6$ Hz, 2H), $\delta$ 2.59 (t, $J = 6$ Hz, $J = 6$ Hz, 2H), $\delta$ 1.63 (s, 3H)

NMR data for 3-ethoxypropionitrile

$^1$H-NMR (CDCl$_3$, 300 MHz, 25°C) $\delta$ 3.63 (t, $J = 9$ Hz, $J = 6$ Hz, 2H), $\delta$ 3.54 (q, $J = 6$ Hz, $J = 9$ Hz, 2H), $\delta$ 2.58 (t, $J = 6$ Hz, $J = 6$ Hz, 2H), $\delta$ 1.21 (t, $J = 6$ Hz, 3H)

NMR data for 3-isopropoxypropionitrile

$^1$H-NMR (CDCl$_3$, 400 MHz, 25°C) $\delta$ 3.63 (septet, $J = 4$ Hz, $J = 8$ Hz, $J = 8$ Hz, $J = 4$ Hz, $J = 8$ Hz, $J = 4$ Hz, 1H), $\delta$ 3.62 (t, $J = 4$ Hz, $J = 8$ Hz, 2H), $\delta$ 2.55 (t, $J = 8$ Hz, $J = 4$ Hz, 2H), $\delta$ 1.16 (d, $J = 8$ Hz, 6H)
3.5 Procedure for Triphenylphosphine Control Reaction

General procedure was followed from published work. Reaction yields were analyzed by NMR spectroscopy methods detailed in Section 3.4.

3.6 General Procedure for Reactions in Acrylonitrile

A volume of dry, degassed acrylonitrile was syringed into an empty vial sealed with a septum purged with nitrogen. 200 equivalents of substrate were added to the vial, and the combined substrates were then heated to 40 degrees Celsius. Once at temperature, the combined substrates were added by syringe to a prepared vial containing 1 with stirring. The reactions were monitored in the same manner as the general screening procedure.

3.7 General Procedure for NMR-scale reactions

A small amount of 1 was weighed out in a tared vial, then dissolved in C\textsubscript{6}D\textsubscript{6}. The catalyst solution was quantitatively transferred into a J. Young tube. A solution with known concentration of substrate was made in C\textsubscript{6}D\textsubscript{6}. One equivalent of substrate was added by microsyringe.

The same method as above was used for the 5-equivalent excess of acrylonitrile reaction.

3.8 Method for Calculation of Percent Yield

The integration of the addition product peak was compared to the integration of the internal standard. This value was correlated to the number of moles of internal standard, yielding the number of moles of product per run. The peak integrated was the triplet resulting from the 2-position hydrogen atoms on each product.
References


8. Salah, A. B.; Offenstein, C.; Zargarian, D., Hydroamination and Alcoholysis of Acrylonitrile Promoted by the Pincer Complex \{κP,κC,κP-2,6-(Ph2PO)2C6H3\}Ni(OSO2CF3). *Organometallics* 2011, 5352-5364; Lefèvre, X.; Durieux, G.; Lesturgez, S.; Zargarian, D.; Addition of amines and phenols to acrylonitrile derivatives catalyzed by the POCOP-type pincer complex \{κP,κC,κP-2,6-(i-Pr2PO)2C6H3\}Ni(NCMe)[OSO2CF3]. *Journal of Molecular Catalysis* 2011, 335, 1-7


