The application of homogeneous transition metal catalysts may facilitate the selective transformation of typically unreactive bonds into more complex molecules such as those which exist in medicinal natural products. These catalysts are used in low quantities and recycled during the course of the reaction, thus minimizing the amounts of toxic waste produced. Specifically, because these complexes are soluble, they can be analyzed by a variety of spectroscopic techniques. As a result, a detailed understanding of the mechanisms behind these reactions can be achieved, allowing for the rational design of new and more effective catalysts.

In our group, the catalytic activation of C-H bonds in benzene has been achieved utilizing Cp*Ir(III)-complexes. In addition, our group achieved the directed C-H activation and functionalization of benzoic acids to generate isocoumarins and benzochromenones by utilizing [Cp*IrCl$_2$]$_2$ as the catalyst. Due to the observed ability of Cp*Ir(III) complexes to catalytically activate and functionalize C-H bonds, we aimed at studying the activation and functionalization of benzamides, the nitrogen derivative of benzoic acid.

Herein, in Chapter 2 the development, optimization, and mechanistic evaluation of the aerobic, [Cp*Ir(H$_2$O)$_3$](OTf)$_2$-catalyzed isoquinolone synthesis from benzamides and alkynes is described. Optimized conditions include 2.5 mol% [Cp*Ir(H$_2$O)$_3$](OTf)$_2$ in cyclohexane at 90 °C under air (40 psi). Reactions of benzamide derivatives and diphenylacetylene afforded the desired products in moderate to high isolated yields. The catalytic system was shown not only to be efficient for the coupling of diphenylacetylene, but also allowed for oxidative annulations of *para*-substituted diphenylacetylene derivatives. Kinetic studies suggest that the
reaction follows first order kinetics with respect to isoquinolone formation, benzamide consumption and $[\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3]\text{(OTf)}_2$, zero order kinetics with respect to diphenylacetylene and a kinetic isotope effect ($k_H/k_D$) of 1.3(1). The mechanism is proposed to proceed via $N$-coordination of the benzamide followed by a concerted-metalation-deprotonation C-H activation. Solvent and Hammett studies suggest that the turnover limiting step is benzamide coordination. The stoichiometric reaction between benzamides and $[\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3]\text{(OTf)}_2$ in cyclohexane resulted in catalyst decomposition or non-identifiable species. However, when $[\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3]\text{(OTf)}_2$ was replaced with $[\text{Cp}^*\text{Ir}(\text{NHC})(\text{H}_2\text{O})_2]\text{(OTf)}_2$, (NHC = N-Heterocyclic Carbene, 1,3-dimethylimidazol-2-ylidene) an oxygen-bound species that does not appear to be part of the catalytic cycle was isolated.
Cp*Ir(III)-Catalyzed Isoquinolone Synthesis via C-H Activation and Functionalization of Benzamides

by
Joan Evaliz Roque-Pena

A dissertation submitted to the Graduate Faculty of North Carolina State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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DEDICATION

To my husband, for his unconditional love, support, and encouragement throughout these years, ¡Te Amo!

To my parents Sonia and Raymond and my sister Raysa, for inspiring me to continue with my education, their support, encouragement, and always believing in me throughout my life. Gracias por su apoyo incondicional, amor, por siempre creer en mi y darme los ánimos que necesito para seguir adelante siempre. ¡Los Amo!

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BIOGRAPHY

Joan Evaliz Roque Peña was born in Bayamón, Puerto Rico. She and her sister, Raysa, were raised by their parents, Sonia and Raymond. While she was growing up she observed her mother’s tireless efforts to ensure the success of her students which set within her the desire to carry on her legacy. As a high school student in Puerto Rico, the desire to help her peers, especially through education, grew stronger every day. After graduating from high school, she moved to Cayey, Puerto Rico, where she pursued undergraduate studies at the University of Puerto Rico at Cayey (UPR-Cayey). During this time she had the opportunity to participate in multiple research programs, the RISE program at the UPR-Cayey, the McNair/SROP REU program at Michigan State University and the AGEP Program at North Carolina State University (NCSU), where she did undergraduate research in different areas of chemistry. During her senior year at UPR-Cayey, she was admitted into the chemistry graduate program at NCSU and after she graduated with a BS in chemistry, she moved to Raleigh, NC to continue with her graduate education. As a graduate student she worked under the direction of Dr. Elon A. Ison in the area of organometallic chemistry and reaction mechanisms. As a graduate student at NCSU Joan also had the opportunity to be a teaching assistant for multiple chemistry courses and participate in the Certificate of Accomplishment in Teaching program, making her passion about teaching grow even stronger. After graduating from NCSU she will be working as a postdoctoral fellow at the University of North Carolina, Chapel Hill, under the direction of Dr. Erik Alexanian.
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CHAPTER 1
General Introduction

1.1. General Background

The ubiquitous nature and lack of reactivity of C–H bonds has recently attracted significant interest in the research community.\textsuperscript{1-15} By activating and functionalizing these bonds, the synthesis of complex and essential organic molecules can be accomplished. Transition-metal catalysis is a promising strategy for the activation and functionalization of C–H bonds under mild conditions.

Traditionally, organic chemists utilize pre-activated C–X bonds to functionalize and/or create new C–H/C–C bonds\textsuperscript{1,2} (Scheme 1.1A). Recently transition-metal-catalyzed C–H bond functionalization has become the focus of synthetic chemists. In this approach, an unreactive C–H bond is activated and functionalized (Scheme 1.1B) \textit{via} transition metal activation.

\textbf{Scheme 1.1.} Functionalized Group Transformation \textit{vs} C–H Bond Functionalization. Adapted from Jazzar, \textit{et al.}\textsuperscript{1}

\begin{center}
\begin{tikzpicture}
\draw[thick,->] (0.5,0) -- (1.5,0);
\node at (0.25,0) {X';};
\node at (2.25,0) {X';};
\node at (0.25,-0.5) {+ RX';};
\node at (2.25,-0.5) {+ RX';};
\node at (-0.5,-0.5) {$\text{RX'}$};
\node at (3.5,-0.5) {$\text{RX'}$};
\node at (-1.5,0) {A. Functional Group Transformation};
\node at (4.5,0) {B. C–H Bond Functionalization};
\node at (-0.5,-2.5) {X' = Functional Group};
\end{tikzpicture}
\end{center}
One of the first examples of transition-metal-catalyzed C–H activation was reported in the 1970’s by Shilov.\(^3\) This “Shilov System” activates the C–H bonds of methane \(\text{via} \) a \(\text{PtCl}_4^{2-}\) catalyst to produce methanol and methyl chloride (Scheme 1.2). Even though this system is considered to occur under mild conditions and is one of the first examples of alkane oxidations, it requires very strong acidic conditions and it is stoichiometric in the Pt(IV) external oxidant. Hence, there is an ongoing effort to optimize reaction conditions by avoiding or lowering acidic conditions and utilizing more economic and readily available oxidants.\(^3\)

**Scheme 1.2.** Shilov System. Adapted from Goldman and Goldberg.\(^3\)

\[
\text{CH}_4 + \text{PtCl}_6^{2-} + \text{H}_2\text{O} (\text{Cl}^-) \xrightarrow{\text{PtCl}_4^{2-} / \text{H}_2\text{O}} 120 ^\circ\text{C} \quad \text{CH}_3\text{OH} (\text{CH}_3\text{Cl}) + \text{PtCl}_4^{2-} + 2\text{HCl}
\]

Transition-metal catalysis provides researchers with an atom economical method for the activation of unreactive C–H bonds. Efforts are ongoing for the optimization of the catalytic
activation and functionalization of these bonds in a variety of ways. An example is the utilization of low catalyst loadings, which avoids stoichiometric amounts of transition metal complexes.\textsuperscript{16} Another example is in the work of Ackermann and co-workers where water is utilized as the reaction solvent, avoiding the use of organic media.\textsuperscript{17} Additionally, Ueura, Satoh and Miura demonstrated that in the oxidative annulation of arenes, copper can be employed catalytically as the external oxidant in the presence of O\textsubscript{2}.\textsuperscript{18,19} This avoids the need for stoichiometric amounts of metal oxidants such as copper, silver, and platinum (refer to scheme 1.2).

An important aspect of catalyzed C–H bond activation is the ability to selectively activate specific C–H bonds in a particular molecule. Functional groups or heteroatoms on a molecule can function as directing groups for the selective activation of C–H bonds.\textsuperscript{4} Examples of heteroatom-directed transition-metal catalysis include chelation-assistance to form a metallacycle (Scheme 1.3A) and the coordination of heteroatoms which facilitates the formation of a metal-carbon bond at a proximal site (Scheme 1.3B). The coordination of heteroatoms or functional groups (aldehyde, ketone, imine, alcohol, amine, carboxylic acid, and nitrile groups) to the transition metal commonly allows for the ortho aromatic or olefinic C–H activation via chelation assistance.\textsuperscript{2,4}
Scheme 1.3. Modes of Heteroatom-Assisted C–H Bond Activation. Adapted from Colby, et al.4

A. Chelation-Assisted C–H Activation

B. Heteroatom-assisted C–H Activation

A well-studied example of chelation-assisted C–H functionalization is the C–H activation and functionalization of benzoic acids to form isocoumarins or benzochromenones.4,20 In this system the carboxylate group functions as the directing group (Figure 1.1). A variety of isocoumarins and benzochromenones have been synthesized via Ru(II),21 Cp*Rh(III),18,19 and Cp*Ir19,20,22 catalysis. A proposed mechanism for the Rh-catalyzed isocoumarin synthesis is shown in Figure 1.1. The mechanism involves the formation of intermediate B from the coordination of benzoic acid to Rh (A) by ligand exchange. Subsequent ortho C–H activation results in the formation of a 5-membered metallacycle (C). Coordination of the alkyne to form a 7-membered metallacycle (D) and subsequent reductive elimination affords the isocoumarin product. The resulting Rh(I) species undergoes oxidation by copper to regenerate the catalyst.
Iridium complexes containing Cp* (Cp* = pentamethylcyclopentadiene)\textsuperscript{19,20,23}, phosphine ligands,\textsuperscript{24-28} and N-heterocyclic carbenes\textsuperscript{23,29} have been shown to efficiently catalyze C–H activation. Our group has previously shown that C–H bonds in benzene are activated by Cp*Ir(III) complexes in catalyzed H/D exchange reactions with deuterium solvents.\textsuperscript{23,29} Additionally, our group has achieved the activation and functionalization of benzoic acids.\textsuperscript{20,22} Therefore, this provided the inspiration for the possibility of applying these catalysts for activating C–H bonds in benzamides.

\textbf{Figure 1.1.} Proposed mechanism for Rh-catalyzed isocoumarin synthesis. Adapted from Colby et al.\textsuperscript{4}
1.2. Scope

In this project the application and efficiency of Ir(III)-catalysts for the C–H bond activation/functionalization of benzamides was investigated. Optimization of a system involving the use of [Cp*Ir(H₂O)₃](OTf)₂ as the catalyst along with its substrate scope and mechanistic studies are presented in Chapter 2. Initial studies of a system involving [Cp*Ir(NHC)(H₂O)₂](OTf)₂ is presented in Appendices 1-3.

1.3. References


CHAPTER 2
[Cp*Ir(H₂O)₃](OTf)₂-Catalyzed Aerobic Isoquinolone Synthesis: Scope and Mechanistic Evaluation

2.1. Abstract

Our group achieved catalytic isocoumarin and benzochromenone synthesis from benzoic acids utilizing [Cp*IrCl₂]₂. Because of the ability of Cp*Ir(III)-complexes to activate and functionalize C-H bonds on benzoic acids, its nitrogen derivative benzamide was studied. Herein, the development, optimization, and mechanistic evaluation of an aerobic [Cp*Ir(H₂O)₃](OTf)₂-catalyzed isoquinolone synthesis from benzamides and alkynes is described. Optimized conditions include 2.5 mol% [Cp*Ir(H₂O)₃](OTf)₂ in cyclohexane at 90 °C under air (40 psi). Reactions of benzamide derivatives and diphenylacetylene afforded the desired products in moderate to high isolated yields. The catalytic system was shown not only to be efficient for the coupling of diphenylacetylene, but also allowed for oxidative annulations of para-substituted diphenylacetylene derivatives. Kinetic studies suggested that the reaction follows first order kinetics with respect to isoquinolone formation, benzamide consumption and catalyst (4), zero order with respect to diphenylacetylene and a kinetic isotope effect of 1.3(1). The mechanism is proposed to proceed via N-Coordination of the benzamide followed by a concerted-metalation-deprotonation C-H activation. Solvent and Hammett studies suggest that the turnover limiting step is benzamide coordination. The stoichiometric reaction between benzamides and [Cp*Ir(H₂O)₃](OTf)₂ in cyclohexane at 60 or 90 °C resulted in catalyst
decomposition or non-identifiable species. However, when \([\text{Cp}^*\text{Ir(H}_2\text{O})_3](\text{OTf})_2\) was replaced for \([\text{Cp}^*\text{Ir(NHC)(H}_2\text{O})_2](\text{OTf})_2\), \((\text{NHC} = \text{N-Heterocyclic Carbene, 1,3-dimethylimidazol-2-ylidene})\) an oxygen-bound species that does not appear to be part of the catalytic cycle was isolated.

2.2. Introduction

Nitrogen-containing compounds are very abundant and essential for many biological processes.\(^1\)\(^-\)\(^3\) Thus, transition-metal catalyzed approaches have begun to address the synthesis of N-heterocycles such as indoles,\(^4\)\(^-\)\(^7\) isoquinolines,\(^2\)\(^,\)\(^8\)\(^-\)\(^{13}\) and isoquinolones.\(^14\)\(^-\)\(^{19}\) Indoles have been successfully synthesized \textit{via} Pd(II)\(^4\)\(^,\)\(^5\) and Rh(III)\(^6\)\(^,\)\(^7\) catalysis and recently Gray and co-workers\(^20\) have employed \text{Cp}^*\text{Ir(III)}-catalysis for their synthesis. The synthesis of isoquinolines has also been achieved \textit{via} Rh(III)\(^2\)\(^,\)\(^8\)\(^-\)\(^{11}\) and Pd(II)\(^12\)\(^,\)\(^13\) catalysis.

Isoquinolones are found in a variety of natural products which have shown potential biological applications.\(^21\)\(^-\)\(^23\) Some examples of natural products derived from isoquinolones are shown in Table 2.1.
Table 2.1 Natural Products Containing Isoquinolone Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Potential Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Compound 1" /></td>
<td>Anti-cancer&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>Anti-cancer&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Compound 3" /></td>
<td>Anti-inflammatory&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Compound 4" /></td>
<td>Anti-cancer&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Compound 5" /></td>
<td>Anti-cancer&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Isoquinolones have been previously synthesized by coupling benzamides and alkynes via Rh(III),\textsuperscript{15,16,19} Ru(II),\textsuperscript{17,25} and Pd(II)\textsuperscript{18} catalysts in the presence of external metal oxidants (Scheme 2.1, A). This coupling reaction has also been investigated by employing benzamides that bear an internal oxidant. This was achieved via Ru(II),\textsuperscript{26,27} Rh(III),\textsuperscript{28,29} and Pd(II)\textsuperscript{30,31} catalysis (Scheme 2.1, B). Moreover, isoquinolones have been synthesized by employing pre-activated benzamides via Ni(II)\textsuperscript{14} catalysis (Scheme 2.1, C).
Scheme 2.1. Previously Reported Isoquinolone Synthesis

A. Oxidative annulation of benzamides with external oxidants

\[
\begin{align*}
\text{Oxidative annulation of benzamides with external oxidants} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\text{O} \\
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\end{array}
\rightarrow \\
\text{5 mol% Ru(II), Rh(III) or Pd(II) catalyst} \\
\text{oxidant, solvent, T, time}
\end{align*}
\]

B. Oxidative annulation of benzamides bearing internal oxidants with additives (redox neutral)

\[
\begin{align*}
\text{Oxidative annulation of benzamides bearing internal oxidants with additives} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{OR}_1 \\
\text{R}_2 \\
\text{O} \\
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\end{array}
\rightarrow \\
\text{5 mol% Ru(II), Rh(III) or Pd(II) catalyst} \\
\text{solvent, T, time}
\end{align*}
\]

C. Oxidative annulation of benzamides containing pre-activated C-X groups

\[
\begin{align*}
\text{Oxidative annulation of benzamides containing pre-activated C-X groups} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R} \\
\text{X}\text{= Cl, Br, I, N=N} \\
\text{O} \\
\text{N} \\
\text{R} \\
\text{R} \\
\end{array}
\rightarrow \\
\text{5 mol% Ni(II)} \\
\text{additive, solvent, T, time}
\end{align*}
\]

As proposed by Liu et al., Hyster and Rovis, and Ackermann et al., the mechanism for isoquinolone formation likely proceeds via an acetate-assisted cyclometallation (Figure 2.1, transition state) to form a 5-membered metallacycle (A) which, subsequently converts into a 7-membered metallacycle (B) upon addition of the alkyne. The isoquinolone is then reductively eliminated from the metal center. The proposed mechanism for the formation of the 5-membered metallacycle involves the direct chelation-assisted activation of the C−H bonds in benzamide. Directing groups provide the advantage of selectively activating ortho C−H bonds.
Figure 2.1. Proposed mechanism for Cp*Rh-catalyzed ortho C–H activation of benzamides. Adapted from Ackermann, et al.\textsuperscript{17}

The application of transition metal catalysts has been shown to be an effective means for obtaining isoquinolones at mild reaction conditions. However, the aforementioned systems are still limited in that they employ sacrificial external oxidants, base additives, substrate pre-
activation, and high reaction temperatures. The employment of benzamides bearing internal oxidants also limits the scope of N-substitution. Thus, our interest was to develop a more efficient and general Cp*Ir(III)-catalyzed system that overcomes the previous needs by employing milder conditions, lower catalyst loadings, and larger N-substitution scope. Moreover, we wanted to investigate the mechanism to improve catalyst design. Additionally, in our laboratory it has been demonstrated that Cp*Ir(III)-catalysts can effectively activate benzoic acids to produce isocoumarins \(^{32}\) and benzochromenones. \(^{33}\) Thus the analogous reaction with the N-derivative of benzoic acid, benzamide, was investigated.

2.3. Results and Discussion

2.3.1. Previously Developed Isoquinolone Synthesis with \([\text{Cp}^*\text{Ir(NHC)}(\text{H}_2\text{O})_2](\text{OTf})_2\)

Initial studies involved the effects of different reaction conditions on the Cp*Ir(III)-catalyzed coupling of benzamides with diphenylacetylene. The reaction of N-methylbenzamide with diphenylacetylene in the presence of \([\text{Cp}^*\text{Ir(NHC)}(\text{H}_2\text{O})_2](\text{OTf})_2\) as the catalyst (5 mol%), and AgOAc as the sacrificial metal oxidant afforded yields of up to 95% after 16 h at 90 °C in cyclohexane (Scheme 2.2). Moreover, a series of oxidants were examined in this reaction, \(\text{AgNO}_3\) (0%), \(\text{Ag}_2\text{CO}_3\) (68%), and \(\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}\) (89%). Silver and copper salts containing carboxylate counter ions worked efficiently as external oxidants in the developed Cp*Ir(III)-catalytic isoquinolone synthesis. The later \((\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O})\) was successfully employed in catalytic amounts in the presence of \(\text{O}_2\). \(^{34,35}\)
Scheme 2.2. [Cp*Ir(NHC)(H$_2$O)$_2$](OTf)$_2$-Catalyzed Isoquinolone Synthesis with External Metal Oxidants

While performing the mechanistic studies on this system (Appendix 3), and comparing different catalysts, it was found that the reaction catalyzed by [Cp*Ir(H$_2$O)$_3$](OTf)$_2$ proceeded efficiently without a metal oxidant. With that result in mind, further optimization of the catalytic system under air (40 psi) (Scheme 2.3) afforded quantitative yields with lower catalyst loadings (2.5 mol%).

Scheme 2.3. Cp*Ir(III)-Catalyzed Isoquinolone Synthesis without Added External Metal Oxidants
2.3.2. System Optimization

2.3.2.1. Catalyst Screening

Figure 2.2. Catalyst screening. Reaction conditions: 0.5 mmol N-ethylbenzamide, 0.5 mmol diphenylacetylene, 0.0125 mmol catalyst in 2.5 mL cyclohexane for 16 h under air (40 psi). Yields were calculated by $^1$H NMR spectroscopy of crude reaction mixture in CDCl$_3$ against 1,3,5-trimethoxybenzene internal standard (0.167 mmol) and are presented as the average of three runs. Error in parenthesis represents the standard deviation. $^a$6.25 μmol 6 and 0.025 mmol AgOTf were used.

Aerobic isoquinolone synthesis (refer to Scheme 2.3) was also investigated using different Cp$^*$Ir(III) catalysts (Figure 2.2). Catalysts 4, 5 and 6 afforded the highest yield of isoquinolone by $^1$H NMR spectroscopy. It is important to note that when catalysts bearing
carboxylate ligands (7-9), were employed, inhibition of isoquinolone formation was observed. This result suggested catalysts employing labile ligands were more effective for substrate coordination.

2.3.2.2. Atmosphere Effect

The catalytic system under study (with catalyst 4) works efficiently under air (40 psi), affording turnover numbers (TON) of up to 32 (81% yield) (Table 2.2, Entry 1). Thus, the effect of changing the atmosphere was investigated (Scheme 2.4, Table 2.2). When the reactions were pressurized with 20 psi of O₂, the reactions afforded similar yields as with 15 psi of air (Table 2.2, Entries 2 and 3, respectively). A recent report by Zhang and coworkers shows that molecular oxygen acts as the sacrificial oxidant in their system,³⁶ leading to consider the possible role of O₂ as the external oxidant. Thus, the reaction under N₂ was investigated and product yield was still observed in the absence of any added external oxidant (Table 2.2, Entry 4). This suggests that the system does not need the presence of an external oxidant in order to regenerate the active catalyst. On the other hand, at high pressures (40 psi air) there is a higher concentration of oxygen in solution, which can also assist in the formation of the active catalyst.
Scheme 2.4. Effect of Changing the Atmosphere on Isoquinolone Yield

Table 2.2. Effect of Changing the Atmosphere on Isoquinolone Yield

<table>
<thead>
<tr>
<th>Entry</th>
<th>Atmosphere, psi</th>
<th>3 Yield&lt;sup&gt;a&lt;/sup&gt;, %</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Air, 40</td>
<td>81(3)</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;, 20</td>
<td>60(1)</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Air, 15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58(1)</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>N&lt;sub&gt;2&lt;/sub&gt;, 15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>53(5)</td>
<td>21</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.5 mmol N-ethylbenzamide, 0.5 mmol diphenylacetylene, and 0.0125 mmol 4 in 2.5 mL cyclohexane at 90 °C for 16 h. The reactions were carried out in 25 mL sealed tubes. <sup>a</sup>Yields were calculated by <sup>1</sup>H NMR spectroscopy of crude reaction mixture in CDCl<sub>3</sub> against 1,3,5-trimethoxybenzene internal standard (0.167 mmol) and are presented as the average of three runs. Error in parenthesis represents the standard deviation. <sup>b</sup>Reaction was run under 1 atm air. <sup>c</sup>Reaction was set up inside an O<sub>2</sub> and H<sub>2</sub>O free glove box maintained at less than 0.1 ppm O<sub>2</sub> and H<sub>2</sub>O in 2.5 mL dry cyclohexane, N<sub>2</sub> = 1 atm. TON = Turnover Number.
2.3.2.3. Solvent Effect

Cyclohexane, a non-polar solvent, was found to be the optimal solvent in the catalytic system when utilizing catalyst 4. The effect of changing the solvent was explored (Scheme 2.5). When the polarity of the solvent increased, isoquinolone yields and TONs decreased (Tables 2.3 and 2.4, and Figures 2.3 and 2.4). The decrease in yield observed with increasing polarity can be attributed to the interaction of polar solvent molecules with benzamide which hinder benzamide coordination, and/or the coordination of polar solvents, which similar to carboxylate ligands (See Section 2.3.2.1), hinder benzamide coordination.

Scheme 2.5. Solvent Effect on Product Formation
Table 2.3. Solvent Effect on Isoquinolone Product Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Polarity Index</th>
<th>3 Yield&lt;sup&gt;a&lt;/sup&gt;, %</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclohexane</td>
<td>0.2</td>
<td>81(3)</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Hexanes</td>
<td>0.1</td>
<td>67(8)</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>Benzene</td>
<td>2.7</td>
<td>22(1)</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>1,2-Dichloroethane</td>
<td>3.5</td>
<td>33(2)</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>Methanol</td>
<td>5.1</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Acetonitrile</td>
<td>5.8</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.5 mmol N-ethylbenzamide, 0.5 mmol diphenylacetylene, and 0.0125 mmol 4 in 2.5 mL solvent at 90 °C for 16 h. The reactions were carried out in 25 mL sealed tubes under air (40 psi). <sup>a</sup>Yields were calculated by <sup>1</sup>H NMR spectroscopy of crude reaction mixture in CDCl<sub>3</sub> against an internal standard (0.167 mmol) and are presented as the average of three runs. Error in parenthesis represents the standard deviation. TON = Turnover Number.
Table 2.4. Solvent Ratio Effect on Isoquinolone Product Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (Ratio)</th>
<th>3 Yield$^a$, %</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclohexane</td>
<td>81(3)</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Cyclohexane:1,2-DCE (99:1)</td>
<td>67(1)</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexane:1,2-DCE (9:1)</td>
<td>53(4)</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexane:1,2-DCE (3:1)</td>
<td>41(2)</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>Cyclohexane:1,2-DCE (1:1)</td>
<td>40(1)</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>Cyclohexane:1,2-DCE (1:3)</td>
<td>40(2)</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>Cyclohexane:1,2-DCE (1:9)</td>
<td>36(1)</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>1,2-Dichloroethane</td>
<td>33(2)</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>Cyclohexane:Methanol (99:1)</td>
<td>70(1)</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>Cyclohexane:Methanol (9:1)</td>
<td>37(1)</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Cyclohexane:Methanol (1:1)</td>
<td>17(1)</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>Cyclohexane:Methanol (1:9)</td>
<td>13(1)</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>Methanol</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.5 mmol N-ethylbenzamide, 0.5 mmol diphenylacetylene, and 0.0125 mmol 4 in 2.5 mL solvent at 90 °C for 16 h. The reactions were carried out in 25 mL sealed tubes under air (40 psi). $^a$Yields were calculated by $^1$H NMR spectroscopy of crude reaction mixture in CDCl$_3$ against an internal standard (0.167 mmol) and are presented as the average of three runs. Error in parenthesis represents the standard deviation. TON = Turnover Number.
Figure 2.3. Changing solvent polarity effect on isoquinolone yield: cyclohexane:1,2-dichloroethane. Graphical representation of data in Table 2.4 (Entries 1-8). \(^a\)Percent relative to cyclohexane. Yields were calculated by \(^1\)H NMR spectroscopy of crude reaction mixture in CDCl\(_3\) against an internal standard (0.167 mmol) and are presented as the average of three runs. Error in parenthesis represents the standard deviation. Reaction conditions: 0.5 mmol \(N\)-ethylbenzamide, 0.5 mmol diphenylacetylene, and 0.0125 mmol 4 in 2.5 mL solvent at 90 °C for 16 h under air (40 psi).
Figure 2.4. Changing solvent polarity effect on isoquinolone yield: cyclohexane:methanol. Percent relative to cyclohexane. Graphical representation of data in Table 2.4 (Entries 1, 9-13). Yields were calculated by $^1$H NMR spectroscopy of crude reaction mixture in CDCl$_3$ against an internal standard (0.167 mmol). Yield is presented as the average of three runs. Error in parenthesis represents the standard deviation. Reaction conditions: 0.5 mmol N-ethylbenzamide, 0.5 mmol diphenylacetylene, and 0.0125 mmol 4 in 2.5 mL solvent at 90 °C for 16 h under air (40 psi).
2.3.2.4. Adding Additional Equivalents of Diphenylacetylene

As part of the optimization studies performed with the initially developed system with catalyst 5 (Appendix 1), it was observed that the addition of higher diphenylacetylene equivalencies can result in the formation of high molecular weight by-products (Figure 2.5).

**Figure 2.5.** High molecular weight by-products detected in GC-MS analysis of crude reaction mixtures while optimizing isoquinolone synthesis with catalyst 5. Compound 11 results from the coupling reaction of two diphenylacetylene equivalents in the presence of a proton donor.\(^{37,38}\) Compound 12 results from the coupling reaction of two diphenylacetylene equivalents to benzamide with loss of (CO)NHR as proposed by Ueura, *et al.*\(^{35}\)

When the crude reaction mixture of the aerobic \([\text{Cp}^*\text{Ir(H}_2\text{O)}_3](\text{OTf})_2\)-catalyzed isoquinolone synthesis was analyzed by GC-MS, stilbene formation was also observed. Therefore, the effect of adding higher diphenylacetylene equivalencies was explored (Scheme 2.6, Table 2.5). When higher equivalencies were utilized no significant improvement in isoquinolone or stilbene yield was observed. This suggests that stilbene formation is a side reaction and not part of the catalytic cycle for isoquinolone formation. Therefore, the reaction
was performed at a 1:1 ratio of benzamide:alkyne, which still afforded high isoquinolone yields (up to 81% yield) and turnover numbers (32).

**Scheme 2.6.** Effect of Changing Diphenylacetylene Equivalency on Isoquinolone and Stilbene Formation

![Scheme 2.6](image)

**Table 2.5.** Product Formation at Various Diphenylacetylene Equivalencies

<table>
<thead>
<tr>
<th>Entry</th>
<th>X Equiv</th>
<th>3 Yield, %</th>
<th>13 Yield, %</th>
<th>14 Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>81(3)</td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>82(8)</td>
<td>3(1)</td>
<td>11(4)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>84(0)</td>
<td>1.7(2)</td>
<td>7.6(4)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>74(3)</td>
<td>1.5(3)</td>
<td>8(2)</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.5 mmol *N*-ethylbenzamide, 0.5–1.5 mmol diphenylacetylene, and 0.0125 mmol 4 in 2.5 mL cyclohexane at 90 °C for 16 h. The reactions were carried out in 25 mL sealed tubes under air (40 psi).<sup>a</sup>Yields were calculated by <sup>1</sup>H NMR spectroscopy of crude reaction mixture in CDCl<sub>3</sub> against 1,3,5-trimethoxybenzene internal standard (0.167 mmol).<sup>b</sup>Yields were calculated by gas chromatography against mesitylene internal standard (0.5 mmol). Yield is presented as the average of three runs. Error in parenthesis represents the standard deviation. <sup>c</sup>Single reaction.
2.3.2.5. Base and Acid Effect

The effect of adding base and acid on the reaction was also investigated. Studies were performed with 4 (2.5 – 5 mol%). The addition of different bases resulted in the inhibition of isoquinolone product (Scheme 2.7 and Table 2.6). The effect of adding sodium trifluoromethanesulfonate (NaOTf) on isoquinolone formation was also studied since it is present as the counter ion of the Cp*Ir(III)-complex. The addition of NaOTf, resulted in lower isoquinolone formation and turnover numbers (Scheme 2.8 and Table 2.7). On the other hand, addition of acetic acid did not affect isoquinolone yield (Scheme 2.9, Table 2.8). These results suggest that the reaction does not require the addition of additives to obtain optimal yields. This is in contrast to previously reported systems that require the addition of external oxidants or bases.14-19,25-31

Scheme 2.7. Effect of Adding Base on Isoquinolone Formation
### Table 2.6. Effect of Adding Base on Isoquinolone Yield

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>3 Yield&lt;sup&gt;a&lt;/sup&gt;, %</th>
<th>TON</th>
<th>pK&lt;sub&gt;b&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>59(4)</td>
<td>12</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>NaOAc</td>
<td>3</td>
<td>0.6</td>
<td>9.25</td>
</tr>
<tr>
<td>3</td>
<td>NaOAc (0.5 equiv)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4</td>
<td>0.8</td>
<td>9.25</td>
</tr>
<tr>
<td>4</td>
<td>CsOAc</td>
<td>2</td>
<td>0.4</td>
<td>9.25</td>
</tr>
<tr>
<td>5</td>
<td>CsOAc (0.5 equiv)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6</td>
<td>1.2</td>
<td>9.25</td>
</tr>
<tr>
<td>6</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>3</td>
<td>0.6</td>
<td>11.0</td>
</tr>
<tr>
<td>7</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4</td>
<td>0.8</td>
<td>3.67</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.2 mmol N-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol base, and 0.01 mmol 4 in 1 mL cyclohexane at 90 °C for 1 day. The reactions were carried out in 3 mL sealed tubes under air (1 atm). <sup>a</sup>Yields were calculated by <sup>1</sup>H NMR spectroscopy of crude reaction mixture in CDCl<sub>3</sub> against an internal standard (0.067 mmol). Single reactions were performed. <sup>b</sup>Reaction was performed in triplicate and yield is presented as the average of the reactions with error in parenthesis. <sup>c</sup>0.1 mmol base. TON = Turnover Number.
Scheme 2.8. Effect of Adding NaOTf on Isoquinolone Formation

![Scheme diagram]

Table 2.7. Effect of Adding NaOTf on Isoquinolone Yield

<table>
<thead>
<tr>
<th>Entry</th>
<th>X Equiv</th>
<th>3 Yield(^a), %</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None(^b)</td>
<td>81(3)</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>70</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>65</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>57</td>
<td>23</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.5 mmol N-ethylbenzamide, 0.5 mmol diphenylacetylene, 0-0.5 mmol NaOTf, and 0.0125 mmol 4 in 2.5 mL cyclohexane at 90 °C for 16 h. The reactions were carried out in 25 mL sealed tubes under air (40 psi). \(^a\)Yields were calculated by \(^1\)H NMR spectroscopy of crude reaction mixture in CDCl\(_3\) against an internal standard (0.167 mmol). Single reactions were performed. \(^b\)Reaction was performed in triplicate and yield is presented as the average of the reactions with error in parenthesis. TON = Turnover Number.
Scheme 2.9. Effect of Adding Acetic Acid on Isoquinolone Formation

![Chemical structure]

Table 2.8. Effect of Adding Acetic Acid on Isoquinolone Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>X Equiv</th>
<th>3 Yield(^a), %</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>81(3)</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>83(4)</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>77(3)</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>76(6)</td>
<td>30</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.5 mmol N-ethylbenzamide, 0.5 mmol diphenylacetylene, 0–5 mmol HOAc, and 0.0125 mmol 4 in 2.5 mL cyclohexane at 90 °C for 16 h. The reactions were carried out in 25 mL sealed tubes under air (25 psi). \(^a\)Yields were calculated by \(^1\)H NMR spectroscopy of crude reaction mixture in CDCl\(_3\) against an internal standard (0.167 mmol). Reactions were performed in triplicate and yield is presented as the average of the reactions with error in parenthesis. TON = Turnover Number
2.3.3. Substrate Scope with Optimized System

With the optimized conditions in hand, which include a 1:1 ratio benzamide:diphenylacetylene and 2.5 mol% catalyst 4 at 90 °C for 16 h under air (40 psi), the application of this catalytic system for the ortho C-H activation and functionalization of benzamides was explored. The catalytic reaction was investigated with different substituents on both the benzamide (Schemes 2.10-2.12) and the alkyne (Schemes 2.13-2.15) substrates.
**Scheme 2.10.** Substrate Scope of [Cp*Ir(H$_2$O)$_3$](OTf)$_2$-Catalyzed Coupling of para-Substituted N-Ethylbenzamides with Diphenylacetylene

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = H</td>
<td>81(3)%$^a$, 73%$^b$</td>
<td></td>
</tr>
<tr>
<td>R = MeO</td>
<td>83(3)%$^a$, 67%$^b$</td>
<td></td>
</tr>
<tr>
<td>R = Cl</td>
<td>56(2)%$^a$, 12%$^b$</td>
<td></td>
</tr>
<tr>
<td>R = F</td>
<td>21(1)%$^a$</td>
<td></td>
</tr>
<tr>
<td>R = F$_3$C</td>
<td>53(7)%$^a$, 59%$^b$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Yields as calculated by $^1$H NMR spectroscopy of crude reaction mixture in CDCl$_3$. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard (0.167 mmol). Yield is presented as the average of three runs. Error represents the standard deviation. $^b$Isolated Yields.
Scheme 2.11. Substrate Scope of [Cp*Ir(H2O)3](OTf)2-Catalyzed Coupling of meta-Substituted N-Ethylbenzamides with Diphenylacetylene

Yields as calculated by 1H NMR spectroscopy of crude reaction mixture in CDCl3. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard (0.167 mmol). Yield is presented as the average of three runs. Error represents the standard deviation. Isolated Yields
Scheme 2.12. Substrate Scope of \([\text{Cp}^*\text{Ir(H}_2\text{O})_3]\)(OTf)_2-Catalyzed Coupling of Benzamides with Diphenylacetylene

\[
\begin{array}{c}
\text{R}_1 \text{N}^- \text{R}_2 \\
\text{Ph} \\
\text{Ph}
\end{array}
\begin{array}{c}
\text{PH} \\
\text{Ph}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\xrightleftharpoons{2.5 \text{ mol}\% \ 4}
\text{cyclohexane, 90 °C, 16 h}
\text{Air = 40 psi, 25 mL tube}
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\]

\[
\begin{array}{c}
\text{Et} \\
\text{N}^- \\
\text{Ph} \\
\text{Ph}
\end{array}
\]
81(3)\%, 73\%

\[
\begin{array}{c}
\text{Me} \\
\text{N}^- \\
\text{Ph} \\
\text{Ph}
\end{array}
\]
67(4)\%, 53\%

\[
\begin{array}{c}
\text{MeO} \\
\text{N}^- \\
\text{Ph} \\
\text{Ph}
\end{array}
\]
73(2)\%\text{a,c} \text{ two samples, } 41\%

\[
\begin{array}{c}
\text{n-Pr} \\
\text{N}^- \\
\text{Ph} \\
\text{Ph}
\end{array}
\]
25(4)\%

No Reaction

\[
\begin{array}{c}
\text{i-Pr} \\
\text{N}^- \\
\text{Ph} \\
\text{Ph}
\end{array}
\]

\[
\begin{array}{c}
\text{n-Bu} \\
\text{N}^- \\
\text{Ph} \\
\text{Ph}
\end{array}
\]
41(14)\%

\[
\begin{array}{c}
t-\text{Bu} \\
\text{N}^- \\
\text{Ph} \\
\text{Ph}
\end{array}
\]
22(1)\%

\text{a}Yields as calculated by \textsuperscript{1}H NMR spectroscopy of crude reaction mixture in CDCl\textsubscript{3}. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard (0.167 mmol). Yield is presented as the average of three runs. Error represents the standard deviation.\textsuperscript{b}Isolated Yields
Scheme 2.13. Substrate Scope of [Cp*Ir(H₂O)₃](OTf)₂-Catalyzed Coupling of N-Ethylbenzamide with Alkyl-Aryl Alkynes

Yields as calculated by ¹H NMR spectroscopy of crude reaction mixture in CDCl₃. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard (0.167 mmol). Yield is presented as the average of three runs. Error represents the standard deviation.
Scheme 2.14. Substrate Scope of $[\text{Cp}^*\text{Ir(}H_2\text{O})_3\text{]}\text{(OTf)}_2$-Catalyzed Coupling of $N$-Ethylbenzamide with Alkyl-Alkyl Alkynes

![Scheme 2.14]

Yields as calculated by $^1$H NMR spectroscopy of crude reaction mixture in CDCl$_3$. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard (0.167 mmol). Yield is presented as the average of three runs. Error represents the standard deviation.
**Scheme 2.15.** Substrate Scope of [Cp*Ir(H₂O)₃](OTf)₂-Catalyzed Coupling of N-Ethylbenzamide with Aryl-Aryl Alkynes

\[
\begin{align*}
\text{C}_6H_5\text{NH}_\text{Et} & + \text{C}_6H_4\text{R} \xrightarrow{\text{2.5 mol\% 4}} \text{C}_6H_5\text{N}_\text{Et} \text{C}_6H_4\text{R} \\
\text{cyclohexane, 90 °C, 16 h} & \quad \text{Air = 40 psi, 25 mL tube}
\end{align*}
\]

\[
\begin{align*}
81(3)^a, 73^b & \\
58(3)^a, 45^b & \\
50(2)^a, 50^b & \\
28(1)^a & \\
58(2)^a, 50^b & \\
63(2)^a, 50^b & \text{; ~1:1 ratio of isomers}
\end{align*}
\]

^aYields as calculated by ¹H NMR spectroscopy of crude reaction mixture in CDCl₃. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard (0.167 mmol). Yield is presented as the average of three runs. Error represents the standard deviation. ^bIsolated Yields.
A variety of substituents on both the benzamide (1) and the alkyne (2) substrates were successfully employed in the developed catalytic system with \([\text{Cp}^\ast \text{Ir}(\text{H}_2\text{O})_3](\text{OTf})_2\) (4). The catalytic system proved not only effective for the conversion of diphenylacetylene, but also for a variety of arylaryl-, or unsymmetrical phenylalkyl- substituents on the acetylene. However, alkyl-alkyl substituted acetylenes, phenyl acetylene, and ethyl-3-phenylpropiolate afforded little or no product formation. Both electron-rich and electron poor substituents on diphenylacetylene and N-ethylbenzamide yielded the corresponding products in moderate isolated yields. Furthermore, the reaction of benzamides bearing N-alkyl groups with diphenylacetylene afforded the respective isoquinolone products in low yields, suggesting that N-coordination is involved in the mechanism and steric at that position hinder this process. No apparent trend was observed when changing the electronics on the benzamide and the diphenylacetylene. When methoxy substituent is present at the meta-position on the N-ethylbenzamide (Scheme 2.11) no steric effect is observed, possibly due to the rotational freedom of the methyl group. When alkenes were employed, no product formation was observed. The substrate scope with the previously developed system with catalyst 5 is presented in Appendix 2. Experimental procedures and spectroscopic data, i.e. $^1$H NMR spectra, consistent with published data, are discussed in section 2.5.
2.3.4. Hydrogenation Studies

Scheme 2.16. Cis- and Trans-1,2-Diphenylethene Formation

As mentioned, 1,2-diphenylethene (cis and trans-stilbene), hydrogenation products of diphenylacetylene, were observed as reaction byproducts (Scheme 2.16). When N-ethyl-2,3,4,5,6-pentadeuterobenzamide was utilized as the substrate, GC-MS analysis of crude reaction mixtures showed deuterium (D) incorporation into the stilbene products. This suggests that the hydrogens incorporated into the diphenylacetylene substrate come from the activated benzamide.

Scheme 2.17. Catalytic Diphenylacetylene Hydrogenation
Iridium complexes have been shown to efficiently catalyze the hydrogenation of a variety of molecules, such as alkenes,^39-44^ quinolines,^45^ and carboxylic acids^46^ (Table 2.9). These studies suggest the possibility of the iridium complex under study, catalyst 4, to catalyze the hydrogenation of diphenylacetylene as a side reaction. Thus, the hydrogenation capacity of complex 4 was evaluated by investigating the catalytic hydrogenation of diphenylacetylene (Scheme 2.17). It was found that complex 4 catalyzes the hydrogenation of diphenylacetylene in both 1,2-dichloroethane (quantitative conversion) and cyclohexane (up to 11% conversion). Reaction conditions included 0.2 mmol diphenylacetylene, 5 μmol 4 in 1 mL solvent at 90 °C under H₂ (20 psi, ~0.17 mmol) for 16 h (See Experimental Section 2.5.5).
**Table 2.9. Examples of Iridium(III) Hydrogenation Catalysts**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iridium(III)-Complex</th>
<th>Proposed By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Complex 1" /></td>
<td>Crabtree’s homogeneous catalysis complex;(^{39-41}) used for alkene hydrogenation</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Complex 2" /></td>
<td>Pfaltz’s first-generation complex;(^{42,43}) used for alkene hydrogenation</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Complex 3" /></td>
<td>Cipot, <em>et al.</em>;(^{44}) used for alkene hydrogenation</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Complex 4" /></td>
<td>Dobereiner and coworkers;(^{45}) used for quinoline hydrogenation</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Complex 5" /></td>
<td>Brewster, <em>et al.</em>;(^{46}) used for carboxylic acid hydrogenation</td>
</tr>
</tbody>
</table>
2.3.5. Mechanistic Evaluation

2.3.5.1. Hydrogen Incorporation into ortho C-D Bond

Hydrogen incorporation into the unreacted benzamide and isoquinolone product was observed when N-ethyl-2,3,4,5,6-pentadeuterobenzamide was used as the substrate (Scheme 2.18). This suggests that the C-H bond activation is a reversible step.\textsuperscript{47,48}

Scheme 2.18. Hydrogen Incorporation into Isoquinolone-D Product and Unreacted N-Ethylbenzamide
2.3.5.2. Reaction Kinetics

2.3.5.2.1. Reaction Order

Kinetic studies were undertaken to further explore the mechanism of this reaction. A first order kinetic plot for the formation of 3 was obtained when monitoring the reaction of 1 with 2 catalyzed by 4 (Scheme 2.19) over a period of 4 h. An observed rate constant ($k_{\text{obs}} = 3.6(5) \times 10^{-4}$ s$^{-1}$) for the formation of 3 was obtained from the exponential fit shown in Figure 2.6. Isoquinolone (3) formation and N-ethylbenzamide (1) consumption were determined by $^1$H NMR spectroscopy of crude reaction mixture in CDCl$_3$ against an internal standard (1,3,5-trimethoxybenzene). The reactions were run in triplicate and the error is presented as the standard deviation of the samples.

Scheme 2.19. [Cp*Ir(H$_2$O)$_3$](OTf)$_2$-Catalyzed Coupling of N-Ethylbenzamide with Diphenylacetylene
Figure 2.6. Kinetic plot for the [Cp*Ir(H2O)3](OTf)2-catalyzed coupling of N-ethylbenzamide with diphenylacetylene. Diamonds represent the [Total] = [1] + [3], circles represent 1 consumption, squares represent 3 formation. Maximum [3] = 0.20 M. Reaction conditions: 0.2 M N-ethylbenzamide, 0.2 M diphenylacetylene, and 5 mM 4, in cyclohexane at 90 °C under air (40 psi). Substrate concentration was calculated by 1H NMR spectroscopy against 1,3,5-trimethoxybenzene internal standard (0.0667 M). Respective kobs were obtained using exponential curve fits defined as y = m1 + m2(1 - e^{(-m3x)}).
2.3.5.2.2. Order with Respect to Diphenylacetylene

The order with respect to diphenylacetylene was determined. The concentration of diphenylacetylene was varied from 0.4 to 1.0 M and the formation of 3 was monitored over time for a period of 20 minutes (1200 s) (Figure 2.7). Data obtained from the log(Rate) versus log[Diphenylacetylene] suggest the reaction has a zero order dependence on diphenylacetylene (Figure 2.8). Isoquinolone (3) formation was determined by $^1$H NMR spectroscopy of crude reaction mixture in CDCl$_3$ using the ratio of leftover benzamide to isoquinolone. Individual reactions in triplicates were performed for each time point. A higher excess of diphenylacetylene was not employed due to the formation of side products such as the ones presented in Figure 2.5.
**Figure 2.7.** Initial rates plots for the [Cp*Ir(H₂O)₃](OTf)₂-catalyzed coupling of N-ethylbenzamide with diphenylacetylene at various diphenylacetylene concentrations. The concentration of diphenylacetylene was varied from 0.4 – 1.0 M. Maximum [3] = 0.10 M. Reaction conditions: 0.1 M N-ethylbenzamide, 0.4 M (circles), 0.6 M (squares), 0.8 M (diamonds), and 1.0 M (triangles) diphenylacetylene, and 2.5 mM 4, in cyclohexane at 90 °C under air (40 psi). Isoquinolone concentration was calculated by ¹H NMR spectroscopy utilizing the ratio of leftover benzamide:isoquinolone (and against 1,3,5-trimethoxybenzene internal standard, 0.0667 M). Respective rates were obtained using the linear fit (y = mx + b).
Figure 2.8. Log-log plot for the determination of the order with respect to diphenylacetylene. The reaction shows zero order dependence on diphenylacetylene.
2.3.5.2.3. Order with Respect to N-Ethylbenzamide

N-Ethylbenzamide consumption was monitored over time for a period of 16 h with excess diphenylacetylene (0.4 M). A higher excess of diphenylacetylene was not employed due to side reactions with diphenylacetylene. The resulting plot is shown in Figure 2.9. N-Ethylbenzamide consumption follows first order kinetics with $k_{obs} = 2.2(6) \times 10^{-4} \text{ s}^{-1}$. 
Figure 2.9. N-ethylbenzamide consumption vs time with excess diphenylacetylene. Reaction conditions: 0.2 M N-ethylbenzamide, 0.4 M diphenylacetylene, and 5 mM 4, in cyclohexane at 90 °C under air (40 psi). N-ethylbenzamide concentration was calculated by 1H NMR spectroscopy against 1,3,5-trimethoxybenzene internal standard (0.0667 M). The $k_{obs}$ was obtained using the exponential decay curve fit defined as $y = m_1 + m_2(1 - e^{-m_3x})$.
2.3.5.2.4. Order with Respect to 4

Finally, the order with respect to catalyst 4 was determined. Isoquinolone formation was monitored over time for a period of 30 minutes (1800 s) at 60 °C with 1.25, 2.5, 5.0, and 7.5 mol% 4. This temperature was chosen in order to slow down the initial portion of the reaction and employ higher catalyst loadings. The resulting plots are shown in Figure 2.10. The order with respect to 4 was determined from the plot of log(Rate) versus log[4] which shows a slope of 0.9(2). Data suggest that the reaction has first order dependence on 4 (Figure 2.11).
Figure 2.10. Isoquinolone formation vs time at 1.25, 2.5, 5.0, and 7.5 mol% 4. Reaction conditions: 0.2 M N-ethylbenzamide, 0.2 M diphenylacetylene, and 2.5 mM (circles), 5 mM (squares), 10 mM (diamonds), or 15 mM 4, in cyclohexane at 60 °C under air (40 psi). Isoquinolone concentration was calculated by $^1$H NMR spectroscopy using the ratio of leftover benzamide:isoquinolone. The respective rates were obtained from a linear fit.
Figure 2.11. Log-log plot for the determination of the order with respect to \([\text{Cp}^*\text{Ir(H}_2\text{O)}_3](\text{OTf})_2\) (4). A slope = 0.9(2) was obtained.
2.3.5.2.5. Kinetic Isotope Effect

After obtaining the kinetic plots and the orders with respect to 1, 2, and 4, the deuterated version of 1 was synthesized. The reaction of 1-D₅ with 2 catalyzed by 4 was monitored over time for a period of 4 h (14400 s) (Scheme 2.20) and isoquinolone yield was determined by ¹H NMR spectroscopy of crude reaction mixture in CDCl₃ against an internal standard (1,3,5-trimethoxybenzene). The reactions were run in triplicates and the error is presented as the standard deviation of the samples. The reactions of 1-H₅ ($k_{obs} = 4.3(4) \times 10^{-4}$ s⁻¹) and 1-D₅ ($k_{obs} = 3.4(1) \times 10^{-4}$ s⁻¹) proceed at similar rates as shown in Figure 2.12.

Scheme 2.20. [Cp*Ir(H₂O)₃](OTf)₂-Catalyzed Coupling of N-Ethyl-2,3,4,5,6-pentadeuterobenzamide with Diphenylacetylene
Figure 2.12. Kinetic plots for the \([\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3](\text{OTf})_2\)-Catalyzed coupling of \(N\)-ethylbenzamide (circles) or \(N\)-ethyl-2,3,4,5,6-pentadeuterobenzamide (squares) with diphenylacetylene. Maximum \([3] = 0.20\) M. Reaction conditions: 0.2 M mmol \(N\)-ethylbenzamide or 0.2 M \(N\)-ethyl-2,3,4,5,6-pentadeuterobenzamide, 0.2 M diphenylacetylene, and 5 mM 4, in cyclohexane at 90 °C under air (40 psi). Isoquinolone concentration was calculated by \(^1\)H NMR spectroscopy against 1,3,5-trimethoxybenzene internal standard (0.0667 M). Respective \(k_{\text{obs}}\) were obtained using the exponential rise curve fit defined as \(y = m_1 + m_2(1 - e^{(-m_3x)})\).
When both $k_{\text{obs-H}}$ and $k_{\text{obs-D}}$ were compared, a kinetic isotope value of 1.3(1) was obtained. A $k_{\text{H}}/k_{\text{D}}$ near unity suggests that C-H activation is not part of the turnover limiting step (TLS) of this reaction. Representative kinetic isotope values from the literature are shown in Table 2.10. Large, primary isotope effects were observed for reactions where C-H activation was part of or prior to the TLS. For example, Guimond and coworkers determined, by comparing the rates of reaction of two parallel reactions of $N$-$(R)$benzamide-\text{H}_5$ and $N$-$(R)$benzamide-\text{D}_5$, a KIE value of 1.0 (when $R = \text{OMe}$, Entry 1) and 15 (when $R = \text{OPiv}$, Entry 2).\textsuperscript{28} They suggested that when $R = \text{methoxy}$, C-H activation is not the TLS; however, when $R = \text{pivalate}$, a large primary isotope effect is observed, and C-H activation is the TLS. Moreover, Suess and coworkers determined a primary KIE of 5.7(8) (Entry 3) when the measured initial rates of the H- and D-labeled substrates were compared.\textsuperscript{49} Their result suggests that C-H activation is the TLS.
Table 2.10. Literature Values for the Kinetic Isotope Effect when C-H Activation is Considered the Turnover Limiting Step

<table>
<thead>
<tr>
<th>Entry</th>
<th>Parallel Reactions</th>
<th>Intermolecular</th>
<th>Intramolecular</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0(1)\textsuperscript{a}</td>
<td>-</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>15(1)</td>
<td></td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>5.7(8)</td>
<td>-</td>
<td>-</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>6.1\textsuperscript{b}</td>
<td>6.7</td>
<td>5.7</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>6.1</td>
<td>4.3</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>2.9\textsuperscript{b}</td>
<td>-</td>
<td>2.3</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>&gt;5\textsuperscript{b}</td>
<td>-</td>
<td>-</td>
<td>52</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Not turnover limiting C-H activation. \textsuperscript{b}Kinetic isotope effect was determined by two parallel reactions, no rates are reported. Two different mechanisms were under study.

2.3.5.3. Electronic Effects

In order to gather additional information about the mechanism and the identity of the turnover limiting step, intermolecular competition experiments were undertaken. These reactions involved the use of \(N\)-ethylbenzamide and \(p\)-substituted \(N\)-ethylbenzamides with limiting diphenylacetylene. Different electronic substituents including electron-donating
groups (-OCH₃) or electron-withdrawing groups (-Cl, CF₃) were employed (Schemes 2.21 and 2.22). The σ meta and σ para effects of the reaction were evaluated. No meta effects were observed as the Hammett plot resulted in a non-linear dependence (linear fit with R² = 0.8206, Figure 2.13). A para-effect was observed for the reaction of N-ethylbenzamide and diphenylacetylene. A ρ value of ~ -0.80 was obtained from a Hammett plot (Figures 2.14 and 2.15). This suggests a positive charge build up at the nitrogen atom (amide) during the reaction where electron-donating groups react at a faster rate. Since a para effect was observed and the reaction is first order with respect to benzamide, it can be suggested that benzamide coordination is the TLS of this mechanism.

**Scheme 2.21.** Intermolecular Competition Reactions Between para-Substituted N-Ethylbenzamides
Figure 2.13. Plot of the \( \log(\rho_R/\rho_H) \) vs \( \sigma_{meta} \) value to determine substituent effects on isoquinolone yield. Reaction conditions: 0.2 M \( N \)-ethylbenzamide, 0.2 M \( p \)-substituted-\( N \)-ethylbenzamide, 0.2 M mmol diphenylacetylene, 5 mM catalyst 4 in cyclohexane at 90 °C for 2 h under air (40 psi).
**σ<sub>para</sub> Effect on Isoquinolone Synthesis**

![Graph showing the relationship between log(ρ<sub>R</sub>/ρ<sub>H</sub>) and σ<sub>para</sub> value to determine substituent effects on isoquinolone yield. Reaction conditions: 0.2 M N-ethylbenzamide, 0.2 M p-substituted-N-ethylbenzamide, 0.2 M mmol diphenylacetylene, 5 mM catalyst 4 in cyclohexane at 90 °C for 2 h under air (40 psi).](image)

**Figure 2.14.** Plot of the log(ρ<sub>R</sub>/ρ<sub>H</sub>) vs σ<sub>para</sub> value to determine substituent effects on isoquinolone yield. Reaction conditions: 0.2 M N-ethylbenzamide, 0.2 M p-substituted-N-ethylbenzamide, 0.2 M mmol diphenylacetylene, 5 mM catalyst 4 in cyclohexane at 90 °C for 2 h under air (40 psi).
Scheme 2.22. Intermolecular Competition Reactions Between \textit{para}-Substituted \textit{N}-Ethylbenzamides

\[
\begin{align*}
\text{3 equiv} & \quad \text{3 equiv} \\
\text{+} & \quad + \quad \text{Ph} \equiv \text{Ph} \\
\text{1 equiv} & \quad 2.5 \text{ mol\% 4} \\
& \quad 90 \degree \text{C, cyclohexane, 2 h,} \\
& \quad \text{Air = 40 psi}
\end{align*}
\]
Figure 2.15. Plot of the log(\(\rho_R/\rho_H\)) vs \(\sigma_{\text{para}}\) value to determine substituent effects on isoquinolone yield. Reaction conditions include 0.2 M \(N\)-Ethylbenzamide, 0.2 M \(p\)-Substituted-\(N\)-Ethylbenzamide, 0.0668 M Diphenylacetylene, 1.68 mM 4 in cyclohexane at 90 °C for 2 h under air (40 psi).
2.3.5.4. Isolation of Possible Reaction Intermediates

In addition to studying the kinetics and the electronic effects of the reaction of 1 and 2 catalyzed by 4, the synthesis of possible reaction intermediates was also undertaken. For this, N-methylbenzamide and derivatives were mixed with [Cp*IrCl₂]₂ (precursor of complex 4) or complex 4 in stoichiometric amounts. N-Methylbenzamide was selected as the substrate due to its identifiable N-CH₃ peak in ¹H NMR spectra. Different reaction conditions were explored including different solvents, temperatures, and reaction times (Schemes 2.23-2.26). The addition of bases was also explored in order to evaluate if benzamide coordination was facilitated. However, these reactions did not afford complexes that could be isolated or identified by ¹H NMR spectroscopy. In most cases the iridium complex appeared to decompose to produce unknown products. Similar results were obtained when N-ethylbenzamide was used as the substrate. These results may also suggest that the species formed when the benzamide coordinates to the iridium center are very reactive, which, in addition to the observed first order dependence with respect to benzamide and the electronic effects, suggest benzamide coordination being the turnover limiting step (TLS).
**Scheme 2.23.** Stoichiometric Reaction of N-Methylbenzamide and [Cp*IrCl₂]₂ with Base in Methanol or Ethanol

\[
\begin{align*}
1 \; &+ \; \text{[Cp*IrCl}_2\text{]} \; &\xrightarrow{\text{MeOH or EtOH, rt, overnight}} \; \text{Unidentifiable Product}
\end{align*}
\]

**Scheme 2.24.** Stoichiometric Reaction of 4,N-Methylbenzamide and [Cp*IrCl₂]₂ with Base

\[
\begin{align*}
\text{Me} \; &+ \; \text{[Cp*IrCl}_2\text{]} \; &\xrightarrow{\text{MeOH, EtOH, Acetonitrile, or EtOAc, rt, overnight}} \; \text{Unidentifiable Product}
\end{align*}
\]

**Scheme 2.25.** Stoichiometric Reaction of 4,N-Methylbenzamide, [Cp*IrCl₂], AgOTf, and NaOTf

\[
\begin{align*}
\text{Me} \; &+ \; \text{[Cp*IrCl}_2\text{]} \; + \; \text{AgOTf} \; &\xrightarrow{\text{MeOH, EtOH, 1,2-DCE, DCM, or Acetone, rt, overnight}} \; \text{Unidentifiable Product}
\end{align*}
\]
Scheme 2.26. Stoichiometric Reaction of N-Methylbenzamide and [Cp*Ir(H₂O)₃]OTf₂ in Cyclohexane at 60 °C

2.3.5.5. Mechanistic Studies with [Cp*Ir(NHC)(C₆H₄(C=O)NHMe)][OTf] (15)

Even though we were not able to identify or isolate any possible intermediates with complex 4, species 15 was obtained when 1 was treated with complex 5. Complex 5 was shown to be efficient at catalyzing the formation of isoquinolones (Section 2.3.2.1). Species 15 was obtained from the stoichiometric reaction between N-methylbenzamide and 5 (cyclohexane, 60 °C, 16 h, Scheme 2.27). The ¹H NMR spectrum of the crude reaction mixture (Figures 2.16 and 2.3ES) revealed the presence of 3 new N-methyl peaks at δ 3.15 (N-methylbenzamide), 3.65, and 3.99 ppm (NHC ligand). Slow diffusion of diethyl ether into a concentrated acetone solution of the obtained red oil yielded X-ray quality crystals of product 15 (Figure 2.17). The ¹H and ¹³C NMR spectra of 15 are shown in Figures 2.18 and 2.19 respectively.
Scheme 2.27. Stoichiometric Reaction of $N$-Methylbenzamide and $[\text{Cp}^*\text{Ir(NHC)(H}_2\text{O)}_2]\text{(OTf)}_2$

**Figure 2.16.** $^1$H NMR spectrum (300 MHz, (CD$_3$)$_2$CO) of the reaction mixture shown in Scheme 2.27. Peaks at 3.15 ppm ($N$-Methyl [benzamide]), and 3.65 ppm and 3.99 ppm ($N$-Methyl [NHC]) correspond to complex 15.
Figure 2.17. X-Ray crystal structure of isolated complex 15. Thermal ellipsoids are at the 50% probability level and hydrogen atoms were omitted for clarity. The complex shows octahedral geometry at the iridium center. Selected bond lengths and angles are presented in the Experimental Section.
Figure 2.18. $^1$H NMR spectrum of 15 (300 MHz, CDCl$_3$). The spectrum shows peaks at δ 1.64 (15H), 3.08 (3H), 3.50 (3H), 3.83 (3H), 6.78 (1H), 6.97 (2H), 7.20 (1H), 7.63 (1H), 7.73 (1H), 8.52 (1H).
Figure 2.19. $^{13}$C NMR spectrum of 15 (125 MHz, CDCl$_3$). The spectrum shows peaks at $\delta$ 9.0, 27.4, 37.8, 38.2, 90.0, 123.1, 123.2, 124.0, 127.1, 132.0, 137.0, 139.0, 156.0, 159.0, and 181.9 ppm.

The chemical shifts for complex 15 were assigned by a series of 2D NMR experiments in CDCl$_3$. Respective peaks were initially assigned by integrating the $^1$H NMR spectrum of complex 15 (Figure 2.18) and were verified by COSY, TOCSY, HSQC, and HMBC experiments (Figures 2.17ES-2.24ES). After investigating the correlation between protons and carbons on complex 15, the respective resonances were assigned and are shown in Figures 2.20 and 2.21.
The formation of 15 was further investigated in the presence of a redox-neutral acetate source (Figure 2.4ES) and silver acetate (Figure 2.5ES), Schemes 2.28 and 2.29, respectively. Silver acetate was chosen due to its efficiency as an oxidant (Section 2.3.1 and Appendices 1 and 3). $^1$H NMR analysis of crude reaction mixture in acetone-$d_6$ shows no product formation in the presence of sodium acetate (Figure 2.4ES). When $N$-methylbenzamide was treated with
5 in the presence of AgOAc, 15 was detected by $^1$H NMR spectroscopy, however in smaller amounts than in its absence (Figure 2.5ES). In addition, another Cp*Ir(NHC) species was observed, possibly the acetate containing species. X-ray analysis of crystals obtained from reaction on Scheme 2.29 revealed the presence of 15. This suggests that acetate anions can inhibit the formation of complex 15. Moreover, the reaction of N-methylbenzamide with [Cp*Ir(NHC)(OAc)][PF$_6$] (7) did not result in the formation of (15) (Scheme 2.30, Figure 2.6ES). This result supports the need of complexes bearing labile ligands for benzamide coordination (See Figure 2.2).

**Scheme 2.28.** Stoichiometric Reaction of N-Methylbenzamide and [Cp*Ir(NHC)(H$_2$O)$_2$](OTf)$_2$ with Excess Sodium Acetate

**Scheme 2.29.** Stoichiometric Reaction of N-Methylbenzamide and [Cp*Ir(NHC)(H$_2$O)$_2$](OTf)$_2$ with Excess Silver Acetate
The intermediacy of complex 15 in the catalytic cycle for isoquinolone formation was studied. For this the reaction of compound 15 with diphenylacetylene (2) was investigated at 60 °C (optimized temperature in previous system, Appendix 1) in cyclohexane for 16 hours (Scheme 2.31, Figure 2.7ES). No product formation (3) was observed by $^1$H NMR spectroscopy in acetone-$d_6$. Subsequently, the reaction was examined in the presence of two equivalents of silver acetate (Scheme 2.32, Figure 2.8ES). No significant product formation was observed. Even though no significant product formation was observed, the possibility that 15 is an intermediate in the catalytic reaction was not discarded because of its poor solubility in cyclohexane. The solubility of 15 in different solvents (toluene, methylene chloride, acetone, and 1,2-dichloroethane) was investigated. Complex 15 proved to be slightly soluble in methylene chloride and completely soluble in acetone and 1,2-dichloroethane. However, methylene chloride and acetone could not be used to study the reactivity of 15 due to their low boiling point and high vapor pressure. Thus, 1,2-dichloroethane was chosen as the reaction solvent. Crystals of 15 were dissolved in 1,2-dichloroethane-$d_4$ and treated with diphenylacetylene (2) in the absence of silver acetate. Additionally, 15 was formed in situ and
subsequently reacted with diphenylacetylene (2) in the absence of silver acetate (Scheme 2.33, Figure 2.9ES). No significant product formation was observed in any of the reactions.

**Scheme 2.31.** Stoichiometric Reaction of Complex 15 and Diphenylacetylene

[Diagram of Scheme 2.31]

**Scheme 2.32.** Stoichiometric Reaction of Complex 15 and Diphenylacetylene with Silver Acetate

[Diagram of Scheme 2.32]
**Scheme 2.33.** Stoichiometric Reaction of Complex 15 and Diphenylacetylene in 1,2-Dichloroethane-$d_4$

![Stoichiometric Reaction Diagram](image)

Additional studies were performed in order to understand the role of complex 15 in the reaction mechanism. For this, complex 15 was mixed in stoichiometric amounts with diphenylacetylene in the presence (Figure 2.10ES) and absence (Figure 2.11ES) of trifluoromethanesulfonic acid (Scheme 2.34) (HOTf, product of the reaction of 1 with 4, refer to Scheme 2.27). The reaction resulted in no isoquinolone product formation. Complex 15 was also studied in catalytic amounts in the coupling reaction of N-ethylbenzamide with diphenylacetylene (Scheme 2.35) however, no significant isoquinolone product (~10% yield) was observed (Figure 2.12ES. These results suggest that the isolated complex is not part of the catalytic cycle.
Scheme 2.34. Stoichiometric Reaction of 15 and Diphenylacetylene

![Scheme 2.34](image)

Scheme 2.35. Isoquinolone Synthesis Utilizing Complex 15

![Scheme 2.35](image)

Formation of complex 15 is observed at 90 °C and at lower temperatures (i.e. 60 °C). In addition, no isoquinolone product is detected in the $^1$H NMR spectrum of the crude reaction mixture of complex 15 with diphenylacetylene at different reaction conditions (Scheme 2.34). Thus, the [Cp*Ir(NHC)(H$_2$O)$_2$](OTf)$_2$-catalyzed coupling of 1 with 2 was investigated at 60 °C (Scheme 2.36). No isoquinolone product was observed at these reaction conditions which suggests that formation of the unreactive species 15 is the possible reason for no product formation, further supporting the hypothesis that complex 15 is not part of the catalytic cycle.
**Scheme 2.36.** [Cp*Ir(NHC)(H₂O)₂](OTf)₂-Catalyzed Coupling of N-Ethylbenzamide with Diphenylacetylene: No External Oxidant at 60 °C

As shown above, complex 15 affords no isoquinolone formation, therefore it was treated with HOTf in different solvents to further understand its reactivity and stability (Schemes 2.1ES – 2.4ES; Figures 2.13ES – 2.16ES). No significant reactivity was observed and in some cases decomposition was observed. This suggests that O-bound coordination of benzamide to Cp*Ir afford species that are not active for the synthesis of isoquinolones.

**2.3.6. Proposed Mechanism of the Aerobic Isoquinolone Synthesis**

A possible mechanism is proposed for the [Cp*Ir(H₂O)₃](OTf)₂-catalyzed isoquinolone synthesis (Figure 2.22). In the first step of the mechanism, the nitrogen on the benzamide coordinates to the Cp*Ir(III)-catalyst (4). This step, to form species I, is proposed to be the turnover limiting step due to the following:

1. a decrease in TON observed when increasing solvent polarity,
2. a decrease in product yield when bulky substituents are present at the N-position,
3. the Hammett parameters, suggesting a positive charge buildup,
(4) the first order dependence on benzamide, where rate = $k_{\text{obs}}[\text{benzamide}]$, and

(5) the small kinetic isotope effect suggesting C-H activation is not TOL.

Additionally, when acetate ligands are present in the coordination sphere of the iridium, no product formation is observed, which suggests that dissociation of ancillary ligands to coordinate benzamide is necessary.

Since benzamide contains a carboxylate moiety, it is possible that a second equivalent coordinates to the Cp*Ir(III) species I to form II. Subsequent C-H activation, proposed to proceed by a concerted metalation deprotonation pathway affords species III. Reports on C-H activation of N-containing heterocycles suggest that this type of mechanism takes place.\textsuperscript{14,15,17} The C-H activation step is proposed to be reversible due to the observed hydrogen incorporation into the D-labeled product at the end of the reaction.

Alkyne coordination affords IV which, followed by alkyne insertion into the ortho-carbon of the benzene ring, forms metallacycle V. This step is followed by reductive elimination to yield species VI. Catalyst oxidation by HOTf or O\textsubscript{2}, affords isoquinolone product and regenerates catalyst 4. The observed increase in TON when utilizing 40 psi air further suggests that O\textsubscript{2} can also be facilitating catalyst oxidation.
Figure 2.22. Proposed mechanism for the [Cp*Ir(H$_2$O)$_3$](OTf)$_2$-catalyzed isoquinolone synthesis.
2.4. Conclusions

A catalytic system for isoquinolone synthesis with \([\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3](\text{OTf})_2\) has been developed. The optimized conditions include a 1:1 ratio benzamide:alyne with 2.5 mol% 4 in cyclohexane at 90 °C under air (40 psi). The reaction is also efficient under N\(_2\) in the absence of external oxidant. It is proposed that HOTf facilitates the oxidation of Ir(I) to Ir(III) to afford the active catalyst. The observed enhancement in isoquinolone yield at high pressure (air = 40 psi) is proposed to be due to the higher concentration of oxygen in solution which may be facilitating the oxidation of Ir(I) to Ir(III).

The effects of \(N\)-substitution, solvent polarity, and electronics on the benzamide, ancillary ligand dissociation, and the first order dependence with respect to benzamide suggest that benzamide coordination is the turnover limiting step of the catalytic cycle. Additionally, a small kinetic isotope effect of 1.3(1) was observed, suggesting that C-H activation is not turnover limiting.

The reaction is proposed to proceed \(via\) a concerted metalation deprotonation mechanism facilitated by a second benzamide molecule. Treating \([\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3](\text{OTf})_2\) (4) or \([\text{Cp}^*\text{IrCl}_2]_2\) (precursor of 4) with benzamides at different reaction conditions did not afford complexes that could be isolated or identified by \(^1\text{H}\) NMR spectroscopy. In most cases the iridium complex appeared to decompose. These results suggest that when benzamide coordinates to \(\text{Cp}^*\text{Ir}(\text{III})\) the resulting complex is unstable. On the other hand, an O-bound species was obtained when benzamide was treated with complex 5. No isoquinolone formation
was observed when the isolated species (15) was treated with diphenylacetylene at various reaction conditions, suggesting that it is not part of the catalytic cycle.

Data suggest that the addition of bases inhibit product formation, while addition of acetic acid does not affect the reaction. Due to the ability of the tested acids and bases to coordinate to the iridium center the role of the base and the acid in the developed catalytic system cannot be determined.
2.5. Experimental Section

2.5.1. General Remarks

All reactions were carried in pre-dried glassware under air with non-dry solvents unless otherwise specified. Catalysts 4-8 and 10 were synthesized by previously published methods. Benzamides and \( p \)-substituted diphenylacetylenes were synthesized by previously published methods. \( \text{IrCl}_3 \cdot 3\text{H}_2\text{O} \) was purchased from Pressure Chemical Company. Other chemicals were obtained from commercial sources and were used without further purification. \( ^1\text{H} \) NMR spectra were recorded in a Varian Mercury 300 MHz or 400 MHz spectrophotometer at room temperature. Chemical shifts (\( \delta \)) are reported in ppm and are referenced to the solvent peak (for \( \text{CDCl}_3 \), \( ^1\text{H} \) NMR = 7.26 ppm, \( ^13\text{C} \) NMR = 77.00 ppm; \( \text{CD}_2\text{Cl}_2 \), \( ^1\text{H} \) NMR = 5.32 ppm, \( ^13\text{C} \) NMR = 53.84 ppm; (\( \text{CD}_3 \))\(_2\text{CO} \), \( ^1\text{H} \) NMR = 2.05 ppm, \( ^13\text{C} \) NMR = 29.84 and 206.26 ppm). Coupling constants (\( J \)) are listed in Hz. Crude reaction mixtures were analyzed using a GCD Series with Electron Ionization Detector. Infrared spectra were obtained in KBr thin films on a Jasco FT/IR-4100 spectrometer and are reported in cm\(^{-1}\). Gas chromatography (GC) was performed on a Varian 3800 Gas Chromatograph with a Varian VF-53ms column. Column chromatography was performed using Silica Gel technical grade (Aldrich), pore size 60 Å, 70-230 mesh, 63-200 \( \mu \text{M} \). Thin layer chromatography (TLC) was performed with Agela Technologies TLC Silica plates: 200x200 mm, pH = 5, MF254, alumina back. Elemental analyses were performed by Atlantic Microlabs, Inc. High Resolution Accurate Mass Measurement – ESI was performed at the Mass Spectrometry Facility of the
Department of Chemistry at North Carolina State University. Analysis was carried out on a high resolution mass spectrometer, the Thermo Fisher Scientific Exactive Plus MS, a benchtop full-scan Orbitrap™ mass spectrometer, using Heated Electrospray Ionization (HESI). The samples were diluted in methylene chloride and methanol and analyzed via flow injection into the mass spectrometer at a flow rate of 200µL/min. The mobile phase was 90% methanol with 0.1% formic acid and 10% water with 0.1% formic acid. The mass spectrometer was operated in positive ion mode. HESI Source parameters: spray voltage – 3.5 kV, capillary temperature – 350 °C, heater temperature – 100 °C, s lens rf level – 70 V, sheath gas flow rate – 25, resolution – 70,000, scan rate – 200-800 m/z. X-Ray crystallography was performed at the X-Ray Structural Facility of North Carolina State University. Bruker-Nonius Kappa Axis X8 Apex2 diffractometer with an Oxford Cryosystems 700 Series Low Temperature attachment.

**Synthesis of [Cp*Ir(TFA)2(H2O)] (9):** A yellow solid was obtained in 85% yield. To a pre-dried storage tube [Cp*IrCl2]2 (300 mg, 1 equiv) and silver trifluoroacetate (AgTFA, 333.0 mg, 4 equiv) were added followed by the addition of deionized H2O (10 mL). The reaction was covered in foil paper and N2 was added after two evacuation cycles. The reaction was left stirring overnight at room temperature. Then, the reaction was filtered over celite with deionized water and solvent was removed under reduced pressure and the resulting solid was dried overnight under vacuum. 1H NMR (400 MHz, (CD3)2CO) δ 1.61 (Cp*). 13C NMR (100 MHz, (CD3)2CO) δ 164.22-163.16 (m), 122.08, 119.19, 116.31, 113.43, 84.66,
9.70. $^{19}$F NMR (376 MHz, (CD$_3$)$_2$CO) $\delta$ 75.75. IR (KBr, cm$^{-1}$) v 1700. Anal. calcd. for C$_{14}$H$_{17}$F$_6$IrO$_3$: C, 31.17; H, 3.18. Found: C, 29.97, H, 3.01. Crystal structure is shown in Figure 2.25ES.

2.5.2 Benzamide Derivate Synthesis

**General Method A: Synthesis of N-Ethylbenzamides from Acid Chlorides**$^{17}$

$$
\begin{align*}
R\overset{\text{Cl}}{\text{C}} + \text{EtNH}_2\text{Cl} & \xrightarrow{1.5 \text{ equiv}} \text{Et}_2\text{O(dry)} \xrightarrow{2.5 \text{ equiv } \text{K}_2\text{CO}_3} R\overset{\text{N}^{\text{Et}}}{\text{C}}
\end{align*}
$$

To a solution of the corresponding benzoyl chloride in anhydrous Et$_2$O (50 mL) was added K$_2$CO$_3$ (2.5 equiv) followed by EtNH$_3$Cl (1.5 equiv). The mixture was stirred at ambient temperature and monitored by TLC until no benzoyl chloride was observed. The reaction was then diluted with EtOAc (100 mL) and washed with H$_2$O (50 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL), and the combined organic phase was dried over Na$_2$SO$_4$, filtrated. The solvent was removed in vacuum to give a crude product, which was dried overnight under reduced pressure. No further purification was required.
General Method B: Synthesis of N-Ethylbenzamides from Benzoic Acids\textsuperscript{17}

\[
\begin{align*}
\text{[R-aryl]COOH} & \quad \text{SOCl}_2 (5.0 \text{ mL}), \quad \text{DMF (1 drop)} \quad \text{Neat, 80 °C} & \quad \text{[R-aryl]COCl} \quad + \quad \text{EtNH}_3\text{Cl} (1.5 \text{ equiv}) \quad 2.5 \text{ equiv K}_2\text{CO}_3 \quad \text{EtO} \text{O(dry)} & \quad \text{[R-aryl]CONH\text{Et}}
\end{align*}
\]

A mixture of the respective benzoic acid (10.0 mmol), SOCl\(_2\) (5.0 mL) and DMF (1 drop) was heated to 80 °C and stirred under N\(_2\) atmosphere for 1h. The excess of SOCl\(_2\) was distilled off, and the crude acid chloride was subsequently dissolved in anhydrous Et\(_2\)O (15 mL). K\(_2\)CO\(_3\) (25.0 mmol) was added followed by EtNH\(_3\)Cl (15.0 mmol). The mixture was stirred at ambient temperature and monitored by TLC until no benzoyl chloride was observed. The reaction was then diluted with EtOAc (100 mL) and washed with H\(_2\)O (50 mL). The aqueous phase was extracted with EtOAc (2-3 x 30 mL), and the combined organic phase was dried over Na\(_2\)SO\(_4\) and filtrated. The solvent was removed in vacuum to give a crude product, which was dried overnight under reduced pressure. No further purification was required unless specified.

General Method C: Synthesis of N-Substituted Benzamides from Amines\textsuperscript{17,57,58}

\[
\begin{align*}
\text{[aryl]COCl} & \quad + \quad \text{H}_2\text{N-R} \quad 1.05 \text{ equiv Et}_3\text{N} \quad \text{EtOAc, 0 °C to rt} & \quad \text{[aryl]CONH-R}
\end{align*}
\]

To a solution of the corresponding aniline/amine (10.0 mmol), in EtOAc at 0 °C, triethylamine (10.5 mmol), and benzoyl chloride (10.5 mmol) were added. The reaction mixture was stirred at room temperature overnight, extracted with EtOAc, washed with brine, dried over Na\(_2\)SO\(_4\),
and filtrated. The solvent was removed *in vacuo* to give the crude product, which was dried overnight under reduced pressure. No further purification was needed.

\[ \text{N-Ethylbenzamide:} \] Following the general method A the reaction yielded a white solid in 93% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) \(\delta\) 7.76 (d, 2H, \(J = 8\)), 7.39 (t, 1H, \(J = 8\)), 7.30 (t, 2H, \(J = 8\)), 7.08 (bs, 1H), 3.39 (m, 2H), 1.15 (t, 3H, \(J = 7\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\) 167.47, 34.52, 130.96, 128.14, 126.79, 34.69, 14.58. IR (KBr, cm\(^{-1}\)) \(\nu\) 2980, 1637, 1544, 1145. Spectrochemical data is consistent with previously reported data.\(^{60}\)

\[ \text{N-Ethyl-4-methoxybenzamide:} \] Following the general method A, the reaction yielded a white solid in 86% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) \(\delta\) 7.73 (d, 2H, \(J = 9\)), 6.82 (d, 2H, \(J = 9\)) 6.68 (bs, 1H), 3.77 (s, 3H), 3.40 (dq, 2H), 1.16 (t, 3H, \(J = 7\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\) 166.94, 161.76, 128.61, 126.89, 113.40, 55.22, 34.67, 14.76. IR (KBr, cm\(^{-1}\)) \(\nu\) 2980, 1633, 1617, 1609, 1506, 1292, 1252, 1183, 1132. Spectrochemical data is consistent with previously reported data.\(^{60}\)

\[ \text{N-Ethyl-4-methylbenzamide:} \] Following the general method A, the reaction yielded a white solid in 89% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) \(\delta\) 7.67 (d, 2H, \(J = 8\)), 7.13 (d, 2H, \(J = 8\)) 6.79 (bs, 1H), 3.41 (dq, 2H), 2.32 (s, 3H), 1.17 (t, 3H, \(J = 7\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\) 167.35, 141.46, 131.79, 129.01, 126.77, 34.74, 21.33, 14.81.
IR (KBr, cm$^{-1}$) ν 2968, 1628, 1547, 1509, 1284, 1263, 1145. Spectrochemical data is consistent with previously reported data.$^{60}$

**N-Ethyl-4-trifluoromethylbenzamide:** Following the general method A, the reaction yielded a white solid in 70% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 7.84 (d, 2H, $J = 9$), 7.59 (d, 2H, $J = 8$), 6.86 (bs, 1H), 3.45 (dq, 2H), 1.21 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 166.29, 137.98, 133.11, 132.77, 127.32, 125.47, 35.10, 14.66. $^{19}$F NMR (CDCl$_3$, 376 MHz, ppm) δ -63.38. IR (KBr, cm$^{-1}$) ν 2983, 1646, 1623, 1579, 1558, 1510, 1163, 1147, 1125.

**N-Ethyl-4-fluorobenzamide:** Following the general method A, the reaction yielded a white solid in 53% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 7.76 (t, 2H, $J = 7$), 7.25 (bs, 1H), 6.95 (t, 2H, $J = 8$), 3.36 (m, 2H), 1.13 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 166.49, 165.65, 163.16, 130.82 129.15 (d, $J = 9$), 115.25 (d, $J = 23$), 34.89, 14.67. $^{19}$F NMR (CDCl$_3$, 376 MHz, ppm) δ -109.17. IR (KBr, cm$^{-1}$) ν 2978, 1638, 1603, 1542, 1503, 1225, 1160, 1143.

**4-Chloro-N-ethylbenzamide:** Following the general method A, the reaction yielded a white solid in 81% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 7.66 (d, 2H, $J = 8$), 7.26 (d, 2H, $J = 9$), 7.18 (bs, 1H), 3.37 (m, 2H), 1.14 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100
N-Ethyl-4-tert-butylbenzamide: Following the general method B, the reaction yielded a white solid in 62% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$ 7.72 (d, 2H, $J = 8$), 7.36 (d, 2H, $J = 8$), 6.78, (bs, 1H), 3.43 (m, 2H), 1.29 (s, 9H), 1.18 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$ 167.35, 154.49, 131.77, 126.65, 125.21, 34.71, 31.04, 14.80. IR (KBr, cm$^{-1}$) ν 2983, 1634, 1595, 1541, 1271, 1148, 1089.

N-Ethyl-3,5-dimethoxybenzamide: Following the general method B, the reaction yielded a tan solid in 34% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$ 6.87 (s, 2H), 6.71 (bs, 1H), 6.48 (s, 1H), 3.71 (s, 6H), 3.42-3.36 (m, 2H), 1.16 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$ 167.20, 160.56, 136.80, 104.66, 103.25, 55.22, 34.80, 14.63. IR (KBr, cm$^{-1}$) ν 2965, 1635, 1612, 1560, 1544, 1499, 1287, 1267, 1146.

N-Ethyl-3,5-dimethylbenzamide: Following the general method B, the reaction yielded a white solid in 28% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$ 7.36 (s, 2H), 7.04 (s, 1H), 6.70 (bs, 1H), 3.41 (q, 2H), 2.26 (s, 6H), 1.18 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$,
100 MHz, ppm) δ 167.79, 137.84, 134.57, 132.62, 132.55, 124.60, 124.50, 34.67, 21.01, 14.70.

IR (KBr, cm⁻¹) ν 2976, 1634, 1599, 1540, 1254, 1148.

**N-Ethyl-3,5-bis(trifluoromethyl)benzamide:** Following the general method A, the reaction yielded a pink solid in 71% yield. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 8.20 (s, 2H), 7.94 (s, 1H), 6.93 (bs, 1H), 3.53-3.46 (m, 2H), 1.25 (t, 3H, J = 7). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 164.71, 136.66, 132.17, 131.84, 121.24, 124.81, 124.21, 121.19, 118.78, 35.36, 14.51. ¹⁹F NMR (CDCl₃, 376 MHz, ppm) δ -63.50. IR (KBr, cm⁻¹) ν 2925, 1646, 1558, 1278, 1135.

**N-Ethyl-3-methoxybenzamide:** Following the general method A, the reaction yielded an oil which was purified by column chromatography with silica gel (2:1 hexanes:ethyl acetate) to yield a colorless oil in 50% yield. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.32 (s, 1H), 7.28 (d, 1H, J = 8), 7.17 (t, 1H, J = 8), 7.16 (bs, 1H), 6.90 (dd, 1H, J = 8), 3.68 (s, 3H), 3.36 (q, 2H), 1.12 (t, 3H, J = 7). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 167.25, 159.33, 135.92, 129.09, 118.69, 117.07, 112.02, 55.00, 34.67, 14.49. IR (KBr, cm⁻¹) ν 2974, 1639, 1583, 1541, 1309.

**N-Ethyl-3-methylbenzamide:** Following the general method A, the reaction yielded a white solid in 83% yield. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.57 (s, 1H),
7.55 (bd, 1H), 7.27 (bs, 1H), 7.15 (bd, 2H), 3.40-3.33 (m, 2H), 2.23 (s, 3H) 1.13 (t, 3H, \( J = 7 \)).

\[^{13}\text{C} \text{NMR}\ (\text{CDCl}_3, 100 \text{ MHz}, \text{ppm}) \delta 167.61, 137.72, 134.38, 131.53, 127.88, 127.44, 123.74, 34.55, 20.92, 14.48. \text{IR (KBr, cm}^{-1}\text{) v 1633, 1543, 1309, 1146.}\]

\[\text{F}_3\text{C} \begin{array}{c} O \\ | \\ \text{Et} \end{array} \text{N} \begin{array}{c} \text{H} \\ \text{n-Pr} \end{array}\]

**N-Ethyl-3-(trifluoromethyl)benzamide**: Following the general method A, the reaction yielded a pink solid in 96% yield. \(^1\text{H NMR}\ (400 \text{ MHz}, \text{CDCl}_3, \text{ppm}) \delta 8.01 (s, 1H), 7.93 (d, 1H, \( J = 8 \)), 7.68 (d, 1H, \( J = 8 \)), 7.47 (t, 1H, \( J = 8 \)), 6.94 (bs, 1H), 3.48-3.42 (m, 2H), 1.21 (t, 3H, \( J = 7 \)). \[^{13}\text{C} \text{NMR}\ (\text{CDCl}_3, 100 \text{ MHz}, \text{ppm}) \delta 166.20, 135.48, 130.65, 130.18, 128.97, 127.76, 125.00, 123.86, 35.07, 14.57. \[^{19}\text{F NMR}\ (\text{CDCl}_3, 376 \text{ MHz}, \text{ppm}) \delta -63.21. \text{IR (KBr, cm}^{-1}\text{) v 3330, 1645, 1546, 1334, 1280, 1122.}\]

\[\text{O} \begin{array}{c} \text{N} \\ \text{n-Pr} \end{array} \text{H} \]

**N-n-Propylbenzamide**: Following the general method C, the reaction yielded a yellow solid. \(^1\text{H NMR}\ (300 \text{ MHz}, \text{CDCl}_3, \text{ppm}) \delta 7.77 (bd, 2H), 7.48-7.39 (m, 3H), 6.27 (bs, 1H), 3.45-3.38 (m, 2 H), 1.70-1.58 (m, 2 H), 0.98 (t, 3H, \( J = 7.4 \)). Spectrochemical data is consistent with previously reported data.\(^{61}\)

\[\text{O} \begin{array}{c} \text{N} \\ \text{i-Pr} \end{array} \text{H} \]

**N-isopropylbenzamide**: Following the general method C, the reaction yielded a white solid. \(^1\text{H NMR}\ (300 \text{ MHz}, \text{CDCl}_3, \text{ppm}) \delta 7.75 (d, 2H, \( J = 8 \)), 7.47-7.38 (m, 3H), 6.03 (bs, 1H), 4.34-4.22 (m, 1H), 1.24 (d, 6H, \( J = 6 \)). Spectrochemical data is consistent with previously reported data.\(^{62}\)
**N-n-butylbenzamide:** Following the general method C, the reaction yielded a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$, ppm) δ 7.76 (d, 2 H, $J = 7$), 7.32-7.48 (m, 3 H), 6.57 (b s, 1 H), 3.36-3.46 (q, 2 H), 1.50-1.62 (quintet, 2 H), 1.29-1.43 (sextet, 2 H), 0.90 (t, 3 H, $J = 7$). Spectrochemical data is consistent with previously reported data.\textsuperscript{17}

**N-t-butylbenzamide:** Following the general method C, the reaction yielded a white solid. $^1$H NMR (300 MHz, CDCl$_3$, ppm) δ 7.71 (d, 2 H, $J = 7$), 7.34-7.49 (m, 3 H), 6.00 (b s, 1 H), 1.47 (s, 9 H). Spectrochemical data is consistent with previously reported data.\textsuperscript{62}

**N-ethyl-2,3,4,5,6-pentadeuterobenzamide:** A white solid was obtained in 82% yield (2.4617 g). To a round bottom flask 2,3,4,5,6-pentadeuterobenzoic acid (2.4902 mg, 19.6 mmol), oxalyl chloride (1.97 mL, 23 mmol, 1.17 equiv), and a drop of dimethylformamide where added. Dry dichloromethane (~20 mL) were then added and the reaction was left stirring at room temperature overnight (16 h). Solvent was removed under reduced pressure and the crude 2,3,4,5,6-pentadeutero benzoyl chloride was utilized. Dry diethylether (~20 mL) and K$_2$CO$_3$ (50 mmol, 2.6 equiv) were added and after stirring at room temperature for a few minutes EtNH$_3$Cl (30 mmol, 1.5 equiv) was added. The reaction was stirred at room temperature until TLC analysis (in silica gel TLC aluminum sheets) showed no 2,3,4,5,6-pentadeuterobenzoyl chloride. The resulting mixture was diluted with ethyl acetate (100 mL),
washed with deionized water (50 mL) and extracted three times with ethyl acetate (3 x 30 mL). Solvent was removed under reduced pressure and the resulting solid was dried under vacuum.

\(^1\)H NMR (400 MHz, CDCl\(_3\), ppm) \(\delta 6.52\) (bs, 1H), 3.49-3.42 (m, 2H), 1.21 (t, 3H, \(J = 7\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta 167.41, 134.58, 130.65\) (t, \(J = 25\)), 127.85 (t, \(J = 25\)), 126.39 (t, \(J = 24\)), 34.81, 14.78. IR (KBr, cm\(^{-1}\)) \(\nu 3318, 2979, 1635, 1546, 1296, 1278, 1146\).

\[\text{N-deutero-N-ethylbenzamide} \quad \text{and} \quad \text{N-deutero-N-ethyl-2,3,4,5,6-pentadeuterobenzamide} \] A solid was obtained in 92% and 73% yield, respectively. To a 20 mL vial N-ethylbenzamide (1 g) or N-ethyl-2,3,4,5,6-pentadeuterobenzamide (500 mg) were added followed by the addition of 5 mL CD\(_3\)OD. The mixture was capped and wrapped with parafilm, stirred at room temperature for 3 days. Solvent was removed under reduced pressure and kept under vacuum. \(\text{N-deutero-N-ethylbenzamide}\): \(^1\)H NMR (300 MHz, CDCl\(_3\), ppm) \(\delta 7.76\) (d, 2H, \(J = 7\)), 7.51-7.39 (m, 3H), 3.50 (q, 2H), 1.24 (t, 3H, \(J = 7\)). \(\text{N-deutero-N-ethylbenzamide}\): \(^1\)H NMR (300 MHz, CDCl\(_3\), ppm) \(\delta 3.47\) (q, 2H), 1.23 (t, 3H, \(J = 7\)).

**2.5.3. Diphenylacetylene Derivative Synthesis**

**General Procedure for Alkyne Synthesis:** Previously published by Novák, \textit{et al.} \(^{59}\)

Aryl halide (5 mmol), 100 mg of PdCl\(_2\)(PPh\(_3\))\(_2\) (0.14 mmol, 2.8%), and 28 mg of CuI (0.14 mmol, 2.8%) were placed into an oven-dried Schlenk flask. Next, 12 mL of toluene and 1200 \(\mu\)L of diisopropylamine were added to the flask, followed by 630 \(\mu\)L of 2-methyl-3-butyn-2-
ol (6.5 mmol, 546 mg). The reaction mixture was stirred at 80 °C under nitrogen for 1 h. Then the temperature of the oil bath was increased to 110 °C, and 400 mg of NaH (55% dispersion, 9.16 mmol) was added slowly to the mixture. After 5 min of stirring, 5 mmol of the appropriate aryl halide was added to the reaction mixture, and the stirring was continued. After 25 min another 100 mg portion of NaH (1.83 mmol) was added carefully, and the solution was stirred further at 110 °C until the reaction was complete (1 h). After cooling to room temperature, the suspension was filtered, and the separated amine-hydrochloride was washed with toluene. Evaporation of the combined toluene solutions gave a crude product, which was purified by column chromatography (usually 20:1 hexanes:ethyl acetate). Further purification was achieved by recrystallization from ethanol.

1,2-bis(4-methylphenyl)ethyne: $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$ 7.44 (d, 4H, $J = 8$), 7.17 (d, 4H, $J = 8$), 2.38 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$ 138.39, 131.62, 129.43, 120.67, 89.21, 21.71. Spectrochemical data is consistent with previously reported data.$^{63}$

1,2-bis(4-methoxyphenyl)ethyne: $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$ 7.45 (d, 4H, $J = 8$), 6.87 (d, 4H, $J = 8$), 3.82 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm)
δ 159.61, 133.08, 115.93, 114.19, 88.18, 55.56. Spectrochemical data is consistent with previously reported data.59,64

1,2-bis(4-(trifluoromethyl)phenyl)ethyne: $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 7.67-7.61 (m, 8H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 132.06, 130.64, 130.30, 129.99, 127.89, 126.36, 125.41, 122.48, 119.78, 90.10. $^{19}$F NMR (CDCl$_3$, 376 MHz, ppm) δ -63.33. Spectrochemical data is consistent with previously reported data.65

1,2-bis(4-fluorophenyl)ethyne: $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 7.55-7.47 (m, 4H), 7.10-7.01 (m, 4H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 163.73-161.24 (d, $J$ = 250), 133.38, 119.13, 115.63 (d, $J$ = 21), 87.92. $^{19}$F NMR (CDCl$_3$, 376 MHz, ppm) δ -111.22. Spectrochemical data is consistent with previously reported data.66,67

1-fluoro-4-(p-methylethynyl)benzene: $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 7.54-7.47 (m, 2H), 7.43 (d, 2H, $J$ = 8), 7.16 (d, 2H, $J$ = 8), 7.08-7.00 (m, 2H), 2.38 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 163.59-161.10 (d, $J$ = 250), 138.45, 133.37 (d, $J$ = 7.6), 131.41, 129.12, 119.96, 119.51, 115.56 (d, $J$ = 21), 89.19, 87.60, 21.50. $^{19}$F NMR
(CDCl₃, 376 MHz, ppm) δ -111.58. Spectrochemical data is consistent with previously reported data.⁶⁷

2.5.4. Isoquinolone Synthesis

**General procedure for Cp*Ir(III)-catalyzed isoquinolone synthesis:** To a storage tube with a stirring bar, the corresponding benzamide (0.50 mmol, 1 equiv), solid alkyne (0.50 mmol, 1 equiv), [Cp*Ir(H₂O)₃](OTf)₂ or [Cp*Ir(NHC)(H₂O)₂](OTf)₂ (0.0125 mmol, 2.5 mol%), and 2.5 mL of cyclohexane were added. If the alkyne was a liquid, it was added after the addition of 2.5 mL of cyclohexane. Air (40 psi) or O₂ (20 psi) was added after two evacuation cycles. The reaction mixture was heated at 90 °C in a mineral oil bath for 16 h. The reaction was allowed to cool to room temperature and diluted with dichloromethane.

**General procedure for [Cp*Ir(H₂O)₃](OTf)₂-catalyzed isoquinolone synthesis under N₂:** To a pre-dried 25 mL storage tube with a stirring bar N-ethylbenzamide (0.5 mmol, 1 equiv), diphenylacetylene (0.5 mmol, 1 equiv) and [Cp*Ir(H₂O)₃](OTf)₂ (0.0125 mmol, 2.5 mol%) were added. The tube was then brought into an O₂ and H₂O free glove box and 2.5 mL of dry cyclohexane were added. The tube was sealed and brought outside the box and heated to 90 °C in a mineral oil bath. After 16 h, the reaction was allowed to cool to room temperature, opened to air and diluted with dichloromethane.
**General procedure for NMR yield determination:** Solvent was removed *in vacuo* and the resulting crude product and the corresponding amount of internal standard, usually 0.167 mmol, of 1,3,5-trimethoxybenzene or mesitylene, were dissolved in 1.25 mL of chloroform-\(d\) and 0.5 mL were added to a NMR tube. Percent yield was calculated by the ratio of product:i.s. based on their respective peak integrations.

**General procedure for isoquinolone isolation:** After following the general procedure for iridium catalyzed isoquinolone synthesis, silica was added to the crude reaction mixture and the solvent was removed *in vacuo* and the resulting solid (mixture of silica with sample) was added to a 1.5 cm x 30 cm column already prepared with silica gel. The column was allowed to run under gravity and was monitored by TLC (silica gel aluminum sheets).

![Chemical Structure](image)

**2-Ethyl-3,4-diphenylisoquinolin-1(2H)-one:** Following the general procedure for isoquinolone synthesis, after purification by column chromatography (9:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 74% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) \(\delta\) 8.57 (d, 1H, \(J = 10\)), 7.55-7.45 (dq, 2H), 7.24-7.10 (m, 9H), 7.05 (d, 2H, \(J = 10\)), 3.99-3.92 (q, 2H), 1.17 (t, 3H, 7). Spectrochemical data is consistent with previously reported data.\(^{15}\)
2-Ethyl-6-methoxy-3,4-diphenylisoquinolin-1(2H)-one: Following the general procedure for isoquinolone synthesis, after purification by column chromatography (7:1 → 3:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 67% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 8.48 (d, 1H, $J = 9$), 7.25-7.02 (m, 12H), 6.47 (d, 1H, $J = 3$), 3.92 (q, 2H), 3.68 (s, 3H), 1.15 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 162.47, 161.68, 141.74, 139.18, 136.70, 136.60, 134.85, 131.41, 130.06, 129.90, 128.08, 127.83, 126.68, 119.19, 118.69, 115.37, 106.83, 55.16, 41.10, 14.20. IR (KBr, cm$^{-1}$) ν 3000, 1644, 1604, 1556, 1477, 1251, 1222, 1191, 1173, 1140, 1118, 1069, 1032, 1015. HRMS (ESI) m/z calcd (M+H) for C$_{24}$H$_{21}$NO$_2$ 356.16451; found 356.16434.

2-Ethyl-6-methyl-3,4-diphenylisoquinolin-1(2H)-one: Following the general procedure for isoquinolone synthesis, after purification by column chromatography (5:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 48% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 8.45 (d, 1H, $J = 8$), 7.31 (d, 1H, $J = 10$), 7.23-7.13 (m, 8H), 7.04 (bd, 2H), 3.93 (q, 2H), 2.33 (s, 3H), 1.16 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 161.92, 142.48, 141.10, 137.19, 136.66, 134.84, 131.49, 130.14, 128.12, 127.77, 126.59, 124.89, 122.98, 41.18, 21.91, 14.14. IR (KBr, cm$^{-1}$) ν 2900, 1645, 1614, 1588, 1482, 1318, 1147, 1069. HRMS (ESI) m/z calcd (M+H) for C$_{24}$H$_{21}$NO 340.16959; found 340.16937.
Following the general procedure for isoquinolone synthesis, after purification by column chromatography (5:1 hexanes:ethyl acetate) a pale pink solid was obtained in 60% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 8.67 (d, 1H, $J = 8$), 7.68 (d, 1H, $J = 8$), 7.39 (s, 1H), 7.28-7.13 (m, 9H), 7.04 (bd, 2H), 3.95 (q, 2H), 1.18 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 161.27, 142.71, 137.20, 135.49, 134.25, 133.76, 131.32, 129.94, 128.94, 128.45, 128.10 (d, $J = 11$), 127.20, 122.59, 122.43, 118.81, 41.68, 14.01. $^{19}$F NMR (CDCl$_3$, 376 MHz, ppm) δ -63.27. IR (KBr, cm$^{-1}$) ν 1655, 1638, 1559, 1355, 1322, 1309, 1263, 1171, 1131, 1065, 1028, 1013, 795, 702. HRMS (ESI) $m/z$ calcd (M+H) for C$_{24}$H$_{18}$F$_3$NO 394.1413; found 394.1410.

Following the general procedure for isoquinolone synthesis, after purification by column chromatography (7:1 hexanes:ethyl acetate) a white solid was obtained in 41% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 8.50 (d, 1H, $J = 9$), 7.57 (d, 1H, $J = 8$), 7.25-7.02 (m, 11H), 3.94 (q, 2H), 1.22 (s, 9H), 1.15 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 161.83, 155.34, 140.94, 136.96, 136.58, 134.90, 131.44, 130.17, 128.03, 127.74, 127.50, 126.60, 124.60, 122.92, 121.28, 119.31, 41.10, 35.10, 30.94, 14.14. IR (KBr, cm$^{-1}$) ν 2974, 1646, 1613, 1584, 1481,
1319, 1260, 1196, 1067, 1021. HRMS (ESI) m/z calcd (M+H) for C_{27}H_{27}NO_{3} 382.21654; found 382.21647.

2-Ethyl-5,7-dimethoxy-3,4-diphenylishoquinolin-1(2H)-one: Following the general procedure for isoquinolone synthesis, after purification by column chromatography (3:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 55% yield. \( ^1H \) NMR (CDCl\(_3\), 400 MHz, ppm) \( \delta \) 7.65 (d, 1H, \( J = 3 \)), 7.19-7.13 (m, 3H), 7.11-7.07 (m, 2H), 7.03-6.92 (m, 5H), 6.59 (d, 1H, \( J = 3 \)), 3.94 (s, 3H), 3.89 (q, 2H), 3.25 (s, 3H), 1.14 (t, 3H, \( J = 7 \)). \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz, ppm) \( \delta \) 161.12, 159.04, 157.33, 140.46, 138.86, 134.91, 130.55, 127.63, 126.30, 125.18, 121.95, 116.97, 104.59, 99.63, 55.58, 41.67, 13.90. IR (KBr, \( \text{cm}^{-1} \)) \( \nu \) 1638, 1609, 1585, 1373, 1153, 1084. HRMS (ESI) m/z calcd (M+H) for C_{25}H_{23}NO_{3} 386.17507; found 386.17441.

2-Ethyl-7-methyl-3,4-diphenylishoquinolin-1(2H)-one

Following the general procedure for isoquinolone synthesis, after purification by column chromatography (5:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 69% yield. \( ^1H \) NMR (CDCl\(_3\), 400 MHz, ppm) \( \delta \) 8.38 (s, 1H), 7.32 (d, 1H, \( J = 7 \)), 7.24-7.08 (m, 9H), 7.08-7.01 (m, 3H), 3.95 (q, 2H), 2.48 (s, 3H), 1.16 (t, 3H, \( J = 7 \)). \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz, ppm) \( \delta \) 161.80, 139.95, 136.60, 136.43, 134.75, 133.34, 131.32, 130.12, 127.95, 127.68, 127.21,
126.50, 125.16, 124.95, 118.87, 41.17, 21.22, 14.04. IR (KBr, cm⁻¹) ν 2982, 1644, 1588, 1499, 1330, 1070. HRMS (ESI) m/z calcd (M+H) for C₂₄H₂₁NO₃ 340.16959; found 340.16913.

**2-Ethyl-7-methoxy-3,4-diphenylisoquinolin-1(2H)-one**

Following the general procedure for isoquinolone synthesis, after purification by column chromatography (7:1 hexanes:ethyl acetate) a white solid was obtained (25 % yield, 50% yield combined isomers). ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.97 (s, 1H), 7.23-7.01 (m, 12H), 3.99-3.90 (m, 5H), 1.17 (t, 3H, J = 7). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 161.54, 158.42, 138.63, 138.63, 134.72, 131.34, 131.18, 127.98, 127.68, 127.01, 126.57, 126.23, 122.46, 118.93, 107.24, 55.57, 41.38, 14.02. IR (KBr, cm⁻¹) v 1638, 1604, 1588, 1498, 1254, 1028. HRMS (ESI) m/z calcd (M+H) for C₂₄H₂₁NO₂ 356.16451; found 356.16521.

**2-Ethyl-5-methoxy-3,4-diphenylisoquinolin-1(2H)-one:** Following the general procedure for isoquinolone synthesis, after purification by column chromatography (7:1 hexanes:ethyl acetate) a white solid was obtained (25 % yield, 50% yield combined isomers). ¹H NMR (CDCl₃, 400 MHz, ppm) δ 8.23 (d, 1H, J = 8), 7.43 (t, 1H, J = 8), 7.19-7.14 (m, 3H), 7.12-7.08 (m, 2H), 7.04-6.93 (m, 6H), 3.89 (q, 2H), 3.27 (s, 3H), 1.14 (t, 3H, J = 7). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 161.94, 141.04, 137.67, 137.31, 135.98, 133.50, 131.85, 131.75, 131.17, 129.85, 128.50, 127.57, 126.21, 125.24, 125.03, 118.87, 41.15, 21.10, 14.07.
IR (KBr, cm$^{-1}$) ν 1636, 1578, 1459, 1339, 1263, 1065. HRMS (ESI) m/z calcd (M+H) for C$_{24}$H$_{21}$NO$_2$ 356.16451; found 356.16483.

2-Ethyl-3,4-bis(4-methylphenyl)isoquinolin-1(2H)-one: Following the general procedure for isoquinolone synthesis, after purification by column chromatography (7:1 → 3:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 49% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 8.55 (d, 1H, $J = 6$), 7.50-7.42 (m, 2H), 7.12 (d, 1H, $J = 8$), 7.07-6.90 (m, 8H), 3.93 (q, 2H), 2.28-2.22 (m, 6H), 1.16 (t, 3H, $J = 7$). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 162.31, 141.41, 138.04, 137.68, 136.34, 133.87, 132.22, 132.11, 131.54, 130.22, 128.87, 127.94, 126.59, 125.61, 125.39, 119.24, 41.52, 21.53, 21.42, 14.43. IR (KBr, cm$^{-1}$) ν 2985, 1647, 1510, 1330, 1073. HRMS (ESI) m/z calcd (M+H) for C$_{25}$H$_{23}$NO 354.18524; found 354.18582.

2-Ethyl-3,4-bis(4-methoxyphenyl)isoquinolin-1(2H)-one:

Following the general procedure for isoquinolone synthesis, after purification by column chromatography (3:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 38% yield. $^1$H
NMR (CDCl₃, 400 MHz, ppm) δ 8.54 (d, 1H, J = 10), 7.55-7.44 (m, 2H), 7.14 (d, 1H, J = 8), 7.06 (d, 2H, J = 8), 6.95 (d, 2H, J = 8), 6.74 (t, 4H, J = 7), 3.94 (q, 2H), 3.79-3.73 (m, 6H), 1.15 (t, 3H, J = 7). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 158.98, 158.03, 141.13, 137.52, 132.46, 131.87, 131.31, 138.99, 127.71, 127.30, 126.36, 125.30, 125.15, 113.30, 55.13, 55.04, 41.23, 14.14. IR (KBr, cm⁻¹) ν 2932, 1646, 1609, 1511, 1290, 1246, 1026. HRMS (ESI) m/z calcd (M+H) for C₂₅H₂₃NO₃ 386.17507; found 386.17559.

![Chemical Structure](image)

3,4-Bis(4-fluorophenyl)-2-ethylisoquinolin-1(2H)-one: Following the general procedure for isoquinolone synthesis, after purification by column chromatography (7:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 50% yield. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 8.53 (d, 1H, J = 8), 7.53-7.43 (m, 2H), 7.17-7.10 (m, 2H), 7.07 (d, 1H, J = 7), 7.02-6.83 (m, 6H), 3.91 (q, 2H), 1.14 (t, 3H, J = 7). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 163.32, 162.67, 161.77, 160.85, 160.21, 136.83, 132.89 (d, J = 8), 132.26, 132.03, 131.80 (d, J = 8), 130.61, 127.73, 126.66, 125.12, 124.98, 118.26, 115.26-114.85(t, J = 20), 41.18, 13.99. ¹⁹F NMR (CDCl₃, 376 MHz, ppm) δ -112.50 (1F), -115.33 (1F). IR (KBr, cm⁻¹) ν 2981, 1642, 1603, 1508, 1327, 1222, 1065. HRMS (ESI) m/z calcd (M+H) for C₂₃H₁₇F₂NO 362.13510; found 362.13563.
2-Ethyl-4-(4-fluorophenyl)-3-(4-methylphenyl)isoquinolin-1(2H)-one and

2-Ethyl-3-(4-fluorophenyl)-4-(4-methylphenyl)isoquinolin-1(2H)-one: Following the general procedure for isoquinolone synthesis, after purification by column chromatography (7:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 50% yield. A mixture of isomers was obtained in a ~1:1 ratio. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$ 8.56-8.53 (m, 2H), 7.52-7.44 (m, 4H), 7.17-7.11 (m, 3H), 7.07 (d, 2H), 7.03-6.98 (m, 8H), 6.94-6.84 (m, 6H), 3.90-3.35 (bq, 4H), 2.27 (s, 3H), 2.26 (s, 3H), 1.15 (t, 6H, $J = 7$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 162.95, 162.29, 161.59, 161.54, 160.48, 159.85, 141.19, 139.49, 137.64, 136.80, 136.73, 135.96, 132.88, 132.62 (b), 132.26, 131.65, 131.58, 131.28, 129.46 (b), 128.33 (b), 127.35 (b) 126.15 (b), 125.07-124.57 (m), 119.02, 117.52, 114.81-114.38 (t, $J$ = 22), 40.91, 40.83, 20.84, 20.74, 13.72. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -115.77 (1F), -112.86 (1F). IR (KBr, cm$^{-1}$) v 2976, 1646, 1604, 1508, 11326, 1223, 1069. HRMS (ESI) $m/z$ calcd (M+H) for C$_{24}$H$_{20}$FNO 358.16017; found 358.16063.

2-Methyl-3,4-diphenylisoquinolin-1(2H)-one: Following the general procedure for isoquinolone synthesis, after purification by column chromatography (3:1
hexanes:ethyl acetate) a pale yellow solid was obtained in 53% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 8.56 (d, 1H, $J = 8$), 7.54-7.47 (m, 2H), 7.25-7.11 (m, 10H), 7.06 (d, 2H, $J = 8$), 3.36 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 162.68, 141.18, 137.10, 136.40, 134.99, 131.97, 131.46, 129.86, 128.14, 127.80, 127.76, 126.74, 126.56, 125.28, 124.83, 118.79, 34.33. IR (KBr, cm$^{-1}$) ν 1649, 1490, 1330, 1027. Spectrochemical data is consistent with previously reported data.$^{17}$

![6-Methoxy-2-methyl-3,4-diphenylisoquinolin-1(2H)-one](image)

Following the general procedure for isoquinolone synthesis, after purification by column chromatography (2:1 hexanes:ethyl acetate) a pale yellow solid was obtained in 41% yield. $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ 8.47 (d, 1H, $J = 9$), 7.22-7.10 (m, 8H), 7.05 (d, 3H, $J = 8$), 6.51 (s, 1H), 3.66 (s, 3H), 3.32 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ 162.41, 141.83, 139.12, 136.42, 135.07, 131.35, 129.90, 128.04, 127.85, 126.71, 118.82, 118.42, 115.35, 106.86, 55.09, 34.07. IR (KBr, cm$^{-1}$) ν 1648, 1609, 1483, 1230, 1037. Spectrochemical data is consistent with previously reported data.$^{17}$

### 2.5.5. Stilbene Quantification by Gas Chromatography

**General procedure for gas chromatography (GC) yields:** After determining isoquinolone yield by $^1$H NMR, the reaction was diluted with dichloromethane and 0.5 mmol mesitylene were added to the crude reaction mixture and analyzed by gas chromatography. The ratio of
stilbene:mesitylene was calculated and the concentration of stilbene was obtained from the calibration curves (Figures 2.1ES and 2.2ES). The calibration curves were obtained by calculating the ratio of stilbene:mesitylene at various stilbene concentrations. Varian CP 3800. Injector temperature: 250 °C, column oven initial temperature: 60 °C, rate: 10 °C/min, column oven final temperature: 300 °C, column flow rate: 4.8 mL/min.

Figure 2.1ES. Calibration curve obtained for cis-stilbene against mesitylene. Conditions: 0.025-0.20 M cis-stilbene and 0.2 M mesitylene in dichloromethane.
**Figure 2.2ES.** Calibration curve obtained for *trans*-stilbene against mesitylene. Conditions: 0.010-0.20 M *trans*-stilbene and 0.2 M mesitylene in dichloromethane.

**General procedure for** [Cp*Ir(H₂O)₃](OTf)₂-catalyzed hydrogenation of diphenylacetylene: To a 3 mL storage tube diphenylacetylene (0.2 mM) and [Cp*Ir(H₂O)₃](OTf)₂ (5 μmol, 2.5 mol%) were added followed by the addition of 1 mL of
solvent (1,2-dichloroethane or cyclohexane). H₂ (20 psi) was added after three evacuation cycles. The reactions were heated to 90 °C for 16 hours. The reactions were allowed to cool to room temperature and were washed with dichloromethane. Stilbene yields were then determined by GC against mesitylene internal standard (0.2 mmol).

2.5.6. Synthesis and Reactivity of Complex 15

**General Method A for the Synthesis of Complex 15 and Derivatives**

To a 20 mL vial, 5 equivalents of N-methylbenzamide (or derivative, 0.125 mmol), 1 equivalent of [Cp*Ir(NHC)(H₂O)]₂(OTf)₂ (5, 0.025 mmol), [2 or 3 equivalents of an acetate source], and 5 mL cyclohexane were added and capped. The reaction was heated to 60 °C for 16 hours. The solvent was removed by decanting and the resulting oil was washed with ether and dried under vacuum overnight before taking the \(^{1}H\) NMR spectrum in acetone-\(d_6\).
**Figure 2.3ES.** $^1$H NMR spectrum (300 MHz, (CD$_3$)$_2$CO) of N-methylbenzamide (5 equiv) and 5 (1 equiv) in cyclohexane at 60 °C after 16 h. The spectrum shows peaks at δ 1.74 (15H), 3.15 (3H), 3.64 (3H), 3.99 (3H), 7.01 (1H), 7.13 (1H), 7.31 (2H), 7.60 (1H), and 8.03 (1H). Leftover N-methylbenzamide (δ 3.04, 7.50, 7.90) and residual acetone solvent (δ 2.05) peaks are shown.
Figure 2.4ES. $^1$H NMR spectra (300 MHz, (CD$_3$)$_2$CO) of (A) 15, (B) 5 and (C) N-methylbenzamide (5 equiv), 5 (1 equiv), and NaOAc (3 equiv) in cyclohexane at 60 °C after 16 h. No complex 15 formation was observed. The spectrum (C) shows peaks at δ 1.76 (15H), 2.85 (3H), 3.79 (6H), 7.46 (2H); solvent residual peaks for diethyl ether and acetone-d$_6$ are at δ 1.11 and 3.40, and 2.06 respectively; aromatic region does not show aromatic signals corresponding to N-methylbenzamide.
Figure 2.5ES. $^1$H NMR spectra (300 MHz, (CD$_3$)$_2$CO) of (A) 15, and (B) N-methylbenzamide (5 equiv), 5 (1 equiv), and AgOAc (2 equiv) in cyclohexane at 60 °C after 16 h. Peaks correspond to two Cp*Ir(NHC)_{L_n} complexes, complex 15 and Cp*Ir(NHC)(OAc)$_2$ (proposed). No aromatic peaks corresponding to a new Cp*Ir(NHC)(Benzamide) complex are observed.
Figure 2.6ES. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of N-methylbenzamide (2 equiv) and 7 (1 equiv) in cyclohexane at 60 °C after 16 h. The spectrum shows peaks at $\delta$ 1.60 (15H), 1.69 (3H), 2.34 (2 x 3H), 3.62 (6H), 6.66 (2 x 1H), 7.11 (2H), 7.33-7.45 (2 x 3H), 7.76 (2 x 2H). Dichloromethane solvent residual peak is observed at $\delta$ 5.27. No reaction was observed.

General Method B for the Synthesis of Complex 15 and Derivatives

To a 20 mL vial, [Cp*Ir(NHC)(H$_2$O)$_2$](OTf)$_2$ (5, 0.20 or 0.25 mmol), benzamide (1, 1 mmol), and 5 mL cyclohexane were added and capped. The reaction was heated to 60 °C for 16 hours. The solvent was removed by decanting and the resulting oil washed with ether, dissolved in acetone and filtered through alumina with acetone and dichloromethane as eluting solvents. Solvent was removed under vacuum and the reaction yielded yellow crystals/powder.
**General Method for the Recrystallization of Complex 15 and Derivatives:** The resulting brown oil from the previous reaction was recrystallized using the layering method. The oil was dissolved in acetone (~0.3 mL) and the solution was added to a 5 mL vial. Diethyl ether was slowly added to create a layer consisting of two phases. X-ray quality crystals were analyzed by the Department of Chemistry’s crystallographer (See section 2.5.9)

![Chemical Structure](image)

**[Cp*Ir(NHC)(N-Methylbenzamide)][OTf]** (15): Following the general method B, a yellow solid was obtained in 65% yield. $^1$H NMR (400 MHz, CD$_3$CO, ppm) δ 1.73 (s, 15H), 3.14 (d, 3H, $J = 5$), 3.36 (s, 3H), 3.99 (s, 3H), 7.00 (t, 1H, $J = 8$), 7.12 (s, 1H), 7.32 (m, 2H), 7.62 (d, 1H, $J = 8$), 8.04 (d, 1H, $J = 7$), and 8.73 (bs, 1H). $^{13}$C NMR (100 MHz, CD$_3$CO, ppm) δ 9.66, 27.87, 38.50, 38.99, 91.47, 121.20, 123.49, 124.47, 125.41, 127.32, 133.25, 139.21, 140.00, 156.39, 162.35, and 182.99. Anal. calcd. for IrC$_{24}$H$_{32}$F$_3$N$_3$O$_4$S: C, 40.73; H, 4.56; N, 5.94. Found: C, 40.79; H, 4.46; N, 5.99. IR (KBr, thin film, cm$^{-1}$): 1595, 1284, 1254, 1159, 1030.

![Chemical Structure](image)

**[Cp*Ir(NHC)(N-Ethylbenzamide)][OTf]** (16): Following the general method B, a yellow solid was obtained in 76% yield. $^1$H NMR (400 MHz, CD$_3$CO, ppm) δ 8.73 (bs, 1H), 8.04 (d, 1H, $J = 7$), 7.64 (d, 1H, $J = 7$), 7.32 (t, 2H, $J = 7$), 7.14 (s, 1H), 7.01 (t,
$^1$H, $J = 8$), 3.99 (s, 3H), 3.67-3.75 (m, 1H), 3.64 (s, 3H), 3.56-3.63 (m, 1H), 1.74 (s, 15H), 1.25 (t, 3H, $J = 7$) $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, ppm) $\delta$ 9.31, 15.09, 36.37, 38.12, 38.61, 91.17, 123.09, 124.14, 125.00, 126.97, 132.90, 138.92, 139.68, 156.05, 162.20, and 181.92. Anal. calcd. for IrC$_{25}$H$_{34}$F$_3$N$_3$O$_4$S: C, 41.60; H, 4.75; N, 5.82. Found: C, 41.91; H, 4.47; N, 5.89. The crystals contained a fraction of diethyl ether that is responsible for the difference in the theoretical and found. IR (KBr, thin film, cm$^{-1}$): 1595, 1286, 1257, 1247, 1235, 1224, 1156, 1031.

Following the general method B, a yellow solid was obtained in 60% yield. $^1$H NMR (400 MHz, (CD$_3$)$_2$CO, ppm) $\delta$ 8.51 (s, 1H), 7.60 (d, 1H, $J = 9$), 7.48 (s, 1H), 7.32 (s, 1H), 7.15 (s, 1H), 6.60 (dd, 1H, $J = 2$), 3.98 (s, 3H), 3.91 (s, 3H), 3.63-3.74 (m, 1H, and s, 3H), 3.50-3.60 (m, 1H), 1.75 (s, 15H), 1.23 (t, 3H, $J = 7$). $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, ppm) $\delta$ 181.78, 164.81, 163.72, 156.36, 132.99, 129.13, 125.49, 124.61, 123.26, 110.22, 91.58, 56.18, 39.20, 38.56, 36.71, 15.66, 9.80. Anal. calcd. for IrC$_{26}$H$_{36}$F$_3$N$_3$O$_5$S: C, 41.54; H, 4.83; N, 5.59. Found: C, 43.01; H, 5.08; N, 5.44. The crystals contained a fraction of diethyl ether that is responsible for the difference in the theoretical and found. IR (KBr, thin film, cm$^{-1}$): 1586, 1517, 1276, 1254, 1154, 1031.
[Cp*Ir(NHC)(N-Ethyl-4-(trifluoromethyl)benzamide)][OTf] (18): Following the general method B, a yellow solid was obtained in 71% yield. $^1$H NMR (400 MHz, (CD$_3$)$_2$CO, ppm) δ 9.05 (bs, 1H), 8.24 (s, 1H), 7.87 (d, 1H, $J = 8$), 7.35 (s, 1H), 7.33 (s, 1H), 7.17 (s, 1H), 4.00 (s, 3H), 3.67-3.79 (m, 1H), 3.60-3.67 (m, 1H, and a s, 3H), 1.77 (s, 15H), 1.25 (t, 3H, $J = 7$). $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, ppm) δ 181.26, 163.20, 155.91, 143.99, 135.12, 133.68, 133.37, 127.91, 125.70, 124.84, 120.16 (m), 92.09, 39.05, 38.65, 37.14, 15.38, 9.77. $^{19}$F NMR (376 MHz, (CD$_3$)$_2$CO), ppm) δ -63.69 (3F), -79.31 (3F). Anal. calcd. for IrC$_{26}$H$_{33}$F$_6$N$_3$O$_4$S: C, 39.54; H, 4.21; N, 5.32. Found: C, 39.63; H, 4.06; N, 5.39. IR (KBr thin film, cm$^{-1}$): 1604, 1323, 1293, 1225, 1155, 1129, 1030.

**General method for reactions with complex 15:** To a 3 mL storage tube 1 equivalent of complex 15 (0.028 mmol), 5 or 1 equivalent of diphenylacetylene (0.14 or 0.028 mmol), [2 equivalents of an acetate salt (0.056 mmol) for some reactions], and 1 mL of cyclohexane were added. The reaction was heated to 60 °C for 16 hours, cooled, (filtered through celite when silver acetate or other salts were added) and washed with acetone. The solvent was removed under vacuum and the resulting oil was analyzed by $^1$H NMR Spectroscopy.
Figure 2.7ES. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 15 (1 equiv) and diphenylacetylene (1 equiv) in cyclohexane at 60 °C after 16 h. The spectrum does not show proton signals corresponding to isoquinolone product. Similar results were observed with 5 equiv diphenylacetylene and with longer reaction times.
Figure 2.8ES. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 15 (1 equiv), diphenylacetylene (1 equiv), and silver acetate (2 equiv) in cyclohexane at 60 °C after 16 h. The spectrum does not show proton signals corresponding to isoquinolone product.
Figure 2.9ES. $^1$H NMR spectra (300 MHz, (ClCD$_2$)$_2$) of 15 (1 equiv) and diphenylacetylene (5 equiv) at (A) rt, (B) 90 °C after 4 h, (C) 90 °C after 16 h, (D) 90 °C with D$_2$O(drops) after 16 h, (E) 90 °C with acetic acid-$d_4$(drops) after 16 h. No isoquinolone formation was observed at those conditions. Complex 15 was formed in situ.
Figure 2.10ES. $^1$H NMR spectrum (300 MHz, (CD$_3$)$_2$CO) of 15 (1 equiv), diphenylacetylene (1 equiv), and HOTf (1 equiv) at 90 °C in cyclohexane after 5 h. No significant isoquinolone formation (δ 3.30 and 8.47) is observed. Similar results are observed with 5 equiv diphenylacetylene and 2 equiv HOTf. About 50% leftover complex 15 is calculated with 1,3,5-trimethylbenzene internal standard.
Figure 2.11ES. $^1$H NMR spectrum (300 MHz, (CD$_3$)$_2$CO) of 15 (isolated, 1 equiv) and diphenylacetylene (1 equiv) at 90 °C in cyclohexane after 16 h. The spectrum shows no isoquinolone peaks. Similar results are observed when a 1:5 ratio complex 15:diphenylacetylene are used.
Figure 2.12ES. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of the isoquinolone synthesis catalyzed by 15 (at 2.5 mol%). The spectra shows a small amount of isoquinolone, about 10% yield.
Scheme 2.1ES. Heating complex 15 in methanol-$d_3$ at 60 °C

![Scheme Diagram]

Figure 2.13ES. $^1$H NMR (300 MHz, CD$_3$OD) spectra of 15 (A) at rt, (B) after heating at 60 °C for 16 h. No change was observed. Peaks at δ 1.70, 3.08, 3.55, 3.90, 7.01, 7.19, 7.31, 7.44, and 7.97 correspond to complex 15. Peaks at 2.23 and 6.74 correspond to 1,3,5-trimethylbenzene (mesitylene) internal standard. Peaks at 2.91, 3.30, and 4.89 are impurities and residual solvent. Iridium concentration at the end of reaction was equal to the initial concentration as calculated with the internal standard.
**Scheme 2.2ES.** Heating Complex 15 in Methanol-$d_3$ at 90 °C

![Scheme 2.2ES](image)

**Figure 2.14ES.** $^1$H NMR (300 MHz, CD$_3$OD) spectra of 15 (A) at rt, (B) after heating at 90 °C for 16 h. No change was observed. Peaks at δ 1.69, 3.07, 3.55, 3.90, 7.00, 7.19, 7.30, 7.41, and 7.96 correspond to complex 15. Peaks at 2.22 and 6.74 correspond to 1,3,5-trimethylbenzene (mesitylene) internal standard. Peaks at 2.91, 3.30, and 4.89 are impurities and residual solvent. Iridium concentration at the end of reaction was equal to the initial concentration as calculated with the internal standard.
No reactivity or decomposition was observed when complex 15 was heated up to 90 °C in methanol-$d_3$. As observed from Figures 2.18ES and 2.20ES, spectrum A (before heating) and B (after heating) overlap, no new peaks are observed, and the calculated [15] utilizing 1,3,5-trimethylbenzene as the internal standard remained the same. This suggests that no ligands are lost from the iridium center.
Scheme 2.3ES. Reaction of 15 and HOTf in Methanol-$d_3$ at 90 °C

\[ \text{Chemical Shift (ppm)} \]

Figure 2.15ES. $^1$H NMR (300 MHz, CD$_3$OD) spectra of 15 (A) at rt, (B) after heating at 90 °C with HOTf (4.5 equiv) for 16 h, (C) 2 d. Peaks at $\delta$ 1.69, 3.08, 3.55, 3.90, 7.00, 7.43, and 7.96 correspond to complex 15. Peaks at 2.22 and 6.75 correspond to mesitylene internal standard. Peaks at 2.92, 3.30, and 4.89 are impurities and residual solvent, which are shifted downfield after HOTf addition. Aromatic signals are missing after addition of HOTf and heating to 90 °C.
Scheme 2.4ES. Reaction of 15 and HOTf in Methanol-$d_3$ at 60 °C

Figure 2.16ES. $^1$H NMR (300 MHz, CD$_3$OD) spectrum of 15 with HOTf (4.5 equiv) at 60 °C after 16 h. Peaks at δ 1.69, 3.08, 3.55, 3.90, 7.00, 7.18, 7.30, 7.44, and 7.97 correspond to complex 15. Peaks at 2.22 and 6.75 correspond to mesitylene internal standard. Peaks at 2.92, 3.30, and 4.89 are impurities and residual solvent.
2.5.7. 2D NMR Spectroscopy of Complex 15

The COSY spectrum (Figures 2.17ES and 2.18ES) revealed 3-bond proton-proton correlations between the protons that resonate at 6.78 and 6.97 ppm; 6.97, 7.20 and 7.63 ppm; and 7.20 and 7.73 ppm. Additionally, the TOCSY spectrum (Figures 2.19ES and 2.22ES) revealed correlations between the protons on each ligand. Protons that resonate at 3.08 and 8.52 ppm, and protons at 6.97, 7.20, 7.63, and 7.73 ppm showed correlation and were assigned to the \textit{N-Methylbenzamide}; protons at 3.50 and 3.83 ppm, and protons at 6.78 and 6.97 ppm; showed correlation and were assigned to the NHC.
Figure 2.17ES. Full COSY spectrum of 15 in CDCl₃
Figure 2.18ES. Aromatic region of COSY spectrum of 15 in CDCl$_3$. Lines represent examples of three bond proton-proton correlations.
Figure 2.19ES. Full TOCSY spectrum of 15 in CDCl$_3$
Figure 2.20ES. Aromatic region of TOCSY spectrum of 15 in CDCl₃. Lines represent examples of long-range proton-proton coupling.
Protons that resonate at 1.64 ppm were assigned to the methyl protons in the Cp* as it has been previously shown to resonate in this range\textsuperscript{53} and integrates to 15 protons. Protons resonating at 3.08 ppm were assigned to the methyl group bound to the \textit{N}-Methylbenzamide and protons at 3.50 ppm and 3.83 ppm which showed three bond proton-proton correlation on the COSY experiment were assigned to the methyl groups belonging to the NHC ligand. The proton at 6.78 ppm showed a three bond correlation to protons at 6.97 ppm, protons at 6.97 ppm were shown to be neighbors to the protons that resonate at 7.20 ppm and 7.63 ppm. Finally, the proton that resonates at 7.73 ppm showed a three bond correlation with proton at 7.20 ppm. One bond HSQC and long range HMBC were utilized to assign the respective aromatic protons and carbons.

The HSQC experiment (Figures 2.21ES and 2.22ES) provided information about the one bond proton-carbon couplings. Protons that resonate at 1.64 ppm showed a one bond correlation with the carbon that resonates at 9.0 ppm. Protons that resonate at 3.08 ppm are bound to the carbon that resonates at 27.4 ppm and protons at 3.50 and 3.83 ppm correspond to carbons at 38.2 and 37.8 ppm, respectively. Protons resonating at 6.78 and 6.97 ppm correspond to carbons at 123.1, 123.2, and 124.0 ppm. Finally protons at 7.20, 7.63, and 7.73 ppm are bound to carbons at 137.0, 132.1, and 139.0 ppm, respectively.
Figure 2.21ES. Full HSQC spectrum of 15 in CDCl₃
Figure 2.22ES. Aromatic region of HSQC spectrum of 15 in CDCl₃
Finally, the HMBC experiment (Figures 2.23ES and 2.24ES) provided information about three and four bond proton-carbon correlations. Protons resonating at 1.64 ppm correlated to the carbon at 92 ppm. Protons at 3.50, 6.78, and 6.97 ppm correlated to carbons resonating at 123.1 and 123.2 ppm, and protons resonating at 3.83 ppm correlated to the carbon resonating at 124.0 ppm. Protons at 7.20 ppm correlated to the carbon at 124.0 ppm. Protons at 7.63 ppm correlated to the carbon at 132.1 ppm, and protons at 6.97 and 7.63 ppm correlate to the carbon at 137.0 ppm. Protons resonating at 6.97 and 7.63 ppm correlate to the carbon resonating at 139.0 ppm. Protons at 6.78 and 6.97 ppm correlate to the carbon at 155 ppm, and protons at 7.20 and 7.63 ppm correlate to the carbon at 159.0 ppm. Finally, the proton resonating at 7.63 ppm correlates to the carbon at 181.9 ppm.
Figure 2.23ES. Full HMBC spectrum of 15 in CDCl₃
Figure 2.24. Aromatic region of HMBC spectrum of 15 in CDCl₃
2.5.8. Mechanistic Studies

2.5.8.1. Kinetic Isotope Effect

**Determination of Rate Constants and the Kinetic Isotope Effect**

\[ \text{D_5/H_5} \begin{array}{c} \text{O} \\ \text{N} \\ \text{Et} \end{array} + \begin{array}{c} \text{Ph} \\ \text{N} \\ \text{Ph} \end{array} \xrightarrow{2.5 \text{ mol}\% \text{ 4}} \begin{array}{c} \text{D_4/H_4} \\ \text{O} \\ \text{Et} \end{array} \]

To 25 mL storage tubes, \(N\)-ethylbenzamide or \(N\)-ethyl-2,3,4,5,6-pentadeuterobenzamide (\(1-H/D\), 0.5 mmol, 1 equiv), diphenylacetylene (2, 0.5 mmol, 1 equiv) [\(\text{Cp}^*\text{Ir(H}_2\text{O})_3\)(OTf)]\(_2\) (4, 0.0125 mmol, 2.5 mol %), and 2.5 mL of cyclohexane were added. Air (40 psi) was added after two evacuation cycles and the tubes were sealed and heated at 90 °C for different times. The reactions were allowed to cool to room temperature and washed with dichloromethane. Solvent was removed *in vacuo* and the resulting crude product and 0.167 mmol of internal standard, 1,3,5-trimethoxybenzene, were dissolved in 1.25 mL of chloroform-\(d\). Percent yield was calculated by \(^1\)H NMR spectroscopy utilizing the ratio of product:i.s. based on their respective peak integrations. Individual reactions were performed in triplicate per time point. The kinetic plots were plotted utilizing KaleidaGraph. Respective \(k_{\text{obs}}\) were obtained using the exponential rise curve fit defined as \(y = m_1 + m_2(e^{m_3x})\).
To 25 mL storage tubes, \( N \)-ethylbenzamide and \( N \)-ethyl-4-\( R \)-benzamide (where \( R = \) OCH\(_3\), CH\(_3\), Cl, and CF\(_3\) ) were added excess, equal amount of moles for a total of 2 or 6 equivalents with respect to diphenylacetylene. Diphenylacetylene (1 equiv: 0.5 mmol or 0.167 mmol), [Cp*Ir(H\(_2\)O\(_3\))(OTf)\(_2\) ] (2.5 mol%) and 2.5 mL cyclohexane were then added. Air (40 psi) was added after two evacuation cycles and the tubes were sealed and heated to 90 °C for 2 hours. The reactions were allowed to cool to room temperature and washed with dichloromethane. Solvent was removed in vacuo and the resulting crude product and internal standard, 1,3,5-trimethoxybenzene, were dissolved in 1.25 mL of chloroform-\( d \). The respective product yields were obtained by \(^1\)H NMR spectroscopy against the internal standard. The ratio of H:R was obtained by comparing the respective isoquinolone yields.
2.5.9. Crystal Structures

**General X-Ray data collection and processing:** The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker-Nonius Kappa Axis X8 Apex2 diffractometer at a temperature of 110 K. The frame integration was performed using SAINT. The resulting raw data was scaled and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS. The structural model was fit to the data using full matrix least-squares based on F². The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the XL program from SHELXTL, graphic plots were produced using the NRCVAX crystallographic program suite or the Cambridge Crystallographic Data Centre (CCDC) Mercury 3.5. The structures were solved by direct methods using the XS program.
Figure 2.25ES. X-ray crystal structure of complex 9. Ellipsoids are at the 50% probability level, hydrogen atoms were omitted for clarity. Selected bond lengths (Å) and angles (degrees): Ir-O1, 2.104; O1-C1, 1.265; Ir-O2, 2.112; O2-C2, 1.262; Ir-O3, 2.152.

X-Ray structural determination for \( \text{C}_{14}\text{H}_{17}\text{F}_6\text{IrO}_5 \) (9): X-Ray quality crystals were obtained by slow evaporation of CH\(_2\)Cl\(_2\). Measurement temperature was 200(2) K. The obtained crystal was a yellow block-like with dimensions (mm) of 0.364 x 0.428 x 0.514 mm.
Figure 2.26. X-ray structure of complex 15. Ellipsoids are at the 50% probability level, the second formula unit, hydrogen atoms and the OTf counter anion were omitted for clarity. Selected bond lengths (Å) and angles (degrees): Ir-O, 2.109; O-C1, 1.287; C1-C2, 1.437; C2-C3, 1.398; Ir-C3, 2.079; Ir-C4, 2.035; Ir-O-C1, 115.44; Ir-C3-C2, 113.49; O-Ir-C3, 77.56.

X-Ray structural determination for C_{24}H_{31}F_3IrN_3O_4S (15): The obtained crystal was a yellow prism with dimensions (mm) of 0.28 x 0.16 x 0.11. There are two formula units in the asymmetric unit. All non-hydrogen atoms were obtained from the initial solution. The hydrogen atoms were introduced at idealized positions and were allowed to ride on the parent atom. The second anion exhibited a disorder wherein the orientation of the SO$_3$CF$_3^-$ pivoted approximately 32º around the carbon atom’s position to give distinct alternate positions for the sulfur and one of the oxygens. All other atoms for the two orientations were coincident.
Figure 2.27ES. X-ray crystal structure of complex 16. Ellipsoids are at the 50% probability level, hydrogen atoms and the OTf counter anion were omitted for clarity. Selected bond lengths (Å) and angles (degrees): Ir-O, 2.144; O-C1, 1.275; C1-C2, 1.468; C2-C3, 1.408; Ir-C3, 2.046; Ir-C4, 2.047; Ir-O-C1, 115.09; Ir-C3-C2, 115.49; O-Ir-C3, 77.87.

X-Ray structural determination for C_{25}H_{33}F_{3}IrN_{3}O_{4}S (16): The obtained crystal was a yellow prism with dimensions (mm) of 0.199 x 0.278 x 0.350. The crystal structure shows hydrogen bonding between the N-H and one oxygen on the trifluoromethanesulfonate counter anion (N-H—O).
Figure 2.28ES. X-ray crystal structure of complex 17. Ellipsoids are at the 50% probability level, hydrogen atoms and the OTf counter anion were omitted for clarity. Selected bond lengths (Å) and angles (degrees): Ir-O, 2.147; O-C1, 1.276; C1-C2, 1.454; C2-C3, 1.416; Ir-C3, 2.054; Ir-C4, 2.041; Ir-O-C1, 114.94; Ir-C3-C4, 114.73; O-Ir-C3, 77.77.

X-Ray structural determination for C_{20}H_{35}F_{3}Ir_{3}O_{5}S (17): Measurement temperature was 100(2) K. The obtained crystal was a yellow block-like with dimensions (mm) of 0.226 x 0.393 x 0.447. The crystal structure shows hydrogen bonding between the N-H and one oxygen on the trifluoromethanesulfonate counter anion (N-H—O). The crystal shows a fraction of ether solvent (C_{2}H_{5}O_{0.5}) that recrystallized with the species.
2.6. References


APPENDIX
APPENDIX 1

Initial Studies on Cp*Ir(III)L₃-Catalyzed Isoquinolone Synthesis

Scheme A1.1. Cp*Ir(III)-Catalyzed Coupling of Benzamide with Diphenylacetylene

The isoquinolone synthesis (Scheme A1.1) was performed with 10 mol% of the three catalysts shown below (Figure A1.1, 4-6). In addition to the desired product a high molecular weight by-product (11) was also observed (Entries 1-5).

Figure A1.1. Cp*Ir(III)-Catalysts Employed
As shown by Huang et al.\textsuperscript{1} and Sakabe et al.\textsuperscript{2}, coupling between two diphenylacetylene equivalents can take place in the presence of a proton donor, and high temperatures, according to the mechanism shown in Figure A1.2, to yield product 11. The same reaction has been observed in our experiments when proton donors, i.e. methanol, or the aqua containing catalysts 4 and 5, are present in the reaction (Table A1.1).

### Table A1.1. Product Formation with Various Cp*Ir(III)-Catalysts\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Product\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methanol</td>
<td>5</td>
<td>11</td>
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<tr>
<td>2</td>
<td>Toluene</td>
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<td>3, 11</td>
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<tr>
<td>3</td>
<td>Toluene</td>
<td>4</td>
<td>3, 11</td>
</tr>
<tr>
<td>4</td>
<td>Methanol</td>
<td>4</td>
<td>3, 11</td>
</tr>
<tr>
<td>5</td>
<td>Methanol</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions were run for 16 h and included 0.2 mmol benzamide, 0.2 mmol diphenylacetylene, 0.4 mmol silver acetate, 0.02 mmol catalyst in 1 mL solvent.

\textsuperscript{b}Product formation was determined by GC-MS analysis of crude reaction mixture.
Figure A1.2. Proposed mechanism for the formation of $^{1,2}$

Scheme A1.2. [Cp*IrCl$_2$]$_2$-Catalyzed Coupling of $N$-Methylbenzamide with Diphenylacetylene

$N$-Methylbenzamide 1 was also reacted with diphenylacetylene 2 in the presence of [Cp*IrCl$_2$]$_2$ (Scheme A1.2). However, the formation of a new product, 12, was observed. This
product was observed by Ueura et al.\textsuperscript{3} in an Cp*Ir(III)-catalyzed coupling of two diphenylacetylene molecules to a carboxylic acid with loss of CO\textsubscript{2}. The plausible mechanism for the formation of 12 is shown in Figure A1.3. Coordination of the carboxylate oxygen to Cp*IrX\textsubscript{2} gives an iridium benzoate complex, A. Subsequent \textit{ortho} C–H bond activation affords a 5-membered metallacycle intermediate B, alkyne insertion forms a 7-membered metallacycle, C. Then, C undergoes decarboxylation to form a 5-membered metallacycle intermediate D rather than reductive elimination that affords the isocoumarin product. Subsequently, the second alkyne insertion and reductive elimination occur to produce 12. In our case, the product is formed when 1 loses CONHMe followed by coupling of two equivalents of 2 to the resulting benzene ring.

\textbf{Figure A1.3.} Plausible mechanism for the formation of 12\textsuperscript{3}
References


APPENDIX 2

Substrate Scope with [Cp*Ir(NHC)(H₂O)₂](OTf)₂ Catalyst with AgOAc as External Metal Oxidant

Scheme A2.1. Optimized conditions for the [Cp*Ir(NHC)(H₂O)₂](OTf)₂-catalyzed coupling of Benzamides with Alkynes

After testing different catalysts and oxidants, the optimized conditions for the Cp*Ir(NHC)(H₂O)₂]OTf₂-catalyzed isoquinolone synthesis included a 1:1 ratio benzamide:alkyne, 5 mol% 5, and 2 equiv AgOAc in cyclohexane at 60 °C or 90 °C under air for 16 h. The [Cp*Ir(NHC)(H₂O)₂](OTf)₂-catalyzed coupling of N-substituted benzamides with diphenylacetylene (Scheme A2.2) and N-Methylbenzamide derivatives with diphenylacetylene (Scheme A2.3) was investigated under these optimized reaction conditions. Finally various alkynes, including diphenylacetylene, 1,2-bis(4-methylphenyl)ethyne, 1,2-bis(4-methoxyphenyl)ethyne, bis[4-(trifluoromethyl)phenyl]acetylene, phenyl acetylene, 1-phenyl-1-pentyne, 1-phenyl-1-propyne, 4-octyne, 2-butyne, 3-hexyne were reacted with N-Methylbenzamide (Scheme A2.4).
Scheme A2.2. Substrate Scope of [Cp*Ir(NHC)(H₂O)₂](OTf)₂-Catalyzed Coupling of Benzamides with Diphenylacetylene: ¹H NMR Yields

Yields as calculated by ¹H NMR spectroscopy of crude reaction mixture in CDCl₃. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard. Yield is presented as the average of three runs. Error represents the standard deviation. ¹Average of two runs. ²Reaction was performed at 60 °C. ³Value presented as a single measurement.
Scheme A2.3. Substrate Scope of the [Cp*Ir(NHC)(H₂O)₂](OTf)₂-Catalyzed Coupling of N-Methylbenzamide Derivatives with Diphenylacetylene: ¹H NMR Yields

\[ \text{R} + \text{Ph} = \text{Ph} + 2\text{AgOAc} \xrightarrow{5 \text{ mol} \% \text{Ir}, 90 \degree \text{C}, \text{cyclohexane, } 16 \text{ h}} \text{R} \]

95(5)%; 94(2)%; 46(1)%; 7(1)%

97(3)%; 74(8)%; 87(3)%; 66(5)%

a Yields as calculated by ¹H NMR spectroscopy of crude reaction mixture in CDCl₃. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard. Yield is presented as the average of three runs. Error represents the standard deviation. b Average of two runs. c Reaction was performed at 60 °C. d NMR solvent: (CD₃)₂CO. e Value presented as a single measurement.
Scheme A2.4. Substrate Scope of the [Cp*Ir(NHC)(H₂O)₂](OTf)₂-Catalyzed Coupling of N-Methylbenzamide with Diphenylacetylene: ¹H NMR Yields

> Yields as calculated by ¹H NMR spectroscopy of crude reaction mixture in CDCl₃. Mesitylene or 1,3,5-trimethoxybenzene were used as the internal standard. Yields are presented as the average of three runs. Error represents the standard deviation. *Average of two runs. **Reaction was performed at 60 °C. ***Two isomers were observed by ¹H NMR. ****Only one isomer could be quantified.
[Cp*Ir(NHC)(H₂O)₂](OTf)₂ catalysts was successfully employed in the coupling of benzamide derivatives (1) with alkyne substrates (2). The catalytic system proved not only effective for the conversion of diphenylacetylene, but also for a variety of arylaryl-, or unsymmetrical phenylalkyl- substituents on the alkyne. However, alkylalkyl- substituted acetylenes and phenyl acetylene were not successfully converted to product. Both electron-rich and electron poor substituents on diphenylacetylene and N-methylbenzamide were successfully reacted yielding the corresponding products in moderate to high yields. The low yields of N-methyl-4-nitrobenzamide can be attributed to the low solubility of the benzamide and isoquinolone product in CDCl₃ and (CD₃)₂CO. Furthermore, benzamide bearing hydrogen or different groups such as N-alkyl, N-benzyl, or N-aryl derivatives were successfully reacted with diphenylacetylene. However, the later resulted in low yields of the desired isoquinolone product, which may suggest that steric play an important role in the reaction. No apparent trend was observed when changing electronics on the benzamide and the diphenylacetylene.
General Procedure for [Cp*Ir(NHC)(H2O)2](OTf)2 Catalyzed Isoquinolone Synthesis

To a 3 mL storage tube, the corresponding benzamide (0.20 mmol, 1 equiv), solid alkyne (0.20 mmol, 1 equiv) AgOAc (0.40 mmol, 2 equiv), [Cp*Ir(NHC)(H2O)2](OTf)2 (0.01 mmol, 5 mol %), and 1.0 mL of cyclohexane were added. If the alkyne was a liquid, it was added after the addition of 1.0 mL of cyclohexane. The reaction mixture was heated at 90 °C for 16 h. The reaction was cooled, diluted with dichloromethane, and filtered through Celite. Solvent was removed in vacuo and the resulting crude product and the corresponding amount of internal standard (1,3,5-trimethoxybenzene or mesitylene) were dissolved in 0.5 mL of chloroform-d. Percent yield was calculated by the ratio of product:i.s. based on their respective peak integrations.
APPENDIX 3

[Cp*Ir(NHC)(H₂O)₂](OTf)₂: Scope and Mechanistic Evaluation Using AgOAc as External Metal Oxidant

The kinetics of the reaction catalyzed by 5 were also explored in order to obtain information about the reaction mechanism and compare it to the mechanism of the reaction catalyzed by 4 under aerobic conditions. The reaction of 1 with 2 catalyzed by 5 was monitored over time (Scheme A3.1). Isoquinolone (3) formation and N-methylbenzamide (1) consumption were determined by ¹H NMR spectroscopy of crude reaction mixture in CDCl₃ against an internal standard (1,3,5-trimethylbenzene or 1,3,5-trimethoxybenzene). The reactions were run in triplicates and the error is presented as the standard deviation of the samples. The reaction was monitored over the course of 3 h (10800 s). Isoquinolone formation follows first order kinetics (Figure A3.1) with a $k_{obs} = 5(1) \times 10^{-4}$ s⁻¹ and 1 consumption also follows first order kinetics with a $k_{obs} = 5(2) \times 10^{-4}$ s⁻¹. The reaction rate was determined by the method of initial rates (Figure A3.2). A rate of $2.6(1) \times 10^{-5}$ M/s was obtained from the initial rates plot, when the reaction was monitored over the course of 20 mins (1200 s).

Scheme A3.1. [Cp*Ir(NHC)(H₂O)₂](OTf)₂-Catalyzed Coupling of N-Methylbenzamide with Diphenylacetylene
Figure A3.1. Kinetic plot for the \([\text{Cp}^*\text{Ir(NHC)}(\text{H}_2\text{O})_2](\text{OTf})_2\)-catalyzed coupling of \(N\)-methylbenzamide with diphenylacetylene. Diamonds represent the [Total] = [1] + [3], squares represent 1 consumption, circles represent 3 formation. Maximum [3] = 0.20 M. Reaction conditions: 0.2 mmol \(N\)-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.01 mmol 5 in 1 mL cyclohexane at 90 °C. Respective \(k_{\text{obs}}\) were obtained using exponential curve fits defined as \(y = m_1 + m_2(1 - e^{m_3x}).\)
Figure A3.2. Initial rates plot for the [Cp*Ir(NHC)(H₂O)₂](OTf)₂-catalyzed coupling of N-methylbenzamide with diphenylacetylene. Maximum [3] = 0.2 M. Reaction conditions: 0.2 mmol N-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.01 mmol 5 in 1 mL cyclohexane at 90 °C. Rate was determined by using the linear fit. The order with respect to catalyst 5 was determined utilizing the method of initial rates. The concentration of [5] was varied from 5 mM (2.5 mol%), 10 mM (5 mol%), and 20 mM (10 mol%) and the formation of 3 was monitored over time (Figure A3.3) for 20 mins (1200 s). Data suggests that catalyst 5 follows first order as a plot of log(Rate) versus log[5] shows a straight line with a slope of 0.8(3).
**Initial Rates at Various [Cp*Ir(NHC)(H₂O)₂]OTf₂ Loadings**

![Graph showing initial rates at various loadings](image)

**Figure A3.3.** Initial rates plots for the [Cp*Ir(NHC)(H₂O)₂]OTf₂-catalyzed coupling of N-methylbenzamide with diphenylacetylene at various [5]. Maximum [3] = 0.2 M. Reaction conditions: 0.2 mmol N-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.005 mmol (circles), 0.01 mmol (squares), or 0.02 mmol (diamonds) 5 in 1 mL cyclohexane at 90 °C. Rates were determined by using a linear fit.
Order with Respect to $\left[ \text{Cp}^*\text{Ir}(\text{NHC})(\text{H}_2\text{O})_2 \right] (\text{OTf})_2$

**Figure A3.4.** Plot of log(Rate) versus log[5]. The slope of the graph suggests a first order with respect to catalyst 5.

After obtaining the kinetic plot and the initial rates plot for the reaction between 1 and 2 catalyzed by 5 (Scheme A3.1), the deuterated version of 1 was synthesized following the procedure on Scheme A3.2.
Scheme A3.2. \( N \)-Methyl-2,3,4,5,6-pentadeuterobenzamide Synthesis from 2,3,4,5,6-Pentadeuterobenzoyl Chloride

The reaction of 1\( \text{D}_5 \) with 2 catalyzed by 5 was monitored over time for a period of 3 h (10800 s) (Scheme A3.2) and isoquinolone yield was determined by \(^1\)H NMR spectroscopy of crude reaction mixture in CDCl\(_3\) against an internal standard (1,3,5-trimethylbenzene or 1,3,5-trimethoxybenzene). The reactions were run in triplicates and the error is presented as the standard deviation of the samples. The reaction follows first order kinetics (Figure A3.5) with a \( k_{\text{obs}} = 3(1) \times 10^{-4} \text{ s}^{-1} \), and the reaction rates were be determined by the method of initial rates (Figure A3.6). A rate of 1.9(2) \times 10^{-5} \text{ M/s} was obtained from our initial rates plot when the reaction was monitored for a period of 20 mins (1200 s).

Scheme A3.3. [Cp*Ir(NHC)(H\(_2\)O)\(_2\)](OTf)\(_2\)-Catalyzed Coupling of \( N \)-Methyl-2,3,4,5,6-pentadeuterobenzamide with Diphenylacetylene
Figure A3.5. Kinetic plot for the \([\text{Cp}^\ast\text{Ir}(\text{NHC})(\text{H}_2\text{O})_2](\text{OTf})_2\)-catalyzed coupling of \(N\)-methyl-2,3,4,5,6-pentadeuterobenzamide with diphenylacetylene. Maximum \([3-\text{D}_4]\) = 0.20 M. Reaction conditions: 0.2 mmol \(N\)-methyl-2,3,4,5,6-pentadeuterobenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.01 mmol 5 in 1 mL cyclohexane at 90 °C. The \(k_{\text{obs}}\) was obtained using the exponential rise curve fit defined as \(y = m_1 + m_2(1 - e^{m_3x})\).
Figure A3.6. Initial rates plot for the \([\text{Cp}^*\text{Ir(NHC)}(\text{H}_2\text{O})_2](\text{OTf})_2\)-catalyzed coupling of \(N\)-methyl-2,3,4,5,6-pentadeuterobenzamide with diphenylacetylene. Maximum \([3-\text{D}_4]\) = 0.2 M. Reaction conditions: 0.2 mmol \(N\)-methyl-2,3,4,5,6-pentadeuterobenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.01 mmol 5 in 1 mL cyclohexane at 90 °C. Rate was determined by using a linear fit.

The kinetic isotope effect was studied for the reaction of 1 (and 1-Ds) and 2 catalyzed by 5. The initial rate plots were utilized to obtain the rate constant for both reactions (Scheme A3.4, Figure A3.7). A KIE value of 1.4(1) was obtained. This small KIE value, compared to literature values, suggests the possibility of the C-H activation step not being part of the rate determining step.
Scheme A3.4. [Cp*Ir(NHC)(H₂O)](OTf)₂-Catalyzed Coupling of N-Methylbenzamide or N-Methyl-2,3,4,5,6-pentadeuterobenzamide with Diphenylacetylene

Figure A3.7. Initial rates plots for the [Cp*Ir(NHC)(H₂O)](OTf)₂-catalyzed coupling of N-methylbenzamide (circles) or N-methyl-2,3,4,5,6-pentadeuterobenzamide (squares) with diphenylacetylene. Maximum [3] or [3-D₄] = 0.2 M. Reaction conditions: 0.2 mmol N-methylbenzamide or N-methylbenzamide-D₅, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.01 mmol 5 in 1 mL cyclohexane at 90 °C. Rates were determined by using a linear fit.
In order to obtain further information about our catalytic system we compared the reaction rates when oxidant and catalyst are changed (Table A3.1). Reaction rates were determined for the catalytic reaction utilizing Cu(OAc)$_2$·H$_2$O as the external oxidant with catalyst 5 (Scheme A3.5, Figure A3.8, Table A3.1, Entry 2) and for the catalytic reaction with catalysts 7 and 13 (Scheme A3.6, Table A3.1, Entries 3 and 4). Substitution of silver acetate for copper acetate showed a two-fold increase in rate (Table A3.1, Entry 2). When the N-Heterocyclic carbene (NHC) ligand was replaced by a water molecule an increase in rate was observed (Table A3.1, Entry 3, Figure A3.9). This suggests that the additional coordination site facilitates the reaction. Lastly, when catalyst 7 was employed, a decrease (15 times smaller) in the rate was observed (Table A3.1, Entry 4, Figures A3.10 and A3.11). This suggests that substrate binding is less favorable when a stronger coordinating ligand like acetate is part of the catalyst’s coordination sphere.

**Scheme A3.5.** [Cp*Ir(NHC)(H$_2$O)$_2$](OTf)$_2$-Catalyzed Coupling of N-Methylbenzamide with Diphenylacetylene: Copper Acetate as Oxidant
Scheme A3.6. \([\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3](\text{OTf})_2\) or \([\text{Cp}^*\text{Ir}(\text{NHC})(\text{OAc})][\text{PF}_6]\)-Catalyzed Coupling of \(N\)-Methylbenzamide with Diphenylacetylene

Table A3.1. Reaction Rates for Different Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(<a href="%5Ctext%7BOTf%7D">\text{Cp}^*\text{Ir}(\text{NHC})(\text{H}_2\text{O})_2</a>_2) (5)</td>
<td>AgOAc</td>
<td>(2.6(1) \times 10^{-5} \text{ M/s})</td>
</tr>
<tr>
<td>2</td>
<td>(<a href="%5Ctext%7BOTf%7D">\text{Cp}^*\text{Ir}(\text{NHC})(\text{H}_2\text{O})_2</a>_2) (5)</td>
<td>Cu(OAc)$_2$·H$_2$O</td>
<td>(6.5(6) \times 10^{-5} \text{ M/s})</td>
</tr>
<tr>
<td>3</td>
<td>(<a href="%5Ctext%7BOTf%7D">\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3</a>_2) (4)</td>
<td>AgOAc</td>
<td>(k_{\text{obs}}, 4.3(4) \times 10^{-4} \text{ s}^{-1})</td>
</tr>
<tr>
<td>4</td>
<td>([\text{Cp}^*\text{Ir}(\text{NHC})(\text{OAc})][\text{PF}_6]) (7)</td>
<td>AgOAc</td>
<td>(1.7(2) \times 10^{-6} \text{ M/s})</td>
</tr>
</tbody>
</table>

Reactions were run with 0.2 mmol N-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol oxidant and 0.01 mmol catalyst in 1 mL of cyclohexane at 90 °C.
Figure A3.8. Initial rates plot of the [Cp*Ir(NHC)(H₂O)₂](OTf)₂-catalyzed coupling of N-methylbenzamide with diphenylacetylene: copper acetate as oxidant. Maximum [3] = 0.2 M. Reaction conditions: 0.2 mmol N-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol Cu(OAc)₂·H₂O, and 0.01 mmol 5 in 1 mL cyclohexane at 90 °C. Reactions were monitored over the course of 20 mins (1200 s). Rate was determined by using a linear fit.
Figure A3.9. Kinetic plot of the \([\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3](\text{OTf})_2\)-catalyzed coupling of \(N\)-methylbenzamide with diphenylacetylene. Maximum \([3]\) = 0.2 M. Reaction conditions: 0.2 mmol \(N\)-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.01 mmol 4 in 1 mL cyclohexane at 90 °C. Reactions were monitored over the course of 10 h (36000 s). The \(k_{\text{obs}}\) was obtained using the exponential rise curve fit defined as \(y = m_1 + m_2(1 - e^{m_3x})\).
**Figure A3.10.** Kinetic plot of the [Cp*Ir(NHC)(OAc)][PF₆]-catalyzed coupling of N-methylbenzamide with diphenylacetylene. Maximum [3] = 0.2 M. Reaction conditions: 0.2 mmol N-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.01 mmol 7 in 1 mL cyclohexane at 90 °C. Reactions were monitored over the course of 80 h. The $k_{\text{obs}}$ was obtained using the exponential rise curve fit defined as $y = m_1 + m_2(1 - e^{m_3x})$. 

$$k_{\text{obs}} = 7(1) \times 10^{-2} \text{ h}^{-1}$$
Figure A3.11. Initial rates plot of the [Cp*Ir(NHC)(OAc)][PF$_6$]-catalyzed coupling of $N$-methylbenzamide with diphenylacetylene. Maximum [3] = 0.2 M. Reaction conditions: 0.2 mmol $N$-methylbenzamide, 0.2 mmol diphenylacetylene, 0.4 mmol AgOAc, and 0.01 mmol 7 in 1 mL cyclohexane at 90 °C. Reactions were monitored over the course of 6 h (21600 s). Rate was obtained by using a linear fit.
Synthesis of *N*-Methyl-2,3,4,5,6-pentadeuterobenzamide\(^1\): A white solid was obtained. To a round bottom flask with a stirring bar, 2,3,4,5,6-pentadueterobenzoyl chloride (1 equiv), K\(_2\)CO\(_3\) (2.5 equiv), and 20 mL dry diethyl ether were added and mixed for a few minutes (~5 min). MeNH\(_3\)HCl (1.5 equiv) were added and the reaction was left stirring at room temperature. The reaction was monitored by TLC until the benzoyl chloride was converted to product. Then, the reaction was diluted with Ethyl Acetate (50 mL), washed with DI-H\(_2\)O and extracted 3 x with Ethyl Acetate (30 mL). The resulting solution was dried with Na\(_2\)SO\(_4\), filtered and solvent was removed under vacuum. The resulting product was used without further purification. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm) \(\delta\) 7.56 (bs, 1H), 2.87 (d, 3H, \(J = 4\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), ppm) \(\delta\) 168.39, 134.00, 130.42 (t, \(J = 25\)), 127.53 (t, \(J = 24\)), 126.36 (t, \(J = 24\)), 26.48.

**General Procedure for Rate Determination**

To a 3 mL storage tube, *N*-methylbenzamide (0.20 mmol, 1 equiv), diphenylacetylene (0.20 mmol, 1 equiv), AgOAc (or Cu(OAc)\(_2\)·2H\(_2\)O) (0.40 mmol, 2 equiv), the respective Cp*Ir(III)-catalyst (0.01 mmol, 5 mol %), and 1.0 mL of cyclohexane were added. The reaction mixture was heated at 90 °C for different times. The reaction was cooled, diluted with dichloromethane and filtered through Celite. Solvent was removed *in vacuo* and the resulting crude product and the corresponding amount of internal standard (1,3,5-trimethoxybenzene, 0.067 mmol) were dissolved in 0.5 mL of chloroform-\(d\). Percent yield was calculated by the ratio of product:i.s. based on their respective peak integrations. Individual reactions were performed per time point. The kinetic plots were plotted utilizing KaleidaGraph. Respective rates were obtained using the exponential fits defined as \(y = m_1 + m_2(1 - e^{m_3x})\) or linear fits.
Determination of Rate Constants and the Kinetic Isotope Effect

To 3 mL storage tubes, N-methylbenzamide or N-methyl-2,3,4,5,6-pentadeuterobenzamide (1-H/D, 0.2 mmol, 1 equiv), diphenylacetylene (2, 0.2 mmol, 1 equiv), AgOAc (0.4 mmol, 2 equiv), [Cp*Ir(NHC)(H₂O)₂](OTf)₂ (5, 0.01 mmol, 5 mol %), and 1 mL of cyclohexane were added. The tubes were sealed and heated at 90 °C for different times. The reactions were allowed to cool to room temperature and filtered over celite with dichloromethane. Solvent was removed in vacuo and the resulting crude product and 0.067 mmol of internal standard, 1,3,5-trimethoxybenzene, were dissolved in 0.5 mL of chloroform-d. Percent yield was calculated by ¹H NMR spectroscopy utilizing the ratio of product:i.s. based on their respective peak integrations. Individual reactions were performed in triplicate per time point. The kinetic plots were plotted utilizing KaleidaGraph. Respective rates were obtained using the linear fit.

References