Synthesis of nitrogen heterocycles via palladium-catalyzed annulation of acetylenes

Kevin Ray Roesch
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Synthesis of nitrogen heterocycles via palladium-catalyzed annulation of acetylenes

by

Kevin Ray Roesch

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of
DOCTOR OF PHILOSOPHY

Major: Organic Chemistry
Major Professor: Richard C. Larock

Iowa State University
Ames, Iowa
1999
Graduate College
Iowa State University

This is to certify that the Doctoral dissertation of

Kevin Ray Roesch

has met the dissertation requirement of Iowa State University

Signature was redacted for privacy.

Major Professor
Signature was redacted for privacy.

For the Major Program
Signature was redacted for privacy.

For the Graduate College
To Julie, for always being there through the best and worst of times (and for putting up with me), and my parents for all of the support from the beginning. Thank you.
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ACKNOWLEDGMENTS
LIST OF ABBREVIATIONS

Ac  acetyl
aq  aqueous
Bn  benzyl
br  broad
brm  broad multiplet
brs  broad singlet
Bu  butyl
t-Bu  tert-butyl
cat.  catalytic
concd  concentrated
d  doublet
dba  dibenzylideneacetone
dd  doublet of doublets
ddd  doublet of doublets of doublets
ddddd  doublet of doublets of doublets of doublets
dm  doublet of multiplets
DMA  N,N-dimethylacetamide
DMF  N,N-dimethylformamide
DMSO  dimethyl sulfoxide
dq  doublet of quartets
dt  doublet of triplets
eq  equation
equiv  equivalent
Et  ethyl
h  hour(s)
HRMS
Hz
IR
m
Me
mL
mol
mp
MS
NMR
o
p
Ph
q
s
t
TBAC
td
tq
tert
Ts
tt
high resolution mass spectroscopy
Hertz
infrared
multiplet
methyl
milliliters
mole(s)
melting point
mass spectrometry
nuclear magnetic resonance
ortho
para
phenyl
quartet
singlet
triplet
tetra-n-butylammonium chloride
triplet of doublets
triplet of quartets
tertiary
p-toluenesulfonyl
triplet of triplets
ABSTRACT

A wide variety of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[f]isoquinoline, pyridine, and pyridine heterocycles have been prepared via annulation of internal acetylenes with the tert-butylimines of o-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst. The best results are obtained by employing 5 mol % Pd(OAc)$_2$, an excess of the alkyne, one equivalent of sodium carbonate as a base, and 10 mol % PPh$_3$ in DMF as the solvent. This annulation methodology is particularly effective for aryl- or alkenyl-substituted alkynes. Trimethylsilyl-substituted alkynes also undergo this annulation process to afford mono-substituted heterocyclic products. Other acetylenes, however, fail to undergo this annulation process.

Mono-substituted isoquinolines and pyridines have been prepared via coupling of terminal acetylenes with the tert-butylimines of o-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst and subsequent copper-catalyzed cyclization of the intermediate iminoalkynes. In addition, isoquinolines have been prepared in excellent yields via copper-catalyzed cyclization of iminoalkynes. The choice of cyclization conditions is dependent upon the nature of the terminal acetylene that is employed, as only aryl and alkenyl acetylenes cyclize under the palladium-catalyzed reaction conditions that have been developed. However, aryl, vinylic, and alkyl substituted acetylenes undergo palladium-catalyzed coupling and subsequent copper-catalyzed cyclization in excellent yields. Finally, the total synthesis of the isoquinoline natural product
decumbenine B has been accomplished in 7 steps and 20% overall yield by employing this palladium-catalyzed coupling and cyclization methodology.

A wide variety of substituted isoindolo[2,1-a]indoles have been prepared via annulation of internal alkynes by imines derived from o-iodoanilines in the presence of a palladium catalyst. This methodology provides an extremely efficient route for the synthesis of these tetracyclic heterocycles from readily available starting materials. The mechanism of this interesting annulation process appears to involve either electrophilic palladation of a σ-palladium intermediate onto the adjacent aromatic ring of the internal alkyne, or oxidative addition of the neighboring aryl carbon-hydrogen bond. A variety of internal acetylenes have been employed in this annulation process in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring.
GENERAL INTRODUCTION

Transition metal-catalyzed processes have proved to be extremely effective in organic synthesis. More specifically, palladium-catalyzed methodology has been extensively utilized in recent years. The ability to create multiple carbon-carbon bonds from simple starting materials, the regio- and stereospecificity of the reactions, the exceptional tolerance for functionality, the insensitivity to air or moisture, and the procedural ease with which the reactions can be carried out have all contributed to the success of this methodology in organic synthesis.

The Larock group has recently shown in a number of recent papers that palladium-catalyzed internal alkyne annihilation methodology can be effectively employed for the synthesis of a variety of carbo- and heterocycles, such as indoles, benzofurans, benzopyrans, isocoumarins, indenones, α-pyrroles, and polycyclic aromatic hydrocarbons. In this dissertation, the scope of this alkyne annihilation methodology has been expanded by employing tert-butylimines derived from o-iodobenzaldehydes and 3-halo-2-alkenals in internal and terminal alkyne annulations to provide access to a variety of substituted isoquinolines, tetrahydroisoquinoline, 5,6-dihydrobenz[f]isoquinoline, pyridine, and pyridine heterocycles. In addition, substituted isoindolo[2,1-a]indole heterocycles have been prepared in good to excellent yields via annulation of internal alkynes by imines derived from o-iodoanilines. The author of this manuscript was the primary investigator and the author of each of the papers reported in this dissertation.
Dissertation Organization

This dissertation is divided into three chapters. Each of the chapters presented herein is written by following the guidelines for a full paper in the Journal of Organic Chemistry and are composed of an abstract, introduction, results and discussion, conclusion, experimental, acknowledgment, and references.

Chapter 1 discusses the synthesis of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[f]isoquinoline, pyridine, and pyridine heterocycles by the palladium-catalyzed iminoannulation of internal alkynes by employing tert-butylimines derived from o-iodobenzaldehydes and 3-halo-2-alkenals. Interestingly, when employing trimethylsilyl-substituted alkynes, monosubstituted heterocycles are obtained. A mechanism involving desilylation of the acetylene and subsequent palladium-catalyzed coupling and cyclization of the intermediate iminoalkynes is proposed.

Chapter 2 presents an extension of the internal alkyne methodology described in Chapter 1. The palladium-catalyzed coupling of terminal acetylenes with the tert-butylimines of o-iodobenzaldehydes and 3-halo-2-alkenals with subsequent copper-catalyzed cyclization of the intermediate iminoalkynes affords a variety of isoquinoline and pyridine heterocycles. The mechanism of this interesting isoquinoline synthesis has been studied and will be presented in detail. In addition, the total synthesis of the isoquinoline natural product decumbenine B will be discussed.

Chapter 3 describes the synthesis of substituted isoindolo[2,1-a]indole heterocycles via annulation of internal acetylenes with imines derived from o-
iodoanilines in the presence of a palladium catalyst. This reaction provides a novel and efficient route to the isoindole skeleton from simple and readily available starting materials. The mechanism of this remarkable process is believed to proceed via (1) reduction of Pd(OAc)$_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and insertion of the acetylene, (4) addition of the vinylpalladium intermediate across the carbon-nitrogen double bond, (5) either electrophilic palladation of the σ-palladium intermediate onto the adjacent aromatic ring, or oxidative addition of the neighboring aryl carbon-hydrogen bond to the σ-palladium intermediate to form a Pd(IV) intermediate, and subsequent elimination of HI by base, and (6) regeneration of the Pd(0) catalyst by reductive elimination to form the isoindole.

Finally, all of the $^1$H and $^{13}$C spectra for the imine starting materials and the palladium-catalyzed reaction products have been compiled in appendices A-C following the general conclusions for this dissertation.

References


CHAPTER 1. SYNTHESIS OF ISOQUINOLINES AND PYRIDINES VIA PALLADIUM-CATALYZED IMINOANNULATION OF INTERNAL ALKYNES

A paper to be submitted to the Journal of Organic Chemistry

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Abstract

A wide variety of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[f]isoquinoline, pyridine, and pyridine heterocycles have been prepared via annulation of internal acetylenes with the tert-butylimines of o-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst. The best results are obtained by employing 5 mol % Pd(OAc)$_2$, an excess of the alkyne, one equivalent of sodium carbonate as a base, and 10 mol % PPh$_3$ in DMF as the solvent. This annulation methodology is particularly effective for aryl- or alkenyl-substituted alkynes. Trimethylsilyl-substituted alkynes also undergo this annulation process to afford mono-substituted heterocyclic products. Other acetylenes, however, fail to undergo this annulation process.
Introduction

Annulation processes have found numerous applications in organic synthesis, primarily due to the ease with which a wide variety of complicated hetero- and carbocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology can be effectively employed for the synthesis of indoles, benzofurans, benzopyrans, isocoumarins, indenones, polycyclic aromatic hydrocarbons, and α-pyrones (eq 1).

\[
\begin{align*}
\text{Ar} &+ R^1\equiv R^2 \xrightarrow{\text{cat. Pd (0)}} \text{Ar}^X_R^1R^2 \\
\text{base} &
\end{align*}
\]

\(XH = \text{C(CO}_2\text{Et)}_2, \text{NR, O, CO, CO}_2\text{Et}
\)

\(R^1, R^2 = \text{alkyl, aryl, silyl, alkenyl}
\)

The synthesis of isoquinoline heterocycles has received considerable attention in the literature due to the fact that the isoquinoline ring system is present in numerous naturally-occurring alkaloids. Although the classical methods for the synthesis of this important ring system, the Bischler-Napieralski reaction, the Pomeranz-Fritsch reaction, and the Pictet-Spengler reaction have been frequently employed in the total synthesis of isoquinoline alkaloids, they are all quite limited synthetically. For example, all of these methods are based on electrophilic cyclizations of a β-phenylethylamine to form the nitrogen-containing
ring, and therefore suffer the disadvantages of employing strong acids for their ring closure steps, and the synthesis of appropriate starting materials is often difficult. Furthermore, the Bischler-Napieralski and Pictet-Spengler reactions require dehydrogenations of dihydro- and tetrahydroisoquinolines, respectively.

Substituted isoquinoline heterocycles have also been synthesized by employing palladium methodology. For instance, Widdowson reported the synthesis of isoquinoline derivatives from cyclopalladated \( N \)-\( \text{tert} \)-butylarylaldimines in yields from 10 to 56\% (eq 2).\(^\text{10}\) However, this synthesis suffers from the disadvantages that stoichiometric amounts of palladium salts are required for the preparation of the intermediate iminoalkenes, and a final pyrolysis step in a diphenyl ether/mesitylene solvent at 180-200 °C greatly limits the synthetic utility.

Pfeffer has reported the formation of the isoquinolinium salt 1 in 14\% yield, as well as the disubstituted isoquinoline derivative 2 in 60\% yield from a cyclopalladated \( N,N \)-dimethylbenzylamine complex (eq 3).\(^\text{11}\) Moreover, an entirely different heterocycle (4) was obtained by the thermal depalladation of the cationic tetrafluoroborate palladium complex 3 (eq 4). These syntheses also have the
disadvantage that they use stoichiometric amounts of palladium salts for the preparation of the starting cyclopalladated complexes.

Heck has also reported the synthesis of isoquinolinium tetrafluoroborate salts in moderate yields from the reaction of cyclopalladated arylaldimine tetrafluoroborates and internal alkynes (eq 5). In one instance, Heck observed the formation of 3,4-diphenylisoquinoline in 22% yield from the reaction of a cationic, tetrafluoroborate N-tert-butylbenzaldimine palladium complex and diphenylacetylene (eq 6). These two syntheses, however, also suffer from the use of stoichiometric amounts of palladium salts.
Our own interest in this type of annulation reaction has prompted us to investigate a catalytic version of these isoquinoline syntheses. Herein, we report that our catalytic annulation chemistry can also be applied to the synthesis of a wide variety of nitrogen heterocycles including isoquinolines, tetrahydroisoquinolines, 5,6-dihydrobenz[f]isoquinolines, pyrindines, and pyridines. A variety of aryl-, alkenyl-, and silyl-substituted alkynes have been employed in the palladium-catalyzed annulations with tert-butylimines derived from o-iodobenzaldehydes and 3-halo-2-alkenals.

**Results and Discussion**

Our initial studies focused on the palladium-catalyzed annulation of internal alkynes employing the methyl imine of o-iodobenzaldehyde. However, this substrate failed to produce any of the desired isoquinoline even at elevated temperatures. Furthermore, use of the corresponding isopropyl, allyl, and benzyl imines also afforded none of the desired heterocyclic products. The reaction of the α-methylbenzyl imine with diphenylacetylene did produce the desired product, 3,4-diphenylisoquinoline, albeit in low yields (6-11%). By employing the tert-butylimine, however, we were able to obtain substantially improved results with a variety of alkynes, after optimization of the reaction conditions (eq 7).
The reaction of diphenylacetylene and the tert-butylimine of o-iodobenzaldehyde was chosen as the model system for the optimization of this annulation process (eq 8). In the early stages of this work, the reaction conditions that were chosen were similar to the conditions employed in our other alkyne annulation chemistry (Table 1). For example, 0.5 mmol of the tert-butylimine, 1.0 mmol of diphenylacetylene, 0.5 mmol of LiCl, with 0.5 mmol of Na2CO3 as a base in 10 mL of DMF at 100 °C afforded 3,4-diphenylisoquinoline in 76% yield after a 53 hour reaction time (entry 1). By increasing the temperature to 110 °C, the reaction time was reduced, while the yield was comparable to that of entry 1 (entry 2). It was also observed that chloride salts significantly increased the reaction times when employing Na2CO3 as a base (compare entries 1-4 and entry 5). Upon removal of the chloride salts from the reaction mixture, we were able to isolate the desired product in a relatively short reaction time, and in yields comparable to the reactions in which chloride salts were employed (compare entries 1-4 and entry 5).
Table 1. Optimization of the Palladium-catalyzed Formation of 3,4-Diphenylisoquinoline (eq 8).

<table>
<thead>
<tr>
<th>entry</th>
<th>chloride source (equiv)</th>
<th>base (equiv)</th>
<th>10% PPh₃</th>
<th>temp (°C), time (h)</th>
<th>% isolated yield of 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiCl (1)</td>
<td>Na₂CO₃ (1)</td>
<td>-</td>
<td>100, 53</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>LiCl (1)</td>
<td>Na₂CO₃ (1)</td>
<td>-</td>
<td>110, 25</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>LiCl (2)</td>
<td>Na₂CO₃ (1)</td>
<td>-</td>
<td>100, 115</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu₄NCl (1)</td>
<td>Na₂CO₃ (1)</td>
<td>-</td>
<td>100, 86</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>Na₂CO₃ (1)</td>
<td>-</td>
<td>100, 23</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>Na₂CO₃ (1)</td>
<td>+</td>
<td>100, 25</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>NaHCO₃ (1)</td>
<td>+</td>
<td>100, 32</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>NaOAc (1)</td>
<td>+</td>
<td>100, 25</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>K₂CO₃ (1)</td>
<td>+</td>
<td>110, 88</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>1-Pr₂NEt (1)</td>
<td>+</td>
<td>100, 9</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>Et₃N (1)</td>
<td>+</td>
<td>100, 8</td>
<td>76</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>Na₂CO₃ (1)</td>
<td>+</td>
<td>80, 115</td>
<td>70</td>
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<tr>
<td>13</td>
<td>-</td>
<td>Et₃N (1)</td>
<td>+</td>
<td>80, 21</td>
<td>63</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>Na₂CO₃ (1)</td>
<td>+</td>
<td>100, 96</td>
<td>77⁺</td>
</tr>
</tbody>
</table>

*Two mol % Pd(OAc)₂, and 4 mol % PPh₃ were used.
The effect of triphenylphosphine on the reaction was then investigated. The yield of 3,4-diphenylisoquinoline was observed to increase upon addition of a catalytic amount of triphenylphosphine (10 mol %) to the reaction mixture (compare entries 5 and 6). Presumably, the added phosphine disrupts the coordination of the neighboring imine substituent to the palladium atom in the arylpalladium intermediate (see the latter mechanistic discussion). Other inorganic bases were also employed in the reaction with triphenylphosphine. However, poorer yields were observed with other bases, and in the case of K₂CO₃, a significant increase in the reaction time was observed (compare entries 7-9 with entry 6). When tertiary organic amine bases were employed, a reduction in the reaction time was observed, in addition to the yield of the product (entries 10 and 11).

Additional attempts to optimize this annulation process included the investigation of two additional reaction variables. First of all, based on the success with Na₂CO₃ and triphenylphosphine (entry 6), the reaction temperature was lowered to 80 °C in order to determine the effect on the reaction rate and yield (entry 12). Unfortunately, the reduction in the temperature of the reaction was accompanied by an increase in the reaction time, and a decrease in the product yield. Furthermore, since the reaction times were relatively short with the organic amine bases employed, a reaction was run with Et₃N at 80 °C (entry 13). Although the reaction time with this base was relatively short, the yield was significantly less than that with Na₂CO₃ at 100 °C (compare entries 6 and 13).
Finally, in an effort to reduce the amount of the palladium catalyst, one reaction was run in which the amount of Pd(OAc)$_2$ was reduced from 5 mol % to 2 mol % (entry 14). However, both a decrease in the reaction rate as well as the yield was observed. These results have led to the development of the following general reaction procedure for our heterocycle synthesis. One equiv of the tert-butylimine, 2 equiv of the acetylene, 5 mol % of Pd(OAc)$_2$, 10 mol % of PPh$_3$, 1 equiv of Na$_2$CO$_3$ in DMF as the solvent at 100 °C give the best results. We then wanted to determine the scope and limitations of this methodology by annulating a wide variety of acetylenes with a number of aryl and vinylic imines. The results from this study are summarized in Table 2.

The annulation of a variety of aryl-substituted alkynes by the tert-butylimine of o-iodobenzaldehyde (5) has afforded the desired disubstituted isoquinoline heterocycles in moderate to excellent yields with high regioselectivity (Table 2, entries 1-6). The regiochemistry of the products is based on analogy with our previous alkyne annulation chemistry$^{26}$ and comparison of the spectral and physical data for compounds 7$^{11}$ and 8$^{13}$ with those already in the literature.

The annulation of a relatively unhindered diyne and enyne by imine 5 also afforded the anticipated isoquinoline products in good yields, although mixtures of regioisomers were obtained (entries 7-9). This is interesting due to the fact that the products 6-11 were isolated as single regioisomers, while the attempted annulation of other substituted alkynes, namely 4-octyne, 3-hexyne, 4,4-dimethyl-2-butyne, and 3,3-dimethyl-1-phenyl-1-butyne by imine 5 failed to produce any of the
Table 2. Synthesis of Nitrogen Heterocycles by the Pd-Catalyzed Annulation of Internal Acetylenes (eq 7).a

<table>
<thead>
<tr>
<th>entry</th>
<th>imine</th>
<th>alkyne</th>
<th>time (h)</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Imine Structure" /></td>
<td><img src="image2" alt="Ph−HPh" /></td>
<td>24</td>
<td><img src="image3" alt="Product Structure" /></td>
<td>96</td>
</tr>
<tr>
<td></td>
<td><img src="image4" alt="Entry 1" /></td>
<td><img src="image2" alt="Ph−HPh" /></td>
<td></td>
<td><img src="image3" alt="Product Structure" /></td>
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<td><img src="image5" alt="Ph−CO_2Et" /></td>
<td>5</td>
<td><img src="image6" alt="Product Structure" /></td>
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<tr>
<td>3</td>
<td></td>
<td><img src="image7" alt="Ph−Me" /></td>
<td>21</td>
<td><img src="image8" alt="Product Structure" /></td>
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<tr>
<td>4</td>
<td></td>
<td><img src="image9" alt="Ph−Et" /></td>
<td>16</td>
<td><img src="image10" alt="Product Structure" /></td>
<td>93</td>
</tr>
<tr>
<td>entry</td>
<td>imine</td>
<td>alkyne</td>
<td>time (h)</td>
<td>product</td>
<td>% yield</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>-----------------</td>
<td>----------</td>
<td>----------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>5</td>
<td>Ph—=—CH₂OH</td>
<td>7</td>
<td></td>
<td><img src="image1.png" alt="Image" /></td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Ph—=—CH(Me)OH</td>
<td>4</td>
<td></td>
<td><img src="image2.png" alt="Image" /></td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>Ph—=—≡—Ph</td>
<td>25</td>
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<td><img src="image3.png" alt="Image" /></td>
<td>72 + 13</td>
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<tr>
<td>8</td>
<td>Et—=—CH₂</td>
<td>21</td>
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<td><img src="image4.png" alt="Image" /></td>
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<tr>
<td>entry</td>
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<td>alkyne</td>
<td>time (h)</td>
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<td>% yield</td>
</tr>
<tr>
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<td>-------------</td>
<td>--------------</td>
<td>----------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>9</td>
<td>Et=CHC6H4</td>
<td></td>
<td>10</td>
<td>16 + 17</td>
<td>69%</td>
</tr>
<tr>
<td>10</td>
<td>Ph=CHSiMe3</td>
<td></td>
<td>21</td>
<td>18</td>
<td>85%</td>
</tr>
<tr>
<td>11</td>
<td>C6H5=CHSiMe3</td>
<td></td>
<td>78</td>
<td>19</td>
<td>77%</td>
</tr>
<tr>
<td>12</td>
<td>MeO2C8H8</td>
<td>Ph=CH2Ph</td>
<td>24</td>
<td>20 + 21</td>
<td>82%</td>
</tr>
<tr>
<td>entry</td>
<td>imine</td>
<td>alkyne</td>
<td>time (h)</td>
<td>product</td>
<td>% yield</td>
</tr>
<tr>
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Table 2. (continued)

*A representative procedure for the annulation of internal acetylenes: 5 mol % Pd(OAc)$_2$, 10 mol % PPh$_3$, Na$_2$CO$_3$ (0.5 mmol), the acetylene (1.0 mmol), the imine (0.5 mmol), and DMF (10 ml) were placed in a 4 dram vial and were heated at 100 °C for the indicated time. $^b$Isolated in an 85:15 ratio of 14 to 15 as an inseparable mixture of isomers. $^c$Isolated in a 95:5 ratio of 16 to 17 as an inseparable mixture of isomers.
desired heterocycles. Based on the observations of Heck,\textsuperscript{12} it is presumed that multiple alkyne insertion products are being formed with these alkynes, although none of these products have been identified. Alternatively, the presumed vinylpalladium intermediate (see the latter mechanistic discussion) may simply be undergoing beta hydride elimination to allenes.

The annihilation of 1,4-diphenylbutadiyne by imine 5 has been observed to give an unexpected major product bearing the more hindered phenyl group in the 4-position (entry 7). This is in contrast to the regiochemical outcome of much of our other alkyne annihilation chemistry in which the palladium adds to the more hindered end of the alkyne.\textsuperscript{26} The regiochemistry of the products from this annihilation has been confirmed by comparison of the \textsuperscript{1}H NMR spectral properties of compounds 12 and 13 with the spectral properties of 3-phenyl-4-(phenylethynyl)-isoquinoline, which has been isolated as a minor product from the annihilation of imine 5 by phenylacetylene.

This annihilation methodology has also been extended to trimethylsilyl-substituted alkynes. To our surprise, the 3-monosubstituted isoquinolines were isolated from these reactions (entries 10 and 11). These are rather surprising results, since the expected products were either the 3,4-disubstituted products retaining the silyl group, or the corresponding 4-substituted isoquinolines arising from desilylation of the 3,4-disubstituted isoquinolines. Based on the results from an extensive investigation of this reaction, it appears that the trimethylsilyl acetylenes are being desilylated by the base in the reaction (see Scheme 1). The terminal alkynes, which are thus produced, are apparently then undergoing
palladium-catalyzed coupling and subsequent cyclization. A full account of this investigation is presented in chapter 2 of this dissertation (Roesch and Larock, 1999).

Scheme 1

Surprisingly, when a more electron-rich imine, such as 20 or 26, was employed in a reaction that previously gave only a single regioisomer, a mixture of regioisomers was observed (compare entries 13, 14, and 16 with entries 2 and 3). In the case of the imine 30 bearing an electron-withdrawing group, only a single regioisomer were obtained (entry 18), with hydrolysis of the imines presumably occurring during the work-up of the reaction.

This annulation chemistry has also been extended to vinylic imines. For example, the tetrahydroisoquinoline derivatives 34-37 have been synthesized by
annulation with the cyclic vinylic imine 33 (entries 19-22). In addition, the pyridine derivatives 39-41 and the dihydrobenzoisoquinoline derivatives 43 and 44 have been synthesized from vinylic imines 38 and 42, respectively (entries 23-27). Finally, the acyclic vinylic imines 45 and 49 have also been successfully employed in this annulation process to produce highly substituted pyridine derivatives (entries 28-32). It is interesting to note that the compounds derived from the vinylic imines were all isolated as single regioisomers. Surprisingly, the imine 49 works quite well in this pyridine synthesis, whereas the corresponding ethyl ester (Z-PhCl=CHCO₂Et) fails to undergo annulation of this same alkyne to produce the corresponding α-pyrone, a process with which we have recently had considerable success.⁶

We propose a mechanism for this process which is similar to our other alkyne annulation chemistry (Scheme 2). Specifically, oxidative addition of the aryl or vinylic halide to Pd(0) produces an organopalladium intermediate, which then inserts the acetylene, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a 7-membered palladacyclic ammonium salt. Subsequent reductive elimination produces a tert-butylisoquinolinium salt and regenerates Pd(0). As previously suggested by Heck,¹² the tert-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.
Scheme 2

Conclusion

An efficient, palladium-catalyzed synthesis of nitrogen heterocycles, including isoquinolines, tetrahydroisoquinolines, 5,6-dihydrobenz[7]isoquinolines, pyridines, and pyridines has been developed. A wide variety of aryl acetylenes undergo this process in moderate to excellent yields, with high regioselectivity being observed in most cases. In addition, a relatively unhindered diyne and enyne have been employed. However, mixtures of regioisomers were observed in both cases. By employing trimethylsilyl-containing acetylenes, we have been able to synthesize monosubstituted heterocyclic products.
Experimental Section

General. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic KMnO$_4$ solution [3 g of KMnO$_4$ + 20 g of K$_2$CO$_3$ + 5 mL of NaOH (5%) + 300 mL of H$_2$O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na$_2$CO$_3$, K$_2$CO$_3$, NaOAc, NaHCO$_3$, LiCl, DMF, THF, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh$_3$ was donated by Kawaken Fine Chemicals Co. Ltd. 2-Iodobenzyl alcohol, piperonal, tert-butylamine, diphenylacetylene, ethyl phenylpropiolate, 1-phenyl-1-propyne, 1-phenyl-2-(trimethylsilyl)acetylene, (1-cyclohexen-1-ylethynyl)trimethylsilane, Et$_3$N, and i-Pr$_2$NEt were purchased from Aldrich Chemical Co., Inc. 4,5-Dimethoxy-2-iodobenzoic acid and dimethyl iodoterephthalate were purchased from Trans World Chemical Co.
propyn-1-ol and n-Bu$_4$NCl were purchased from Lancaster Synthesis, Inc. 1-
Phenyl-1-butyne, 1,4-diphenylbutadiyne, 2-methyl-1-hexen-3-yne, 4-phenyl-3-
butyn-2-ol, and 1-butynyl-1-cyclohexanol was purchased from Farchan Chemical
Co. 2-Iodobenzaldehyde,$^4$ 2-bromopiperonal,$^1$ 2-bromocyclohexene-1-
carboxaldehyde,$^5$ 2-bromocyclopentene-1-carboxaldehyde,$^6$ 1-bromo-3,4-
dihydronaphthalene-2-carboxaldehyde,$^7$ (Z)-3-iodo-2-methyl-3-phenyl-2-
propenal,$^8$ and (Z)-3-iodo-3-phenyl-2-propenal,$^9$ were prepared according to
previous literature procedures. The following starting materials were prepared as
indicated.

1-(1-Butynyl)cyclohexene. To a solution of 1-(1-butynyl)cyclohexanol
(2.00 g, 13.14 mmol) in 50 mL of pyridine was added methanesulfonyl chloride
(4.14 g, 36.14 mmol). The mixture was stirred for 60 h at room temperature and
water (50 mL) was then added. The aqueous layer was extracted with ether (4 x 25
mL) and the extracts were combined and washed with 5% HCl, saturated aqueous
NaHCO$_3$, water and brine, and then dried (Na$_2$SO$_4$) and filtered. The solvent was
removed under reduced pressure and the resulting oil was purified by flash column
chromatography using 10:1 hexanes/EtOAc to afford 1.3 g (74%) of the desired
compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.13 (t, $J$ = 7.5 Hz, 3H), 1.50-1.64 (m,
4H), 2.04-2.10 (m, 4H), 2.28 (q, $J$ = 7.5 Hz, 2H), 5.97-6.00 (m, 1H); $^{13}$C NMR
(CDCl$_3$) $\delta$ 13.0, 14.2, 21.7, 22.5, 25.6, 29.6, 81.7, 88.7, 121.0, 133.2.

2-Iodopiperonal. 2-Iodopiperonal was prepared according to a modified
literature procedure.$^{19}$ To a solution of N-(6-bromobenzo[1,3]dioxol-5-
ylmethylene)-tert-butylamine (1.50 g, 5.28 mmol) in 50 mL of ether at -78 °C was added 2.3 mL of n-BuLi (2.5 M in hexanes) dropwise over a five minute period. The solution was stirred for 30 min at -78 °C and a solution of I₂ (2.68 g, 10.6 mmol) in 5 mL of THF was added dropwise. The resulting solution was warmed to room temperature and stirred for 1 h. The reaction mixture was then quenched with saturated aqueous NH₄Cl (25 mL), and solid NaHSO₃ was added until the solution was decolorized. The layers were then separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄) and filtered. The solvent was removed under reduced pressure to afford 0.80 g of the crude aldehyde. Recrystallization from 95% EtOH afforded 0.54 g (37%) of the desired compound with spectral properties identical to those previously reported.²⁰

2-Iodobenzene-1,4-dicarbaldehyde. To a solution of dimethyl iodoterephthalate (2.56 g, 8 mmol) in hexanes (25 mL) and THF (25 mL) at -78 °C was added 32 mL of DIBAL-H (32 mmol, 1M in hexanes) dropwise. The solution was stirred for 6 h at -78 °C and then quenched with saturated aqueous NH₄Cl (40 mL). The mixture was warmed to room temperature and the precipitate was destroyed with 2M HCl (50 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 40 mL). The extracts were washed with 5% NaHCO₃ and brine, and then dried (Na₂SO₄) and filtered. The solvent was removed under reduced pressure to afford the crude diol, which was then oxidized without further purification. The crude diol and PCC (2.53 mmol) were stirred at room temperature in CH₂Cl₂ (20 mL) for 24 h. Ether (50 mL) was added and the resulting solution
was filtered through Florisil. The solvent was removed under reduced pressure and the resulting solid was chromatographed using 15:1 hexanes/EtOAc to afford 0.53 g (25%) of the desired compound as a white solid: mp 91-92 °C; \(^1\text{H}\) NMR (CDCl\(_3\)) \(\delta\) 10.15 (d, \(J = 0.6\) Hz, 1H), 10.04 (s, 1H), 8.44 (d, \(J = 0.9\) Hz, 1H), 8.01 (d, \(J = 6.0\) Hz, 1H), 7.95 (dq, \(J = 0.6, 6.0\) Hz, 1H).

Imines Prepared

\textit{N-}(2-Iodobenzylidene)-\textit{tert}-butylamine (5). To a mixture of 2-iodobenzaldehyde (1.00 g, 4.3 mmol) and \(\text{H}_2\text{O}\) (0.25 mL/mmol) was added \textit{tert}-butylamine (12.9 mmol, 3 equivalents). The mixture was then stirred under a nitrogen atmosphere at room temperature for 12 h. The excess \textit{tert}-butylamine was removed under reduced pressure and the resulting mixture was extracted with ether. The combined organic layers were dried (Na\(_2\)SO\(_4\)) and filtered. Removal of the solvent afforded 1.18 g (95%) of the imine as a yellow oil: \(^1\text{H}\) NMR (CDCl\(_3\)) \(\delta\) 1.33 (s, 9H), 7.07 (td, \(J = 1.5, 7.2\) Hz, 1H), 7.36 (tt, \(J = 0.6, 7.2\) Hz, 1H), 7.83 (dd, \(J = 0.9, 7.8\) Hz, 1H), 7.94 (dd, \(J = 1.8, 7.8\) Hz, 1H), 8.41 (s, 1H); \(^{13}\text{C}\) NMR (CDCl\(_3\)) \(\delta\) 29.8, 58.0, 100.4, 128.5, 128.7, 131.6, 137.9, 139.4, 159.2; IR (neat, cm\(^{-1}\)) 3059, 2966, 1633; HRMS Calcd for C\(_{11}\)H\(_{14}\)IN: 287.0170. Found: 287.0173.

\textit{N-}(2-Iodo-4,5-dimethoxybenzylidene)-\textit{tert}-butylamine (20). The imine was prepared by the same method used for 5, but employing 2-iodo-4,5-dimethoxybenzaldehyde (1.00 g, 3.42 mmol). Removal of the solvent afforded
1.14 g (96%) of the imine 20 as a white solid: mp 80-81 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.30 (s, 9H), 3.89 (s, 3H), 3.94 (s, 3H), 7.22 (s, 1H), 7.53 (s, 1H), 8.29 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 30.0, 56.1, 56.3, 57.6, 90.2, 110.3, 121.1, 130.7, 149.6, 151.3, 158.8; IR (CHCl$_3$, cm$^{-1}$) 3006, 2962, 1628; HRMS Calcd for C$_{13}$H$_{18}$NO$_2$: 347.0382. Found: 347.01382.

$N$-(6-Bromobenzo[1,3]dioxol-5-ylmethylene)-tert-butylamine. The imine was prepared by the same method used for 5, but employing 2-bromopiperonal (2.00 g, 8.73 mmol). Removal of the solvent afforded 2.27 g (92%) of the imine as a white solid: mp 73-74 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.29 (s, 9H), 5.99 (s, 2H), 6.98 (s, 1H), 7.52 (s, 1H), 8.50 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 29.8, 57.8, 102.1, 107.8, 112.5, 117.2, 129.5, 147.9, 150.1, 154.2; IR (CHCl$_3$, cm$^{-1}$) 3077, 2963, 1627; HRMS Calcd for C$_{12}$H$_{14}$BrNO$_2$: 283.0208. Found: 283.0205.

$N$-(6-Iodobenzo[1,3]dioxol-5-ylmethylene)-tert-butylamine (26). The imine was prepared by the same method used for 5, but employing 2-iodo-4,5-methylenedioxybenzaldehyde (0.54 g, 1.97 mmol). Removal of the solvent afforded 0.47 g (73%) of the imine 26 as an off-white solid: mp 89-90 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.29 (s, 9H), 5.99 (s, 2H), 7.24 (s, 1H), 7.50 (s, 1H), 8.31 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 29.9, 57.7, 90.1, 102.00, 108.2, 118.4, 131.9, 148.9, 150.3, 158.6; IR (CHCl$_3$, cm$^{-1}$) 3081, 2962, 1622; HRMS Calcd for C$_{12}$H$_{14}$I NO$_2$: 331.0069. Found: 331.0072.

$N$-[2-Iodo-4-(tert-butyliminomethyl)benzylidene]-tert-butylamine (30). The imine was prepared by the same method used for 5, but employing 2-
iodobenzene-1,4-dicarbaldehyde (0.53 g, 2.04 mmol). Removal of the solvent afforded 0.75 g (100%) of the imine 30 as a white solid: mp 67-69 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.27 (s, 9H), 1.31 (s, 9H), 7.64 (d, $J = 6$ Hz, 1H), 7.93 (d, $J = 6$ Hz, 1H), 8.16 (s, 1H), 8.25 (d, $J = 0.9$ Hz, 1H), 8.40 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 29.7, 29.8, 57.8, 58.2, 100.6, 128.2, 128.5, 138.4, 139.0, 140.1, 153.3, 159.0; IR (CHCl$_3$, cm$^{-1}$) 2966, 1635; HRMS Calcd for C$_{18}$H$_{19}$N: 370.0906. Found: 370.0916.

$N$-(2-Bromocyclohex-1-enylmethylene)-tert-butylamine (33). The imine was prepared by the same method used for 5, but employing 2-bromocyclohexene-1-carboxaldehyde (0.50 g, 2.64 mmol). Removal of the solvent afforded 0.59 g (92%) of the imine 33 as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.20 (s, 9H), 1.65-1.75 (m, 4H), 2.38-2.43 (m, 2H), 2.62-2.66 (m, 2H), 8.35 (s, 1H); $^1$C NMR (CDCl$_3$) $\delta$ 21.8, 24.8, 27.3, 29.9, 38.2, 57.6, 131.7, 133.9, 157.0; IR (neat, cm$^{-1}$) 2964, 1624; HRMS Calcd for C$_{11}$H$_{18}$BrN: 243.0623. Found: 243.0616.

$N$-(2-Bromocyclopent-1-enylmethylene)-tert-butylamine (38). The imine was prepared by the same method used for 5, but employing 2-bromocyclopentene-1-carboxaldehyde (0.75 g, 4.31 mmol). Removal of the solvent afforded 0.89 g (90%) of the imine 38 as a dark yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.22 (s, 9H), 1.97 (quintet, 2H), 2.59 (tt, $J = 2.1$, 7.5 Hz, 2H), 2.79 (tt, $J = 2.4$, 7.5 Hz, 2H), 8.18 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.6, 29.8, 31.1, 41.6, 57.7, 127.9, 139.1, 151.8; IR (neat, cm$^{-1}$) 2965, 1630; HRMS Calcd for C$_{10}$H$_{16}$BrN: 229.0466. Found: 229.0460.
**N-(1-Bromo-3,4-dihydronaphthalen-2-ylmethylene)-tert-butylamine (42).** The imine was prepared by the same method used for 5, but employing 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde (0.77 g, 3.26 mmol). Removal of the solvent afforded 0.85 g (89%) of the imine 42 as a viscous yellow oil: 

**1H NMR (CDCl₃)** δ 1.31 (s, 9H), 2.81-2.83 (m, 4H), 7.16 (dd, J = 1.8, 6.9 Hz, 1H), 7.22-7.31 (m, 2H), 7.79 (dd, J = 1.8, 7.2 Hz, 1H), 8.61 (s, 1H); **13C NMR (CDCl₃)** δ 25.3, 27.7, 30.0, 58.1, 126.8, 127.3, 127.6, 128.6, 129.1, 134.2, 135.9, 138.3, 157.0; **IR (neat, cm⁻¹)** 3063, 2965, 1612; **HRMS Calcd** for C₁₅H₁₆BrN: 291.0623. **Found:** 290.0548 (M-H).

**N-[(Z)-3-Iodo-2-methyl-3-phenylallylidene]-tert-butylamine (45).** The imine was prepared by the same method used for 5, but employing Z-3-iodo-2-methyl-3-phenyl-2-propenal (0.61 g, 2.22 mmol). Removal of the solvent afforded 0.70 g (96%) of the imine 45 as a viscous yellow oil: 

**1H NMR (CDCl₃)** δ 1.29 (s, 9H), 1.88 (s, 3H), 7.24-7.28 (m, 3H), 7.34-7.39 (m, 2H), 8.30 (s, 1H); **13C NMR (CDCl₃)** δ 17.0, 29.9, 57.9, 107.0, 128.2, 128.3, 128.4, 139.0, 144.5, 162.8; **IR (neat, cm⁻¹)** 3075, 2966, 1618; **HRMS Calcd** for C₁₄H₁₈IN: 327.0484. **Found:** 327.0477.

**N-[(Z)-3-Iodo-3-phenylallylidene]-tert-butylamine (49).** The imine was prepared by the same method used for 5, but employing Z-3-iodo-3-phenyl-2-propenal (0.60 g, 2.33 mmol). Removal of the solvent afforded 0.64 g (87%) of the imine 49 as a yellow solid: 

**mp 81-83 °C; 1H NMR (CDCl₃)** δ 1.29 (s, 9H), 6.77 (d, J = 7.8 Hz, 1H), 7.32-7.35 (m, 3H), 7.56-7.60 (m, 2H), 8.15 (d, J = 7.5 Hz, 1H); **13C NMR (CDCl₃)** δ 29.7, 58.4, 113.6, 128.5, 128.8, 129.6, 134.9, 142.0, 161.4; **IR
(CHCl₃, cm⁻¹) 3078, 2967, 1614; HRMS Calcd for C₁₃H₁₆IN: 313.0328. Found: 313.0332.

General Procedure for the Palladium-Catalyzed Formation of Isoquinoines and Pyridines. DMF (10 mL), Pd(OAc)₂ (6 mg, 0.027 mmol), PPh₃ (13 mg, 0.05 mmol), Na₂CO₃ (53 mg, 0.5 mmol), and the alkyne (1.0 mmol) were placed in a 4 dram vial. The contents were then stirred for 1 minute and the appropriate imine (0.5 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 30 mL of ether, washed with 45 mL of saturated NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

3,4-Diphenylisoquinoline (6). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 135 mg (96%) of the indicated compound with spectral properties identical to those previously reported¹²a: mp 154-155 °C (lit.¹²a mp 155-156 °C).

Ethyl 3-phenylisoquinoline-4-carboxylate (7). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 138 mg (99%) of the
indicated compound with spectral properties identical to those previously reported.$^{11}$

4-Methyl-3-phenylisoquinoline (8). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 92 mg (84%) of the indicated compound as a white solid: mp 101-102 °C (lit.$^{13}$ mp 103-104 °C); $^1$H NMR (CDCl$_3$) δ 2.65 (s, 3H), 7.38-7.53 (m, 3H), 7.57-7.63 (m, 3H), 7.74 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 8.04 (dd, J = 0.6, 8.4 Hz, 1H), 9.22 (s, 1H); $^{13}$C NMR (CDCl$_3$) δ 15.6, 123.7, 124.1, 126.7, 127.3, 127.7, 128.16, 128.21, 129.9, 130.5, 136.3, 141.4, 150.3, 151.9; MS m/z (rel intensity) 219 (50, M$^+$), 218 (100), 217 (22). Anal. Calcd for C$_{18}$H$_{13}$N: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.30; H, 6.09; N, 6.32.

4-Ethyl-3-phenylisoquinoline (9). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 109 mg (93%) of the indicated compound as a white solid: mp 117-118 °C; $^1$H NMR (CDCl$_3$) δ 1.30 (t, J = 7.5 Hz, 3H), 3.07 (q, J = 7.5 Hz, 2H), 7.39-7.56 (m, 5H), 7.62 (ddd J = 1.2, 6.9, 8.4 Hz, 1H), 7.77 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 9.19 (s, 1H); $^{13}$C NMR (CDCl$_3$) δ 15.7, 21.9, 123.7, 126.6, 127.6, 127.9, 128.2, 128.5, 129.3, 130.4, 130.5, 135.3, 141.6, 150.2, 151.9; IR (CHCl$_3$, cm$^{-1}$) 3027, 2976, 1653, 1559; MS m/z (rel intensity) 233 (76, M$^+$), 232 (100), 217 (44). Anal. Calcd for C$_{17}$H$_{15}$N: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.48; H, 6.68; N, 5.91.

4-Hydroxymethyl-3-phenylisoquinoline (10). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 118 mg (100%) of the
Indicated compound as a white solid: mp 175-176 °C (hexanes/EtOAc); \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 4.89 (br s, 1H), 4.96 (s, 2H), 7.44-7.54 (m, 3H), 7.65 (dd, \(J = 1.2, 8.4\) Hz, 2H), 7.72 (dd, \(J = 0.9, 8.1\) Hz, 1H), 7.88 (ddd, \(J = 1.2, 7.2, 8.4\) Hz, 1H), 8.13 (d, \(J = 8.1\) Hz, 1H), 8.38 (d, \(J = 8.4\) Hz, 1H), 9.21 (s, 1H); \(^{13}\)C NMR (CD\(_3\)OD) \(\delta\) 57.9, 124.2, 126.9, 127.3, 127.9, 128.0, 128.0, 128.1, 129.6, 131.3, 136.2, 139.9, 151.7, 152.1; IR (CHCl\(_3\), cm\(^{-1}\)) 3270, 1622, 1576; MS m/z (rel intensity) 235 (100, M\(^+\)), 262 (100).

Anal. Calcd for C\(_{16}\)H\(_{13}\)NO: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.57; H, 5.84; N, 5.88.

4-(1-Hydroxyethyl)-3-phenylisoquinoline (11). The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 80 mg (65%) of the indicated compound as a white solid: mp 146-147 °C (hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.75 (d, \(J = 6.6\) Hz, 3H), 2.49 (br s, 1H), 5.44 (q, \(J = 6.6\) Hz, 1H), 7.41 (s, 5H), 7.62 (t, \(J = 6\) Hz, 1H), 7.74 (ddd, \(J = 1.2, 5.7, 6.9\) Hz, 1H), 7.99 (d, \(J = 8.1\) Hz, 1H), 8.82 (d, \(J = 8.7\) Hz, 1H), 9.13 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 23.9, 67.9, 126.6, 126.8, 127.7, 128.1, 128.5, 128.7, 129.2, 130.0, 131.1, 134.5, 140.7, 150.6, 151.5; IR (CHCl\(_3\), cm\(^{-1}\)) 3266, 1621, 1574, 1497; HRMS calcd for C\(_{17}\)H\(_{15}\)NO: 249.1154. Found: 249.1151.

4-Phenyl-3-(phenylethynyl)-isoquinoline (12). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 110 mg (72%) of the indicated compound as an off-white solid: mp 113-114 °C (hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.25 (br s, 5H), 7.49-7.68 (m, 8H), 7.99-8.02 (m, 1H), 9.26 (s, 1H);


\[ ^{13}\text{C NMR (CDCl}_3 \delta 89.4, 92.5, 122.8, 125.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.5, 130.8, 131.0, 131.8, 135.0, 135.5, 136.4, 136.5, 152.3; IR (CHCl}_3, \text{cm}^{-1}) 2213, 1610, 1554, 1489; \text{HRMS calcd for C}_{23}\text{H}_{15}\text{N: 305.1205. Found: 305.1197.} \]

3-Phenyl-4-(phenylethynyl)-isoquinoline (13). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 20 mg (13%) of the indicated compound as an off-white solid: mp 115-116 °C (hexanes/EtOAc); \(^1\text{H NMR (CDCl}_3 \delta 7.35-7.40 (m, 3H), 7.43-7.57 (m, 5H), 7.68 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 7.85 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H), 8.04 (dd, J = 0.9, 7.2 Hz, 1H), 8.12-8.16 (m, 2H), 8.50 (dd, J = 0.9, 7.5 Hz, 1H), 9.30 (d, J = 0.9 Hz, 1H); ^{13}\text{C NMR (CDCl}_3 \delta 85.9, 99.3, 112.6, 123.3, 125.8, 126.7, 127.7, 128.0, 128.0, 128.6, 128.7, 128.8, 130.1, 131.4, 131.6, 136.8, 140.1, 151.6, 154.5; IR (CHCl}_3, \text{cm}^{-1}) 2210, 1653, 1558, 1495; \text{HRMS calcd for C}_{23}\text{H}_{15}\text{N: 305.1205. Found: 305.1196.} \]

4-Ethyl-3-isopropenylisoquinoline (14) and 3-ethyl-4-isopropenylisoquinoline (15). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 68 mg (69%) of the indicated compounds as a yellow oil (85:15 inseparable mixture of isomers). 4-Ethyl-3-isopropenylisoquinoline (major isomer): \(^1\text{H NMR (CDCl}_3 \delta 1.29 (t, J = 7.5 Hz, 3H), 2.20-2.21 (m, 3H), 3.10 (q, J = 7.5 Hz, 2H), 5.04-5.05 (m, 1H), 5.36-5.38 (m, 1H), 7.52 (ddd, J = 0.9, 7.2, 8.1 Hz, 1H), 7.68 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 8.00 (dd, J = 0.6, 8.4 Hz, 1H), 9.09 (s, 1H).} \]

3-Ethyl-4-isopropenylisoquinoline (minor isomer): \(^1\text{H NMR (CDCl}_3 \delta 1.34 (t, J = 7.5 Hz,}
3-(Cyclohex-1-enyl)-4-ethylisoquinoline (16) and 4-(Cyclohex-1-enyl)-3-ethylisoquinoline (17). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 82 mg (69%) of the indicated compounds as a yellow oil (96:4 inseparable mixture of isomers). 3-(Cyclohex-1-enyl)-4-ethylisoquinoline (major isomer): \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 1.29 (t, \( J = 7.5 \) Hz, 3H), 1.71-1.89 (m, 4H), 2.21-2.27 (m, 2H), 2.37-2.42 (m, 2H), 3.07 (q, \( J = 7.5 \) Hz, 2H), 5.77 (dddd, \( J = 1.8, 1.8, 3.6, 3.6 \) Hz, 1H), 7.51 (ddd, \( J = 0.9, 6.9, 7.8 \) Hz, 1H), 7.67 (ddd, \( J = 1.2, 6.9, 9.9 \) Hz, 1H), 7.91 (d, \( J = 8.1 \) Hz, 1H), 7.99 (d, \( J = 8.7 \) Hz, 1H), 9.08 (s, 1H). 4-(Cyclohex-1-enyl)-3-ethylisoquinoline (minor isomer): \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 1.33 (t, \( J = 7.5 \) Hz, 3H), 2.90 (dq, \( J = 1.5, 14.7 \) Hz, 2H), 5.68 (dddd, \( J = 2.1, 2.1, 3.3, 3.3 \) Hz, 1H), 7.47 (ddd, \( J = 0.9, 6.9, 7.8 \) Hz, 1H), 7.60 (ddd, \( J = 1.5, 6.9, 8.4 \) Hz, 1H), 7.79 (d, \( J = 8.7 \) Hz, 1H), 7.85 (d, \( J = 11.7 \) Hz, 1H), 9.13 (s, 1H). Additional spectral data for the product mixture: \(^{13}C\) NMR (CDCl\(_3\)) \( \delta \) 16.1, 21.8, 22.2, 23.1, 25.4, 26.6, 123.6, 126.1, 126.9, 127.6, 128.3, 129.3, 130.1, 135.3, 138.7, 150.1, 154.5; IR

3-Phenylisoquinoline (18). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 88 mg (85%) of the indicated compound with spectral properties identical to those previously reported: mp 102-103 °C (lit. mp 101-102 °C).

3-(Cyclohex-1-enyl)isoquinoline (19). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 81 mg (77%) of the indicated compound as a yellow solid: mp 114-115 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.67-1.75 (m, 2H), 1.81-1.89 (m, 2H), 2.29-2.36 (m, 2H), 2.54-2.60 (m, 2H), 7.02 (tt, J = 2.4, 3.6 Hz, 1H), 7.48 (dt, J = 0.6, 14.4 Hz, 1H), 7.57 (s, 1H), 7.63 (dd, J = 1.2, 6.9 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 9.18 (s, 1H); NMR (CDCl₆) δ 22.3, 23.1, 25.1, 26.1, 26.2, 114.2, 126.4, 126.8, 127.6, 128.4, 130.3, 135.7, 136.7, 151.7, 152.5 (one sp² carbon missing due to overlap); IR (CHCl₃, cm⁻¹) 3060, 2919, 1621, 1574; MS m/z (rel intensity) 209 (100, M⁺), 208 (89), 194 (42), 180 (51). Anal. Calcd for C₁₅H₁₅N: C, 86.09; H, 7.23; N, 6.69. Found: C, 86.03; H, 7.30; N, 6.73.

6,7-Dimethoxy-3,4-diphenylisoquinoline (21). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 138 mg (82%) of the indicated compound as a white solid (mp 181-182 °C): ¹H NMR (CDCl₃) δ 3.76 (s, 3H), 4.03 (s, 3H), 6.91 (s, 1H), 7.16-7.18 (m, 3H), 7.23-7.26 (m, 3H), 7.33-7.36 (m, 5H), 9.16 (s, 1H); ¹³C NMR (CDCl₃) δ 55.9, 56.2, 104.0, 105.3, 123.7, 126.9, 127.4,
40

127.6, 128.5, 129.7, 130.3, 131.1, 132.6, 137.8, 141.2, 149.2, 149.7, 150.1, 153.0; IR (CHCl₃, cm⁻¹) 3055, 3021, 2960, 1620, 1501; MS (Cl) m/z 342 (M+1). Anal. Calcd for C₂₃H₁₉NO₂: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.74; H, 5.69; N, 3.99.

**Ethyl 6,7-dimethoxy-3-phenylisoquinoline-4-carboxylate (22).** The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 146 mg (95%) of the indicated compound as a white solid: mp 110-111 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 0.92 (t, J = 7.2 Hz, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.13 (q, J = 7.2 Hz, 2H), 7.17 (s, 1H), 7.31 (s, 1H), 7.34-7.40 (m, 3H), 7.62 (dd, J = 1.5, 6.6 Hz, 2H), 9.08 (s, 1H); ¹³C NMR (CDCl₃) δ 13.6, 56.1, 56.2, 61.6, 102.5, 105.5, 121.9, 123.3, 128.2, 128.3, 128.7, 130.4, 140.9, 150.5, 150.7, 150.8, 154.1, 169.2; IR (CHCl₃, cm⁻¹) 3068, 2978, 1716, 1620, 1578, 1505; MS m/z (rel intensity) 337 (82, M⁺), 308 (100), 292 (38). Anal. Calcd for C₂₀H₁₉NO₄: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.85; H, 5.70; N, 4.02.

**Ethyl 6,7-dimethoxy-4-phenylisoquinoline-3-carboxylate (23).** The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 7 mg (5%) of the indicated compound as a yellow oil: ¹H NMR (CDCl₃) δ 1.07 (t, J = 7.2 Hz, 3H), 3.77 (s, 3H), 4.06 (s, 3H), 4.16 (q, J = 7.2 Hz, 2H), 6.83 (s, 1H), 7.25 (s, 1H), 7.33 (dd, J = 1.8, 7.5 Hz, 2H), 7.44-7.56 (m, 3H), 9.13 (s, 1H); ¹³C NMR (CDCl₃) δ 13.9, 56.0, 56.3, 61.3, 104.7, 105.4, 127.9, 128.4, 128.5, 129.5, 132.0, 132.1, 132.2, 132.3, 151.5, 153.4; HRMS calcd for C₂₀H₁₉NO₄: 337.1315. Found: 337.1314.
6,7-Dimethoxy-4-methyl-3-phenylisoquinoline (24). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 94 mg (67%) of the indicated compound as a white solid: mp 155-156 °C; $^1$H NMR (CDCl$_3$) $\delta$ 2.56 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 7.16 (s, 1H), 7.19 (s, 1H), 7.36 (ddd, $J$ = 1.2, 7.2, 8.4 Hz, 1H), 7.44 (ddd, $J$ = 1.8, 5.1, 7.5 Hz, 2H), 7.55 (dd, $J$ = 1.5, 8.4 Hz, 2H), 8.97 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 15.8, 56.1, 102.1, 105.8, 122.8, 123.4, 127.4, 128.1, 129.9, 132.8, 141.7, 147.7, 149.9, 151.0, 153.0 (one sp$^3$ carbon missing due to overlap); IR (CHCl$_3$, cm$^{-1}$) 3058, 2942, 1620, 1579, 1506; MS (Cl) m/z 280 (M+1). Anal. Calcd for C$_{15}$H$_{14}$NO$_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.14; H, 6.20; N, 4.95.

6,7-Dimethoxy-3-methyl-4-phenylisoquinoline (25). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 24 mg (17%) of the indicated compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 2.42 (s, 3H), 3.74 (s, 3H), 4.02 (s, 3H), 6.62 (s, 1H), 7.20 (s, 1H), 7.30 (dt, $J$ = 1.8, 6.6 Hz, 2H), 7.41-7.55 (m, 3H), 8.99 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 22.9, 55.9, 56.1, 103.3, 105.3, 123.0, 127.6, 128.5, 128.8, 130.0, 132.1, 132.2, 132.7, 138.1, 147.6, 148.4, 149.7, 153.1; HRMS calcd for C$_{18}$H$_{17}$NO$_2$: 279.1259. Found: 279.1256.

7,8-Diphenyl-1,3-dioxolo[4,5-g]isoquinoline (27). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 135 mg (83%) of the indicated compound as an off-white solid: mp 234-235 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 6.04 (s, 2H), 6.90 (s, 1H), 7.15-7.33 (m, 11H), 9.08 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 101.7, 102.1, 103.0, 124.9, 127.0, 127.4, 127.6, 128.4, 130.2, 131.1,
134.5, 137.7, 140.9, 148.1, 150.1, 151.3; IR (CDCl₃, cm⁻¹) 3082, 3060, 1457;
HRMS calc'd for C₂₂H₁₅NO₂: 325.1103. Found: 325.1098.

8-Methyl-7-phenyl-1,3-dioxolo[4,5-g]isoquinoline (28). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 101 mg (77%) of the indicated compound as an off-white solid: mp 153-154 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 2.49 (s, 3H), 6.05 (s, 2H), 7.15 (s, 1H), 7.23 (s, 1H), 7.35 (ddd, J = 1.8, 5.4, 6.6 Hz, 1H), 7.43 (t, J = 5.4 Hz, 2H), 7.52 (dd, J = 0.9, 6.3 Hz, 2H), 8.89 (s, 1H); ¹³C NMR (CDCl₃) δ 16.0, 100.2, 101.7, 103.5, 123.6, 124.6, 127.5, 128.1, 129.8, 134.6, 141.4, 147.8, 148.0, 151.2, 151.3; IR (CHCl₃, cm⁻¹) 1584, 1486, 1462; MS m/z (rel intensity) 263 (47, M⁺), 262 (100). Anal. Calc'd for C₁₇H₁₃NO₂: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.95; H, 5.19; N, 5.29.

7-Methyl-8-phenyl-1,3-dioxolo[4,5-g]isoquinoline (29). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 18 mg (14%) of the indicated compound as a viscous yellow oil: ¹H NMR (CDCl₃) δ 2.41 (s, 3H), 6.03 (s, 2H), 6.64 (s, 1H), 7.19 (s, 1H), 7.25 (dt, J = 1.5, 6.6 Hz, 2H), 7.41-7.54 (m, 3H), 8.94 (s, 1H); ¹³C NMR (CDCl₃) δ 23.0, 101.5, 101.6, 102.9, 124.2, 127.6, 128.8, 130.0, 130.9, 134.4, 138.2, 147.5, 148.2, 149.0, 151.1; IR (CDCl₃, cm⁻¹) 1653, 1450, 1521, 1456; HRMS calc'd for C₁₇H₁₃NO₂: 263.0946. Found: 263.0943.

3,4-Diphenyl-6-isoquinolinecarboxaldehyde (31). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 134 mg (87%) of the indicated compound as a white solid: mp 154-155 °C; ¹H NMR (CDCl₃) δ 7.19-7.29 (m, 5H), 7.35-7.43 (m, 5H), 8.04-8.17 (m, 3H), 9.45 (d, J = 0.6 Hz, 1H), 10.02
(s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 123.8, 127.6, 127.9, 128.0, 128.8, 128.9, 129.4, 130.3, 131.2, 131.7, 132.1, 135.8, 136.4, 137.5, 140.2, 151.9, 152.2, 192.1; IR (CDCl$_3$, cm$^{-1}$) 3055, 2962, 1699, 1558; MS m/z (rel intensity) 309 (62, M$^+$), 308 (100). Anal. Calcd for C$_{22}$H$_{15}$NO: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.09; H, 5.04; N, 4.47.

4-Methyl-3-phenyl-6-isoquinolinecarboxaldehyde (32). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 86 mg (69%) of the indicated compound as an off-white solid: mp 126-127 ºC (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 2.73 (s, 3H), 7.39-7.52 (m, 3H), 7.59 (dd, J = 1.5, 8.4 Hz, 2H), 8.03-8.10 (m, 2H), 8.54 (s, 1H), 9.27 (s, 1H), 10.24 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 15.7, 124.0, 125.5, 128.1, 128.3, 129.4, 129.5, 129.9, 136.0, 137.2, 140.7, 150.3, 153.4, 192.2; IR (CHCl$_3$, cm$^{-1}$) 1696, 1684, 1577, 1417; HRMS calcd for C$_{17}$H$_{13}$NO: 247.0997. Found: 247.0991.

3,4-Diphenyl-5,6,7,8-tetrahydroisoquinoline (34). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 103 mg (72%) of the indicated compound as an off-white solid: mp 143-144 ºC (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 1.71-1.84 (m, 4H), 2.46 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 6.3 Hz, 2H), 7.05-7.08 (m, 2H), 7.12-7.15 (m, 3H), 7.22-7.27 (m, 5H), 8.44 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 22.3, 22.9, 26.8, 28.2, 126.98, 127.00, 127.5, 128.2, 129.8, 130.3, 131.5, 135.4, 138.4, 141.0, 145.2, 149.3, 154.6; IR (CHCl$_3$, cm$^{-1}$) 1552, 1449, 1433; MS m/z (rel intensity) 285 (50, M$^+$), 284 (100). Anal. Calcd for C$_{21}$H$_{19}$N: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.32; H, 6.76; N, 4.99.
Ethyl 3-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxylate (35).
The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 140 mg (99%) of the indicated compound as a red solid: mp 77-78 °C (hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.99 (t, \(J = 6.9\) Hz, 3H), 1.81 (tt, \(J = 3.6, 6.0\) Hz, 4H), 2.77-2.81 (m, 4H), 4.10 (q, \(J = 7.2\) Hz, 2H), 7.31-7.41 (m, 3H), 7.53-7.57 (m, 2H), 8.40 (s, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 13.7, 22.1, 22.3, 26.4, 26.5, 61.4, 128.3, 128.3, 128.4, 128.6, 131.5, 140.2, 144.1, 150.8, 153.6, 168.9; IR (CHCl\(_3\), cm\(^{-1}\)) 2977, 1718, 1558; MS \(m/z\) (rel intensity) 281 (39, M\(^+\)), 252 (100), 209 (40). Anal. Calcd for C\(_{18}\)H\(_{19}\)NO\(_2\): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.92; H, 6.85; N, 4.93.

4-Methyl-3-phenyl-5,6,7,8-tetrahydroisoquinoline (36). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 83 mg (74%) of the desired compound as a white solid: mp 49-50 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.76-1.92 (m, 4H), 2.17 (s, 3H), 2.66 (t, \(J = 6.0\) Hz, 2H), 2.78 (t, \(J = 6.3\) Hz, 2H), 7.34-7.48 (m, 5H), 8.25 (s, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 15.9, 22.3, 23.0, 26.9, 127.5, 128.1, 128.9, 129.3, 131.2, 141.5, 145.4, 147.4, 156.0; IR (Et\(_2\)O, cm\(^{-1}\)) 3026, 2931, 1653, 1558; MS \(m/z\) (rel intensity) 223 (39, M\(^+\)), 222 (100). Anal. Calcd for C\(_{16}\)H\(_{17}\)N: C, 86.06; H, 7.67; N, 6.27. Found: C, 85.90; H, 7.83; N, 6.25.

4-Hydroxymethyl-3-phenyl-5,6,7,8-tetrahydroisoquinoline (37).
The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 120 mg (100%) of the desired compound as a white solid: mp 175-176 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.79-1.83 (m, 4H), 2.77 (t, \(J = 6.0\) Hz, 2H), 2.91 (t, \(J = 5.4\) Hz, 2H) 4.53 (s, 2H), 7.34-7.41 (m, 3H), 7.50-7.53 (m, 2H), 8.24 (s, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 22.2,
22.7, 25.7, 26.8, 59.0, 127.9, 128.2, 129.3, 130.7, 132.1, 140.4, 147.2, 149.4, 156.8; IR (CHCl₃, cm⁻¹) 3232, 2933, 1558; HRMS calcd for C₁₇H₁₇NO: 239.1310. Found: 239.1307.

6,7-Dihydro-5H-[2]-3,4-diphenylpyrindine (39). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 96 mg (71%) of the indicated compound with spectral properties identical to those previously reported: mp 101-102 °C (lit. mp 104-105 °C); ¹H NMR (CDCl₃) δ 2.10 (quintet, J = 7.5 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 3.05 (t, J = 7.5 Hz, 2H), 7.10-7.14 (m, 2H), 7.16-7.20 (m, 3H), 7.22-7.33 (m, 5H), 8.57 (s, 1H); ¹³C NMR (CDCl₃) δ 25.4, 30.8, 32.9, 127.0, 127.3, 127.7, 128.2, 129.9, 130.0, 132.7, 138.6, 138.9, 140.7, 144.2, 153.7, 155.1; HRMS calcd for C₂₀H₁₅N: 270.1283. Found: 270.1283.

6,7-Dihydro-5H-[2]-4-methyl-3-phenylpyrindine (40). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 100 mg (96%) of the indicated compound as an off-white solid: mp 60-61 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 2.15 (quintet, 2H), 2.25 (s, 3H), 2.90 (t, J = 7.5 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 7.33-7.51 (m, 5H), 8.40 (s, 1H); ¹³C NMR (CDCl₃) δ 16.6, 24.8, 30.7, 32.0, 127.0, 127.6, 128.1, 129.2, 138.4, 141.1, 142.6, 153.9, 156.4; IR (CHCl₃, cm⁻¹) 1591, 1459, 1437, 1397; MS m/z (rel intensity) 209 (34, M⁺), 208 (100). Anal. Calcd for C₁₅H₁₄N: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.12; H, 7.40; N, 6.71.

6,7-Dihydro-5H-[2]-4-hydroxymethyl-3-phenylpyrindine (41). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 81 mg (72%) of the indicated compound as a white solid: mp 158-159 °C
1,2-Diphenyl-5,6-dihydrobenzo[f]isoquinoline (43). The reaction mixture was chromatographed using hexanes/EtOAc to afford 142 mg (85%) of the desired compound as a white solid: mp 198-199 °C; 'H NMR (CDCl₃) δ 1.93 (br s, 1H), 2.18 (quintet, J = 7.5 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 4.64 (s, 2H), 7.36-7.46 (m, 3H), 7.55-7.58 (m, 2H), 8.46 (s, 1H); ¹³C NMR (CDCl₃) δ 25.1, 30.5, 31.5, 60.4, 128.1, 128.3, 129.0, 129.2, 139.4, 140.1, 144.7, 155.1, 156.8; IR (CH₂Cl₂, cm⁻¹) 3207, 2915, 1594, 1432; MS m/z (rel intensity) 225 (58, M⁺), 224 (100). Anal. Calcd for C₁₅H₁₃NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.91; H, 6.72; N, 6.33.

1-Ethyl-2-phenyl-5,6-dihydrobenzo[f]isoquinoline (44). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 135 mg (94%) of the indicated compound as a white solid: mp 121-122 °C (hexanes/EtOAc); 'H NMR (CDCl₃) δ 0.93 (t, J = 7.2 Hz, 3H), 2.79 (dddd, J = 3.9, 6.6, 11.4, 11.4 Hz, 4H), 3.06 (t, J = 7.5 Hz, 2H), 7.31-7.35 (m, 3H), 7.37-7.52 (m, 5H) 7.80 (ddd, J = 1.2, 1.2, 3.9 Hz, 1H), 8.42 (s, 1H); ¹³C NMR (CDCl₃) δ 14.9, 23.2, 27.2, 29.8, 126.5, 127.6, 128.2, 128.6, 129.0, 133.0, 133.2, 140.7, 142.2, 145.3, 160.1;

5-Methyl-2,3,4-triphenylpyridine (46). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 110 mg (68%) of the indicated compound as a white solid: mp 119-120 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 2.17 (s, 3H), 6.81-6.85 (m, 2H), 6.95-7.00 (m, 5H), 7.14-7.29 (m, 8H), 8.63 (s, 1H); ¹³C NMR (CDCl₃) δ 17.9, 126.3, 127.0, 127.2, 127.4, 127.7, 128.0, 129.3, 129.9, 130.2, 131.3, 134.8, 138.2, 138.3, 141.0, 149.6, 149.9, 155.9; IR (CHCl₃, cm⁻¹) 3055, 3026, 2971, 1560, 1431; HRMS calcd for C₂₄H₁₉N: 321.1518. Found: 321.1510.

3,5-Dimethyl-2,4-diphenylpyridine (47). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 85 mg (65%) of the indicated compound as a white solid: mp 84-85 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 2.02 (s, 3H), 2.06 (s, 3H), 7.17 (dt, J = 1.5, 8.1 Hz, 2H), 7.34-7.55 (m, 8H), 8.46 (s, 1H); ¹³C NMR (CDCl₃) δ 17.6, 18.1, 127.6, 127.7, 128.2, 128.2, 128.5, 128.9, 129.2, 129.9, 139.0, 141.4, 147.7, 150.7, 157.1; IR (CHCl₃, cm⁻¹) 3057, 2924, 1604, 1577, 1458; HRMS calcd for C₁₉H₁₇N: 259.1361. Found: 258.1288 (M-H).

3-(Hydroxymethyl)-5-methyl-2,4-diphenylpyridine (48). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 131 mg (95%) of the indicated compound as a white solid: mp 152-153 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 2.00 (s, 3H), 2.24 (br s, 1H), 4.24 (s, 2H), 7.24 (dd, J = 1.2, 6.3 Hz, 2H), 7.35-7.47 (m, 6H), 7.65 (dd, J = 1.5, 6.3 Hz, 2H), 8.44 (s, 1H); ¹³C NMR (CDCl₃)
δ 17.5, 59.5, 127.9, 128.1, 128.2, 128.4, 128.8, 129.3, 130.6, 130.7, 137.6, 140.2, 149.5, 151.5, 157.9; IR (CHCl₃, cm⁻¹) 3237, 3058, 2967, 1574, 1545, 1441; MS m/z (rel intensity) 275 (61, M⁺), 274 (100). Anal. Calcd for C₁₉H₁₇NO: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.84; H, 6.32; N, 5.17.

2,3,4-Triphenylpyridine (50). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 81 mg (52%) of the indicated compound with spectral properties identical to those previously reported: mp 188-189 °C (lit. mp 189-190 °C).

3-(Hydroxymethyl)-2,4-diphenylpyridine (51). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 104 mg (79%) of the desired compound as a white solid: mp 153-154 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.59 (br s, 1H), 4.51 (d, J = 5.4 Hz, 2H), 7.24 (d, J = 5.1 Hz, 1H), 7.44-7.54 (m, 8H), 7.70 (dd, J = 1.8, 6.3 Hz, 2H), 8.66 (d, J = 4.8 Hz, 2H); ¹³C NMR (CDCl₃) δ 59.4, 123.9, 128.3, 128.4, 128.5, 129.0, 129.3, 130.8, 138.9, 140.2, 148.3, 152.1, 160.9; IR (CHCl₃, cm⁻¹) 3246, 3059, 2975, 1576, 1496, 1443; MS m/z (rel intensity) 261 (62, M⁺), 260 (100). Anal. Calcd for C₁₉H₁₈NO: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.43; H, 5.72; N, 5.36.

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References


CHAPTER 2. SYNTHESIS OF ISOQUINOLINES AND PYRIDINES VIA PALLADIUM- AND COPPER-CATALYZED COUPLING AND CYCLIZATION OF TERMINAL ACETYLENES: THE TOTAL SYNTHESIS OF DECUMBENINE B

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Abstract

Mono-substituted isoquinolines and pyridines have been prepared in good to excellent yields via coupling of terminal acetylenes with the tert-butylimines of o-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst and subsequent copper-catalyzed cyclization of the intermediate iminoalkynes. In addition, isoquinoline heterocycles have been prepared in excellent yields via copper-catalyzed cyclization of iminoalkynes. The choice of cyclization conditions is dependent upon the nature of the terminal acetylene that is employed, as only aryl and alkenyl acetylenes cyclize under the palladium-catalyzed reaction conditions that have been developed. However, aryl-, vinylic-, and alkyl-substituted acetylenes undergo palladium-catalyzed coupling and subsequent copper-catalyzed cyclization in excellent yields. Finally, the total synthesis of the isoquinoline natural product decumbenine B has been accomplished in 7 steps
and 20% overall yield by employing this palladium-catalyzed coupling and cyclization methodology.

Introduction

The palladium-catalyzed annulation of alkynes has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles. For example, the annulation of internal alkynes has been employed by Larock and co-workers for the synthesis of indoles, benzofurans, benzopyrans, isocoumarins, indenones, isoquinolines, α-pyrones, and polycyclic aromatic hydrocarbons. The transition metal-catalyzed cyclization of disubstituted alkynes (formed from coupling of aryl and vinylic halides with terminal alkynes), which possess a nucleophile in proximity to the triple bond, by either copper or palladium-based methodologies, has also been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles (eq 1).

\[
\begin{align*}
\text{NuH} & \quad \text{Cu or Pd} \quad \text{Nu} \\
\text{R} & \quad \text{R}
\end{align*}
\]

The copper-promoted cyclization of disubstituted alkynes containing nucleophilic sites in the ortho position was first reported by Castro and co-workers in 1963 for the synthesis of benzofurans, indoles, and phthalides (eq 2). However, the synthesis of these heterocycles suffers the disadvantage of requiring
harsh reaction conditions (110-120 °C) and stoichiometric amounts of copper acetylides. In subsequent years, considerable attention has been given to the development of other transition metal-based methods for the synthesis of the indole nucleus from substituted o-alkynyl and o-arylethynylanilines. However, the procedures that have been developed also suffer from the use of stoichiometric amounts of organometallic intermediates, elevated temperatures, and the inability to accommodate a wide variety of functionality.

\[ 
\begin{align*}
\text{Ar}^\text{XH} & + \text{R} = \equiv \text{Cu} \quad \text{pyridine, reflux} \\
\rightarrow & \quad \text{Ar}^\text{X} \text{R} \\
\text{R} &= \text{aryl} \\
\text{X} &= \text{O, NH, COO}
\end{align*}
\]

The synthesis of the aforementioned heterocycles was considerably improved by the use of palladium-catalyzed coupling and cyclization methodology. Cacchi and co-workers subsequently reported improved procedures for the benzofuran and indole syntheses by employing catalytic amounts of palladium and copper salts. The synthesis of the benzofuran nucleus has been accomplished by the palladium-catalyzed coupling of o-iodophenol and terminal alkynes, followed by a Pd(II)-catalyzed cyclization of the resulting disubstituted alkynes (eq 3), while the indole synthesis has been achieved by the coupling of o-ethynylaniline with aryl and vinylic halides, followed by a Pd(II)-catalyzed cyclization of the resulting disubstituted alkynes (eq 4). The
advantages of these processes over previously reported syntheses are the ready availability of starting materials, the decreased need for the synthesis of organometallic starting materials, and exceptional tolerance of functionality. Since the first reports of this palladium-catalyzed coupling and cyclization methodology, numerous syntheses of carbo- and heterocycles have been reported by employing this methodology with a wide variety of nucleophiles,\textsuperscript{11} as well as syntheses employing solid supports.\textsuperscript{12}

\[
\begin{align*}
& \text{OH} & + & R\equiv\text{H} & \xrightarrow{2\% \text{Pd(OAc)}_2(\text{PPh}_3)_2, 4\% \text{CuI, piperidine}} & \text{X} \\
& & & R = \text{alkyl, aryl} \\
& & & X = \text{iodide, bromide, triflate}
\end{align*}
\]

\[
\begin{align*}
& \text{NH}_2 & + & RX & \xrightarrow{1\% \text{Pd(PPPh}_3)_4, 2\% \text{CuI}} & \text{NH}_2 \\
& & & R = \text{aryl, vinylic, heteroaryl} \\
& & & X = \text{iodide, bromide, triflate}
\end{align*}
\]

The cyclization of disubstituted alkynes promoted by $\sigma$-vinyl-, $\sigma$-aryl-, and $\sigma$-alkynylpalladium complexes generated \textit{in situ} from unsaturated halides or triflates is also currently of great interest (eq 5). The utilization of readily available
acetylenic and unsaturated triflate and halide precursors, in addition to the ability to generate complex molecular skeletons regio- and stereoselectively, has made this methodology especially attractive.

\[
\begin{align*}
\text{NuH} + R^2X & \xrightarrow{\text{cat. Pd(0)}} \text{Nu}R^1 \\
R^1 & = \text{alkyl, aryl, vinylic} \\
R^2 & = \text{aryl, alkenyl, vinylic} \\
X & = \text{halide, triflate}
\end{align*}
\]

In the first reports of this type of cyclization reaction, it was shown that enol lactones 2 could be produced regio- and stereoselectively from the palladium-catalyzed reaction of pentynoic acids (1) and aryl halides or vinylic triflates (eq 6). Moreover, as an extension of the palladium-catalyzed indole synthesis discussed previously, a two-component approach to the synthesis of 2,3-disubstituted indoles based on the palladium-catalyzed heteroannulation of \(\alpha\)-alkynyl trifluoroacetanilides with aryl halides and vinylic triflates has been reported (eq 7). In addition to these examples, this methodology has been employed in the synthesis of a wide variety of functionalized carbo- and heterocycles.
Isoquinoline derivatives have been synthesized via base-catalyzed cyclization of terminal and disubstituted alkynes. For example, Sharp reported the synthesis of N-p-toluenesulfonylimine isoquinoline, N-methanesulfonylimine isoquinoline, and N-benzenesulfonyl isoquinoline heterocycles (4) in modest yields (40-77%) from the base-induced cyclization of o-ethynyl hydrazones 3 (eq 8). The synthesis of these heterocycles is not general, however, as only terminal acetylenes could be cyclized under the reaction conditions employed. The synthesis of isoquinoline N-oxides has also been reported using similar methodology (eq 9). Treatment of o-alkynyl oximes 5 with K₂CO₃ afforded isoquinoline N-oxides 6 in modest yields (39-78%). Finally, the synthesis of 3-substituted isoquinolines has been reported from o-ethynylbenzaldehydes and ammonia in modest to excellent yields (45-95%) (eq 10). Few examples of the
latter two syntheses were reported. Therefore, the synthetic utility of these processes cannot be fully determined at this time.

\[
\begin{align*}
\text{3} & \xrightarrow{\text{Na}_2\text{CO}_3 \text{ or DBU}} \text{4} \\
\text{R}^1 & = \text{Ts, SO}_2\text{Me, SO}_2\text{Ph} \\
\text{5} & \xrightarrow{\text{K}_2\text{CO}_3} \text{6} \\
\text{R} & = \text{H, OMe} \\
\text{R}^1 & = \text{Ph, n-Bu, SiMe_3} \\
\text{7} & \xrightarrow{\text{NH}_3, \text{EtOH}} \text{8} \\
\text{R} & = \text{H, Ph, n-Bu}
\end{align*}
\]

During the course of our investigation of the iminoannulation of internal alkynes, we also observed an interesting isoquinoline synthesis (eq 11). To our surprise, 3-phenylisoquinoline, and not the expected disubstituted heterocycle, 4-phenyl-3-(trimethylsilyl)isoquinoline, was isolated in 85% yield from the palladium-catalyzed reaction of \(N\)-(2-iodobenzylidene)-\(\text{tert}\)butylamine (7) and 1-phenyl-2-(trimethylsilyl)acetylene. Herein, we report a full investigation of this intriguing...
reaction and the application of this methodology to the synthesis of the naturally-occurring isoquinoline alkaloid decumenine B (46).

\[
\begin{align*}
&\text{N}^\text{t-Bu} \quad + \quad \text{Ph} &\rightarrow 5\% \text{Pd(OAc)}_2, 10\% \text{PPh}_3 \\
&\text{Ph} &\rightarrow 1 \text{Na}_2\text{CO}_3, \text{DMF} \\
&21\text{ h}, 100\ ^\circ\text{C} &\rightarrow 85\%
\end{align*}
\]

Results and Discussion

From the results of our internal alkyne annulation investigation, we were compelled to determine the mechanism of this interesting transformation and to define the scope and limitations of this new isoquinoline synthesis. Based on the regiochemical outcome of much of our other alkyne annulation chemistry in which the palladium adds to the more hindered end of the alkyne (Scheme 1), the expected products from the reaction with trimethylsilyl-substituted alkynes were either the 3,4-disubstituted products retaining the silyl group, or the corresponding 4-substituted isoquinoline arising from desilylation of the 3,4-disubstituted isoquinoline.
However, since a product was isolated from this reaction in which the trimethylsilyl substituent was not incorporated, and the phenyl substituent was in the 3-position of the isoquinoline, other mechanisms must be operating in this system. This was confirmed by the observation that aldehyde 8 could be isolated if the reactions were not allowed to proceed to completion. Therefore, an alternative mechanistic picture was envisioned for this transformation (Scheme 2). Specifically, oxidative addition of the aryl halide to Pd(0) produces an organopalladium intermediate, which then couples with a terminal acetylene or
acetylide that is formed \textit{in situ}. The disubstituted alkyne that is subsequently produced can then be cyclized by palladium catalysis, thus producing a tert-butylisoquinolinium salt. As in our internal alkyne annulation chemistry, the tert-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.⁴

\begin{center}
\textbf{Scheme 2}
\end{center}
To gain additional insight into this process, iminoalkyne 9 was independently synthesized by a palladium-catalyzed coupling of 2-bromobenzaldehyde and phenylacetylene, followed by imine formation (Scheme 3). Imine 9 was then subjected to a variety of reaction conditions in order to effect its cyclization to 3-phenylisoquinoline (10) (eq 12, Table 1). Under the standard palladium reaction conditions that were developed for our internal alkyne isoquinoline synthesis [5 mol % Pd(OAc)$_2$, 10 mol % PPh$_3$, and 1 equiv of Na$_2$CO$_3$ in 10 mL of DMF at 100 °C], isoquinoline 10 was isolated in 75% yield after a 39 h reaction time (entry 1). Thus, our assumptions about the mechanism of this process appeared to be correct. We then were interested in optimizing the yield and reaction time for this process.

**Scheme 3**

\[
\begin{align*}
\text{O} & \quad 2\% \text{PdCl}_2(\text{PPh}_3)_2, 1\% \text{Cu} \\
\text{O} & \quad \text{Et}_3\text{N}, 50 ^\circ\text{C}, 4 \text{ h}, 91\% \\
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad + \quad 1.2\text{H} \rightarrow \text{Ph} \\
\text{H} & \quad \text{25 ^\circ C, 2 h} \\
\text{N} & \quad \text{97%} \\
\end{align*}
\]

(12)
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<th>1 equiv Na₂CO₃</th>
<th>10 mol % PPh₃</th>
<th>temp (°C), time (h)</th>
<th>% yield</th>
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<td>+</td>
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<td>2</td>
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<td>-</td>
<td>100 (14)</td>
<td>78</td>
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<tr>
<td>3</td>
<td>PdCl₂</td>
<td>-</td>
<td>-</td>
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<tr>
<td>4</td>
<td>PdCl₂</td>
<td>+</td>
<td>-</td>
<td>100 (36)</td>
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<td>5</td>
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<td>-</td>
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<tr>
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</table>

*aAll reactions were run with 0.25 mmol of the imine in 5 mL of DMF. †10 mol % Cul was added. ‡5 mol % Cul was added.*
Upon removal of the base and the phosphine from the reaction, the desired product was isolated in 78% yield in a shorter reaction time (compare entries 1 and 2). PdCl₂ was also observed to promote the cyclization, although a decrease in yield was observed (entries 3 and 4). By employing PdCl₂(PhCN)₂ as the palladium catalyst and Na₂CO₃, the desired product was isolated in 88% yield after a 48 hour reaction time (entry 5). Removal of the base from the PdCl₂(PhCN)₂ catalyzed reaction, however, resulted in a lower isolated yield of the desired product (entry 6). Interestingly, by employing only Cul as a catalyst, the desired product was obtained in quantitative yield in a short reaction time (entry 7). In an effort to reduce the amount of catalyst that was employed in the reaction, 5 mol % of Cul was added, but a decrease in the yield was observed (entry 8). Finally, this iminoalkyne can also be cyclized thermally, although the yields are lower than either of the palladium or copper-catalyzed cyclizations (entries 9 and 10).

Based on the mechanistic picture that we envisioned for this process, it was expected that terminal acetylenes would also undergo this annulation. Indeed, phenylacetylene was subsequently observed to participate in this palladium-catalyzed annulation (eq 13). However, under the standard internal alkyne annulation conditions, 3-phenylisoquinoline could only be obtained in 62% isolated yield. Thus, we again were interested in optimizing the yield and reaction time for this process. The results of this investigation are shown in Table 2. After optimization of the reaction conditions, we found that by employing 1 equiv of 7, 1.1 equiv of phenylacetylene, 5 mol % PdCl₂(PhCN)₂, and 1 equiv of Na₂CO₃ in DMF at 100 °C, isoquinoline 10 could be isolated in 85% yield after a 14 h
reaction time (entry 10). It is interesting to note that Cul was not required as a co-catalyst for this annulation.

\[
\begin{align*}
\text{Ph} \quad \text{Ph} \\
\text{Ph} \quad \text{Ph}
\end{align*}
\]

(13)

Table 2. Synthesis of 3-Phenylisoquinoline by Pd-Catalyzed Coupling and Cyclization (eq 13).*

<table>
<thead>
<tr>
<th>entry</th>
<th>base (equiv)</th>
<th>5 mol % Pd catalyst</th>
<th>5 mol % Cul</th>
<th>10 mol % PPh₃</th>
<th>temp (°C), time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na₂CO₃ (1)</td>
<td>Pd(OAc)₂</td>
<td>-</td>
<td>+</td>
<td>100 (58)</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>Na₂CO₃ (1)</td>
<td>Pd(OAc)₂</td>
<td>+</td>
<td>+</td>
<td>rt (12), 100 (75)</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>NEt₃ (2)</td>
<td>Pd(OAc)₂</td>
<td>+</td>
<td>+</td>
<td>rt (12), 100 (22)</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr₂NEt (2)</td>
<td>Pd(OAc)₂</td>
<td>+</td>
<td>+</td>
<td>rt (1), 100 (14)</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>Na₂CO₃ (1)</td>
<td>Pd(OAc)₂</td>
<td>-</td>
<td>-</td>
<td>100 (11)</td>
<td>83ᵇ</td>
</tr>
<tr>
<td>6</td>
<td>NEt₃ (2)</td>
<td>PdCl₂(PPh₃)₂</td>
<td>+</td>
<td>-</td>
<td>rt (3), 100 (15)</td>
<td>59</td>
</tr>
<tr>
<td>7</td>
<td>Na₂CO₃ (1)</td>
<td>PdCl₂(PPh₃)₂</td>
<td>-</td>
<td>-</td>
<td>100 (12)</td>
<td>77ᵇ</td>
</tr>
<tr>
<td>8</td>
<td>Na₂CO₃ (1)</td>
<td>PdCl₂(PhCN)₂</td>
<td>-</td>
<td>+</td>
<td>100 (72)</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>---</td>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Na₂CO₃&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>PdCl₂(PhCN)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
<td>100 (30)</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>Na₂CO₃&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>PdCl₂(PhCN)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
<td>100 (14)</td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Na₂CO₃&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>PdCl₂(PhCN)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>+</td>
<td>-</td>
<td>100 (12)</td>
<td>75&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Na₂CO₃&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>PdCl₂(PhCN)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>+</td>
<td>100 (23)</td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were run with 0.5 mmol of the imine and 1.0 mmol of phenylacetylene in 10 mL of DMF unless otherwise noted. <sup>b</sup>1.1 Equiv of phenylacetylene were used. <sup>c</sup>10 Mol % Cul was added.

After optimization of the reaction conditions with phenylacetylene, we then proceeded to define the scope and limitations of the terminal acetylene annulation. The reaction in which 1-ethynylcyclohexene was employed also afforded the desired isoquinoline in good yield (eq 14). Unfortunately, when cyclohexyl acetylene was employed, none of the desired isoquinoline was obtained (eq 15). In addition, the standard isoquinoline internal alkyne annulation conditions also afforded none of the desired heterocycle. Therefore, we again were interested in finding reaction conditions that would increase the generality of this annulation process.
Due to the success of the copper-catalyzed cyclization of iminoalkyne 9 (Table 1, entry 7), the cyclization of iminoalkynes with differing functionality was investigated (Table 3). All of the iminoalkynes employed in this cyclization process were synthesized in excellent yields by the same sequence of transformations used for alkyne 9 (Scheme 4). Although limited success was obtained from the terminal acetylene coupling/cyclization chemistry discussed previously, the copper-catalyzed cyclization proved to be more general with respect to the functionality that can be introduced into the products. For example, iminoalkynes containing aryl, alkenyl, and alkyl substituents afford excellent yields of the desired monosubstituted isoquinoline heterocycles (Table 3, entries 1-4). However, free hydroxy groups are not tolerated in these cyclization reactions (entries 5 and 6), nor were highly hindered iminoalkynes (entry 7).
Scheme 4

\[
\begin{align*}
\text{Br} & & \text{H} + 1.2 \text{H} = \text{C} - \text{R} \\
& & \xrightarrow{\text{Et}_3\text{N}, 50 \degree \text{C}} \text{Et}_2\text{N}, 50 \degree \text{C} \\
\text{H} & & \text{H} \xrightarrow{3 \text{t-BuNH}_2} 25 \degree \text{C} \\
& & \xrightarrow{2\% \text{PdCl}_2(\text{PPh}_3)_2, \text{1}\% \text{CuI}} \text{N-t-Bu}
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>% yield</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>95</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>95</td>
<td>18</td>
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<td>13</td>
<td>99</td>
<td>19</td>
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<td>14</td>
<td>89</td>
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<td>15</td>
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<td>21</td>
</tr>
<tr>
<td>16</td>
<td>92</td>
<td>22</td>
</tr>
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</table>
Table 3. Synthesis of Isoquinoline Heterocycles by the Cu-Catalyzed Cyclization of Iminoalkynes.

<table>
<thead>
<tr>
<th>entry</th>
<th>imine</th>
<th>time (h)</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Ph} \text{-} \text{Bu} ) ( \text{N} ) ( \text{C} ) ( \text{C} )</td>
<td>3</td>
<td>( \text{Ph} ) ( \text{N} ) ( \text{C} ) ( \text{C} )</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Ph} ) ( \text{C} ) ( \text{C} ) ( \text{N} ) ( \text{Bu} )</td>
<td>3</td>
<td>( \text{N} ) ( \text{C} ) ( \text{C} ) ( \text{C} ) ( \text{C} )</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Ph} ) ( \text{N} ) ( \text{Bu} ) ( \text{C} ) ( \text{C} )</td>
<td>6</td>
<td>( \text{N} ) ( \text{C} ) ( \text{C} ) ( \text{C} ) ( \text{C} )</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Bu} ) ( \text{N} ) ( \text{Bu} ) ( \text{C} ) ( \text{C} ) ( \text{C} ) ( \text{CH} ) ( \text{CH} ) ( \text{C} ) ( \text{C} ) ( \text{C} ) ( \text{C} )</td>
<td>5</td>
<td>( \text{Bu} ) ( \text{N} ) ( \text{Bu} ) ( \text{C} ) ( \text{C} ) ( \text{C} ) ( \text{C} ) ( \text{C} ) ( \text{C} )</td>
<td>83</td>
</tr>
</tbody>
</table>
Table 3. (continued)

<table>
<thead>
<tr>
<th></th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Structure 3</th>
</tr>
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<tr>
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<td><img src="image2" alt="Structure 2" /></td>
<td><img src="image3" alt="Structure 3" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="image4" alt="Structure 1" /></td>
<td><img src="image5" alt="Structure 2" /></td>
<td><img src="image6" alt="Structure 3" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Structure 1" /></td>
<td><img src="image8" alt="Structure 2" /></td>
<td><img src="image9" alt="Structure 3" /></td>
</tr>
</tbody>
</table>

*A representative procedure for the cyclization of iminoalkynes: 10 mol % Cul, the imine (0.25 mmol), and DMF (5 mL) were placed in a 2 dram vial and heated at 100 °C for the indicated time. b100% of the starting material was recovered.

Although the copper-catalyzed synthesis was more general than the palladium-catalyzed terminal acetylene coupling/cyclization reactions with respect to the types of functionality that could be incorporated into the isoquinoline, this synthesis was still not as efficient as the one-pot reaction discussed previously (eqs 13 and 14), since three transformations (coupling, imine formation, and
copper-catalyzed cyclization) were required. Consequently, we more closely examined the reaction of imine 7 and cyclohexyl acetylene with different bases and palladium catalysts (Table 4). By employing Et₃N, instead of Na₂CO₃, as a base in the presence of 5 mol % Pd(OAc)₂ and 2.5 mol % Cul, 3-cyclohexylisoquinoline could be isolated in low yield (entry 3). By increasing the amount of Cul to 10 mol %, a slight increase in yield was observed (entry 4). All additional attempts to increase the yield by changing bases and palladium catalysts in this reaction, however, proved futile (entries 5-11).

Table 4. Synthesis of Compound 24 by the Pd-Catalyzed Coupling and Cyclization of Imine 7 and Cyclohexyl Acetylene.

<table>
<thead>
<tr>
<th>entry</th>
<th>base (equiv)</th>
<th>5 mol % Pd catalyst</th>
<th>Cul (mol %)</th>
<th>temp (°C), time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na₂CO₃ (1)</td>
<td>Pd(OAc)₂</td>
<td>0</td>
<td>100 (24)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Na₂CO₃ (1)</td>
<td>Pd(OAc)₂</td>
<td>10</td>
<td>100 (24)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Et₃N (1)</td>
<td>Pd(OAc)₂</td>
<td>2.5</td>
<td>100 (12)</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Et₃N (1)</td>
<td>Pd(OAc)₂</td>
<td>10</td>
<td>100 (12)</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>Et₃N (1)</td>
<td>Pd(OAc)₂</td>
<td>10</td>
<td>100 (12)</td>
<td>19ᵇ</td>
</tr>
<tr>
<td>6</td>
<td>Et₃N (0.15)</td>
<td>Pd(OAc)₂</td>
<td>10</td>
<td>100 (12)</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>i-Pr₂NEt (1)</td>
<td>Pd(OAc)₂</td>
<td>10</td>
<td>100 (11)</td>
<td>15</td>
</tr>
</tbody>
</table>
Table 4. (continued)

<table>
<thead>
<tr>
<th></th>
<th>Reagent</th>
<th>Catalyst</th>
<th>Cost</th>
<th>Yield (mol%)</th>
<th>Isolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>pyridine (1)</td>
<td>Pd(OAc)$_2$</td>
<td>10</td>
<td>100 (11)</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>Et$_3$N (1)</td>
<td>Pd(dba)$_2$</td>
<td>10</td>
<td>100 (10)</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>Et$_3$N (1)</td>
<td>PdCl$_2$(CH$_3$CN)$_2$</td>
<td>10</td>
<td>100 (10)</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>Et$_3$N (1)</td>
<td>PdCl$_2$(PPh$_3$)$_2$</td>
<td>10</td>
<td>100 (10)</td>
<td>13</td>
</tr>
</tbody>
</table>

*a*All reactions were run with 0.25 mmol of the imine and 1.1 mmol of cyclohexyl acetylene in 5 mL of DMF unless otherwise noted. *b*1.1 Mmol of the imine and 1.0 mmol of cyclohexyl acetylene were employed.

Based on our work up to this point, it was felt that a reasonable mechanism had been formulated for this annulation process (Scheme 2). Specifically, coupling of the aryl halide and terminal acetylene must first occur to produce the intermediate iminoalkyne, followed by a cyclization step to produce the isoquinoline. Therefore, the reaction conditions employed for a one-pot synthesis must be compatible with both steps in the catalytic cycle. Since we had considerable success with the palladium-catalyzed coupling of α-bromobenzaldehyde and terminal acetylenes (Scheme 4), and also with the copper-catalyzed cyclization of iminoalkynes (Table 3), we felt that by an appropriate choice of reaction conditions, it should be possible to efficiently synthesize the desired isoquinolines.
We then investigated the use of the coupling conditions employed in Scheme 4 for both the coupling and cyclization steps (eq 16), since triethylamine was employed for the coupling reactions and afforded the best yield of isoquinoline 24 (Table 4, entry 4). The results of this investigation are shown in Table 5. The reactions were run with 2 mol % PdCl$_2$(PPh$_3$)$_2$ and 1 mol % Cul in Et$_3$N at 50 °C to effect the coupling, and then 100 °C to promote the cyclization of the intermediate iminoalkyne 18. Although only a trace of product was observed under these reactions conditions, it was possible to recover 95% of the intermediate coupled product, thus indicating an efficient coupling step (entry 1). Based on this result, an additional 10 mol % of Cul was added to the reaction mixture after the coupling step had gone to completion, in hopes of promoting the cyclization step. Unfortunately, this also was quite inefficient, although some product was observed (entry 2). Finally, two reactions were run in which an additional 10 mol % of Cul and 3 mL of a solvent were added after the coupling was complete. Unfortunately, this also afforded only trace amounts of the desired isoquinoline (entries 3 and 4).
Table 5. Synthesis of 3-Cyclohexylisoquinoline (eq 16).*  

<table>
<thead>
<tr>
<th>entry</th>
<th>coupling time (h)</th>
<th>cyclization time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>48</td>
<td>trace\textsuperscript{b}</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>48</td>
<td>22\textsuperscript{c}</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>48</td>
<td>0\textsuperscript{d}</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>48</td>
<td>trace\textsuperscript{e}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions were run with 0.5 mmol of the imine, 0.6 mmol of cyclohexyl acetylene, 2 mol % of PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, and 1 mol % of Cul in 2 mL of Et\textsubscript{3}N unless otherwise noted. \textsuperscript{b}A 95% yield of the intermediate alkyne was recovered. \textsuperscript{c}An additional 10 mol % of Cul was added after the coupling step was complete. \textsuperscript{d}An additional 10 mol % of Cul and 3 mL of Et\textsubscript{3}N was added after the coupling step. \textsuperscript{e}An additional 10 mol % of Cul and 3 mL of DMF was added after the coupling step.
Based on the results in Table 5, it appeared that the coupling of imine 7 and cyclohexyl acetylene was proceeding in high yield to produce iminoalkyne 18. However, under the reaction conditions employed, 18 was not efficiently cyclized to isoquinoline 24. Thus, since the coupling reaction proceeded in high yield in Et₃N, which serves as both the solvent and the base, and our considerable success with the copper-catalyzed cyclization in DMF, modified reaction conditions were developed to incorporate both of these transformations into a single reaction sequence (eq 17).

We then employed the following reaction conditions for the isoquinoline synthesis: the imine (0.5 mmol), the terminal acetylene (0.6 mmol), 2 mol % of PdCl₂(PPh₃)₂, and 1 mol % of Cul in 2 mL of Et₃N were heated at 55 °C until the coupling was judged complete by thin-layer chromatography. The solvent and the precipitates were subsequently removed, and DMF (5 mL) and 10 mol % of Cul were added to the residue. The resulting mixtures were then heated at 100 °C until the cyclization was judged complete by thin-layer chromatography. By employing this reaction sequence, a variety of isoquinolines have been synthesized in good to excellent yields (Table 6).
A variety of functionalized terminal acetylenes has been employed in this palladium and copper-catalyzed process. For example, the reaction of imine 7 with aryl-, alkenyl-, and alkyl-substituted acetylenes affords the desired isoquinolines in good to excellent yields (Table 6, entries 1-7). As in our copper-catalyzed cyclization of iminoalkynes, free hydroxy groups are not tolerated, as the reaction of 7 with 3-butyn-1-ol afforded none of the desired heterocycle. Protection of the free hydroxy group as the tetrahydropyranyl ether on the acetylene, however, afforded the desired isoquinoline in 95% yield (entry 4). Acetal and nitrile functional groups were also tolerated (entries 5 and 6). Using 1,6-heptadiyne as the terminal acetylene afforded bis-isoquinoline 31 in 58% yield. Unfortunately, when the highly hindered terminal alkyne 3,3-dimethyl-1-butyne was employed, aldehyde 45 (imine hydrolysis occurred during purification) was isolated in 95% yield after a 24 hour cyclization time. Thus, this isoquinoline synthesis appears to also be limited to the use of relatively unhindered acetylenes. Finally, isoquinolines 33 and 34 and naphthyridines 36 and 37 have also been synthesized in good yields from imines 32 and 35, respectively (entries 8-11).
Table 6. Synthesis of Isoquinolines and Pyridines by the Pd-Catalyzed Coupling and Copper-
Catalyzed Cyclization of Terminal Acetylenes (eq 17).^a

<table>
<thead>
<tr>
<th>entry</th>
<th>imine</th>
<th>alkyne</th>
<th>coupling time (h)</th>
<th>cyclization time (h)</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
</table>
| 1     | \[
\text{\text{-}Bu}
\] | \[
H \equiv -\text{Ph}
\] | 2                 | 1                    | \[
\text{10}
\] | 91      |
| 2     | \[
\text{-H}
\] | \[
H \equiv -\text{C}(CH_2)_{10}THP
\] | 1                 | 5                    | \[
\text{23}
\] | 81      |
| 3     | \[
H \equiv -\text{C}(CH_2)_{10}THP
\] | \[
H \equiv -\text{C}(CH_2)_{10}THP
\] | 1                 | 2                    | \[
\text{24}
\] | 88      |
| 4     | \[
H \equiv -(CH_2)_{10}THP
\] | \[
H \equiv -(CH_2)_{10}THP
\] | 6                 | 2                    | \[
\text{25}
\] | 95      |
Table 6. (continued)

<table>
<thead>
<tr>
<th>entry</th>
<th>imine</th>
<th>alkyne</th>
<th>coupling time (h)</th>
<th>cyclization time (h)</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>H≡-CH(OEt)₂</td>
<td>(CH₂)₃CN</td>
<td>1</td>
<td>2</td>
<td><img src="29" alt="image" /></td>
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</tr>
<tr>
<td>6</td>
<td>H≡-(CH₂)₃CN</td>
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<td>3</td>
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<tr>
<td>7</td>
<td>H≡-(CH₂)₃≡-H</td>
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<td>7</td>
<td>8</td>
<td><img src="31" alt="image" /></td>
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Table 6. (continued)

<table>
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<tr>
<th>entry</th>
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<th>alkyne</th>
<th>coupling time (h)</th>
<th>cyclization time (h)</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>[\text{N}^\text{t-Bu}] \text{Br} \text{N}</td>
<td>H-\equiv-\text{CH}_2\text{CH}_2\text{O}\text{THP}</td>
<td>2</td>
<td>12</td>
<td>[\text{33}]</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>[\text{32}]</td>
<td>H-\equiv-(\text{CH}_2)_2\text{O}\text{THP}</td>
<td>8</td>
<td>12</td>
<td>[\text{34}]</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>[\text{N}^\text{t-Bu}] \text{Br} \text{N}</td>
<td>H-\equiv-\text{Ph}</td>
<td>2</td>
<td>15</td>
<td>[\text{36}]</td>
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<td>cyclization time (h)</td>
<td>product</td>
<td>% yield</td>
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Table 6. (continued)

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<th>alkyne</th>
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<th>cyclization time (h)</th>
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<th>% yield</th>
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<td><img src="image4" alt="Product 44" /></td>
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*All reactions were run using 2 mol % of PdCl$_2$(PPh$_3$)$_2$ and 1 mol % of Cul in 2 mL of Et$_3$N to effect the coupling step, and 10 mol % of Cul in 5 mL of DMF to effect cyclization to the nitrogen heterocycle.*
As in our isoquinoline synthesis from internal alkynes (Chapter 1), pyridines can be synthesized by employing vinylic imines. Pyridines 36 and 37 have been synthesized from cyclic imine 35. Unfortunately, this pyridine synthesis appears to be limited to aryl- and alkenyl-substituted acetylenes, since the reaction of imine 35 and \(N-(2\text{-bromocyclohex-1-enylmethylene})\)-\(\text{tert-butylamine}\) with various alkyl-substituted acetylenes afforded only low yields of the desired pyridines (~10%). Interestingly, the reaction of 1-hexyne and imine 38 did afford pyridine 38 in 46% yield. Finally, pyridine 40 has been synthesized from the acyclic imine 39 in 57% yield.

To demonstrate the utility of this annulation methodology, we have applied this coupling/cyclization process to the synthesis of the naturally-occurring isoquinoline alkaloid decumbenine B (46). Decumbenine B was recently isolated in small amounts from the plant tubers of *Corydalis decumbens*, which have been used in Chinese folk herbal medicine for the treatment of paralytic stroke and rheumatic arthritis.\(^{19}\) One total synthesis of this alkaloid has recently appeared.\(^{20}\) However, the reported synthesis was accomplished in a low overall yield and 18 steps, by employing as a key step, the condensation of benzyl imine 47 with 5,6-(methylenedioxy)homophthalic anhydride 48 (Scheme 5). Upon observation of
the structure of decumbenine B, we felt that it could be efficiently synthesized by employing the palladium-catalyzed coupling and cyclization methodology discussed previously.

**Scheme 5**

The retrosynthetic analysis for the synthesis of 46 is shown in Scheme 6. It was envisioned that decumbenine B could be synthesized by the palladium-catalyzed coupling of imine 49 and alkyne 50 with subsequent cyclization of the intermediate iminoalkyne. The starting materials required for the synthesis of decumbenine B were easily prepared in a minimal number of synthetic transformations from the commercially available aldehydes piperonal and 2,3-(methylene dioxy)benzaldehyde.

**Scheme 6**
The synthesis of imine 49 was accomplished in two steps as shown in Scheme 7. The tert-butyl imine of piperonal was synthesized in high yield and was subjected to previously reported reaction conditions for the metallation of cyclohexylimines derived from piperonal. Treatment of the imine with n-BuLi and subsequent quenching with iodine afforded the desired iodinated imine in 70% yield. It is interesting to note that the tert-butyl imine served as an excellent protecting group for the lithiation reaction, with no addition products of n-BuLi to the imine being observed. In addition, by employing the tert-butyl imine, rather than the cyclohexylimine as was reported, several steps involving imine formation and hydrolysis were avoided.

\[
\text{Scheme 7}
\]

![Scheme 7](image)

The synthesis of alkyne 50 was accomplished in four steps by the synthetic route shown in Scheme 8. Reduction of 3,4-(methyleneedioxy)benzaldehyde to the benzyl alcohol and subsequent iodination afforded the intermediate iodide in 57% overall yield. Alkyne 50 was then synthesized in 98% overall yield by a palladium-catalyzed coupling of the aryl iodide with trimethylsilylacetylene and subsequent desilylation with potassium carbonate.
With imine 49 and alkyne 50 in hand, the synthesis of decumbenine B was completed in 52% yield by employing the palladium-catalyzed methodology developed previously (eq 18). In spite of the low yield for the key palladium-catalyzed reaction, this synthesis of decumbenine B was completed in 7 steps and 20% overall yield, which demonstrates the functionality tolerance and effectiveness of this methodology.
The palladium-catalyzed cyclization/coupling of iminoalkynes and aryl halides has also been investigated for the synthesis of 3,4-disubstituted isoquinolines (eq 19). The reaction of 9 and iodobenzene was chosen as the model system for optimization of the reaction conditions, since the product 3,4-diphenylisoquinoline (51) had been synthesized previously via our internal alkyne methodology. The results of those preliminary studies are summarized in Table 7.
Table 7. Synthesis of 3,4-Diphenylisoquinoline by the Pd-Catalyzed Cyclization of Iminoalkynes (eq 19).\textsuperscript{a}

<table>
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<th>entry</th>
<th>Phl (equiv)</th>
<th>5 mol % Pd catalyst</th>
<th>base</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>% isolated yield (51 + 10)</th>
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<td>100</td>
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<td>54 + 14</td>
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<td>Na\textsubscript{2}CO\textsubscript{3}</td>
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<td>2</td>
<td>80 + 16</td>
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<tr>
<td>4</td>
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<td>Na\textsubscript{2}CO\textsubscript{3}</td>
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<td>8</td>
<td>73 + 0</td>
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<td>9</td>
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<td>Na\textsubscript{2}CO\textsubscript{3}</td>
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<tr>
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### Table 7. (continued)

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*All reactions were run with 0.25 mmol of the imine, 10 mol % PPh$_3$, and 1 equivalent of a base in 5 mL of DMF unless otherwise noted. *0.5 Mmol of the imine and 10 mL of DMF were used. *No PPh$_3$ was added. *2 Ml of DMF were used. *10 Ml of DMF were used. *One equiv of LiCl was added.

In all reactions two products were observed, 3-phenylisoquinoline and 3,4-diphenylisoquinoline. After a thorough investigation of this reaction, the following reaction conditions were observed to give the best ratio of 51 to 10, as well as the highest overall yield: 0.25 mmol of the imine, 0.75 mmol of iodobenzene, 5 mol % Pd(dba)$_2$, 10 mol % PPh$_3$, and 1 equiv of Na$_2$CO$_3$ at 100 °C in 5 mL DMF. By employing these conditions, we were able to obtain 51 in an 84% yield (entry 5). Unfortunately, no reactions conditions were found that exclusively formed disubstituted heterocycle 51. Isoquinoline 10 is presumably being formed from the thermal cyclization of iminoalkyne 9, as had been observed during the optimization
studies for the palladium- and copper-catalyzed cyclizations (Table 1). Therefore, the reaction temperature was lowered for two reactions that were run. Upon lowering the reaction temperature to 80 °C, isoquinoline 51 was the only observed product, but the yield was considerably lower when compared to the reaction that was run at 100 °C (Table 7, entry 4). A reaction was also run at 90 °C. However, only a moderate yield of isoquinoline 51 was obtained, in addition to minor amounts of isoquinoline 10 (Table 7, entry 6).

Reactions have also been run with imine 9 and other aryl iodides, namely 2-iodotoluene, 4-iodoanisole, and ethyl 4-iodobenzoate. However, the reactions with these substrates were much slower than the reactions with iodobenzene and afforded mixtures (~50:50) of the coupled products and 10. Also, one reaction was run with imine 18 under the conditions that were developed for imine 9. Unfortunately, none of the desired product 52 or the cyclization product 53 were observed from this reaction.
This palladium-catalyzed cyclization/coupling process is believed to proceed mechanistically as illustrated in Scheme 9. Specifically, oxidative addition of the aryl halide to Pd(0) produces an arylpalladium intermediate, which then coordinates to the alkyne. Subsequent attack of the neighboring imine substituent onto the coordinated alkyne then forms a diarylpalladium intermediate, which undergoes reductive elimination, thus producing a tert-butylisoquinolinium salt and regenerating Pd(0). As in our internal alkyne annulation chemistry, the tert-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.\(^4\)
We have also discovered that electrophilic cyclizations of iminoalkyne 9 also produce substituted isoquinolines. For example, the reaction of 9 with 3 equiv of iodine and 3 equiv of NaHCO₃ in CH₃CN at 25 °C afforded the halogenated isoquinoline 54 in 55% yield. The mechanism of this process also appears to involve nucleophilic attack of the neighboring imine substituent onto the coordinated alkyne.
Conclusion

Efficient, palladium and copper-catalyzed syntheses of isoquinolines and pyridines have been developed. Only aryl and alkenyl-substituted alkynes cyclize by employing the palladium-catalyzed reaction conditions that have been developed. However, a wide variety of functionalized terminal acetylenes participate in a palladium-catalyzed coupling and copper-catalyzed cyclization process to afford the desired nitrogen heterocycles in moderate to excellent yields. The effectiveness of the palladium-catalyzed terminal acetylene annulation methodology has been demonstrated by the total synthesis of the isoquinoline alkaloid decumbenine B in 7 steps and 20% overall yield. Finally, diaryl iminoalkynes afforded diarylisoquinolines and a halogenated isoquinoline from palladium-catalyzed cyclization/coupling reactions and electrophilic cyclizations, respectively.

Experimental Section

General. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic KMnO$_4$ solution [3 g of KMnO$_4$ + 20 g of K$_2$CO$_3$ + 5 mL of NaOH (5%) + 300 mL of H$_2$O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High
resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer.

**Reagents.** All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na$_2$CO$_3$, Li$_2$CO$_3$, K$_2$CO$_3$, Cs$_2$CO$_3$, NaOAc, DMF, THF, methanol, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. Pd(OAc)$_2$ and PdCl$_2$ were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh$_3$ was donated by Kawaken Fine Chemicals Co. Ltd. 2-Iodobenzyl alcohol, 2-bromobenzaldehyde, phenylacetylene, 1-ethynylcyclohexene, 2-(3-butylnyloxy)tetrahydro-2H-pyran, propargyl alcohol, 2-methyl-3-butyn-2-ol, 3-butyln-1-ol, (triisopropylsilyl)acetylene, (trimethylsilyl)acetylene, propionaldehyde diethyl acetal, 3,3-dimethyl-1-butyne, piperonal, 2,3-(methylenedioxy)benzaldehyde, tert-butylamine, copper iodide, Et$_3$N, and i-Pr$_2$NEt were purchased from Aldrich Chemical Co., Inc. 1,6-Heptadiyne was purchased from Lancaster Synthesis, Inc. Cyclohexylacetylene and 5-cyano-1-pentyne were purchased from Farchan Chemical Co. 2-Iodobenzaldehyde,$^3$ 2-bromopiperonal,$^{22}$ 2-bromocyclopentene-1-carboxaldehyde,$^{23}$ 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde,$^{24}$ (Z)-3-iodo-3-phenyl-2-propenal$^{25}$ and 2-bromo-3-formylpyridine$^{26}$ were prepared according to previous literature procedures. The following starting materials were prepared as indicated.
Aldehydes Prepared

2-(2-Phenylethynyl)benzaldehyde (8). To a solution of 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and phenylacetylene (1.23 g, 12.0 mmol) in Et$_3$N (40 mL) was added PdCl$_2$(PPh$_3$)$_2$ (140 mg, 2 mol %). The mixture was stirred for 5 min and Cul (20 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 20:1 hexanes/EtOAc to afford 1.88 g (91%) of the compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.35-7.44 (m, 4H), 7.52-7.64 (m, 4H), 7.94 (dd, $J = 0.3, 7.8$ Hz, 1H), 10.65 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 85.1, 96.5, 122.4, 126.9, 127.3, 128.6, 128.7, 129.2, 131.8, 133.3, 133.9, 135.9, 191.7.

2-(2-Cyclohex-1-enylethynyl)benzaldehyde (11). The aldehyde was prepared by the same method used for 8, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and 1-ethynylcyclohexene (1.27 g, 12.0 mmol) for 3 h. Column chromatography using 25:1 hexanes/EtOAc afforded 2.00 g (95%) of the compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.57-1.72 (m, 4H), 2.11-2.18 (m, 2H), 2.20-2.25 (m, 2H), 6.27 (dddd, $J = 1.8, 1.8, 6.0, 6.0$ Hz, 1H), 7.33-7.39 (m, 1H), 7.49-7.51 (m, 2H), 7.87 (dt, $J = 1.2, 7.8$ Hz, 1H), 10.52 (d, $J = 0.9$ Hz, 1H).
Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 21.5, 22.3, 25.9, 29.0, 82.5, 98.6, 120.4, 127.1, 127.7, 128.1, 133.1, 133.8, 135.7, 136.9, 192.0.

2-(2-Cyclohexylethynyl)benzaldehyde (12). The aldehyde was prepared by the same method used for 8, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and cyclohexyl acetylene (1.29 g, 12.0 mmol) for 2 h. Column chromatography using 25:1 hexanes/EtOAc afforded 2.01 g (95%) of the compound as a yellow oil: $^1$H NMR (CDCl$_3$) δ 1.34-1.45 (m, 3H), 1.52-1.63 (m, 3H), 1.71-1.78 (m, 2H), 1.87-1.92 (m, 2H), 2.68 (dddd, $J = 3.6, 3.6, 12.6, 12.6$ Hz, 1H), 7.34-7.39 (m, 1H), 7.48-7.54 (m, 2H), 7.88 (d, $J = 8.1$ Hz, 1H), 10.56 (d, $J = 0.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 24.9, 25.9, 29.9, 32.5, 76.3, 102.2, 126.9, 127.9, 128.1, 133.3, 133.7, 136.0, 192.3.

2-[4-(Tetrahydropyran-2-yloxy)but-1-ynyl]benzaldehyde (13). The aldehyde was prepared by the same method used for 8, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and 2-(3-butylnyloxy)tetrahydro-2H-pyran (1.85 g, 12.0 mmol) for 2 h. Column chromatography using 10:1 hexanes/EtOAc afforded 2.56 g (99%) of the compound as a yellow oil: $^1$H NMR (CDCl$_3$) δ 1.48-1.66 (m, 4H), 1.67-1.89 (m, 2H), 2.78 (t, $J = 6.9$ Hz, 2H), 3.49-3.56 (m, 1H), 3.57 (ddd, $J = 6.9, 9.6$ Hz, 1H), 3.85-3.98 (m, 2H), 3.45-3.41 (m, 1H), 7.49-7.51 (m, 2H), 7.87 (ddd, $J = 0.6, 0.6, 7.2$ Hz, 1H) 10.54 (d, $J = 0.9$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 19.5, 21.2, 25.5, 30.6, 62.3, 65.5, 77.2, 94.9, 98.9, 127.0, 127.6, 128.2, 133.3, 133.8, 136.2, 192.2.
2-(3-Hydroxyprop-1-ynyl)benzaldehyde (14). The aldehyde was prepared by the same method used for 8, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and propargyl alcohol (0.67 g, 12.0 mmol) for 6 h. Column chromatography using 1:1 hexanes/EtOAc afforded 1.43 g (89%) of the compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.68 (br s, 1H), 4.51 (s, 2H), 7.34 (dddd, $J$ = 0.6, 3.9, 3.9, 8.7 Hz, 1H), 7.45 (ddd, $J$ = 1.2, 1.2, 5.1 Hz, 2H), 7.80 (ddd, $J$ = 0.9, 0.9, 7.8 Hz, 1H), 10.41 (d, $J$ = 0.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 51.3, 81.0, 94.9, 126.2, 127.5, 128.8, 133.5, 133.9, 135.9, 192.1.

2-(3-Hydroxy-3-methylbut-1-ynyl)benzaldehyde (15). The aldehyde was prepared by the same method used for 8, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and 2-methyl-3-butyn-2-ol (1.01 g, 12.0 mmol) for 2 h. Column chromatography using 3:1 hexanes/EtOAc afforded 1.80 g (96%) of the compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.64 (s, 6H), 2.73 (br s, 1H), 7.36-7.42 (m, 1H), 7.48-7.51 (m, 2H), 7.86 (ddd, $J$ = 0.9, 0.9, 6.9 Hz, 1H), 10.46 (d, $J$ = 0.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 31.4, 65.7, 77.8, 101.2, 126.4, 127.4, 128.7, 133.4, 133.8, 135.9, 191.9.

2-(2-Triisopropylsilylethynyl)benzaldehyde (16). The aldehyde was prepared by the same method used for 8, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and (triisopropylsilyl)acetylene (2.19 g, 12.0 mmol) for 2 h. Column chromatography using 35:1 hexanes/EtOAc afforded 2.65 g (92%) of the compound as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.15 (s, 21H), 7.44 (dddd, $J$ = 0.6, 0.6, 7.8, 7.8 Hz, 1H), 7.52-7.62 (m, 2H), 7.92 (ddd, $J$ = 0.6, 0.6,
7.8 Hz, 1H), 10.62 (d, J = 0.9 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 11.3, 18.7, 99.2, 102.1, 126.9, 127.2, 128.8, 133.7, 134.0, 136.3, 191.8.

**Imines Prepared**

$N$-(2-Iodobenzylidene)-*tert*-butylamine (7). To a mixture of 2-iodobenzaldehyde (1.00 g, 4.3 mmol) and H$_2$O (0.25 mL/mmols) was added *tert*-butylamine (12.9 mmol, 3 equivalents). The mixture was then stirred under a nitrogen atmosphere at room temperature for 12 h. The excess *tert*-butylamine was removed under reduced pressure and the resulting mixture was extracted with ether. The combined organic layers were dried (Na$_2$SO$_4$) and filtered. Removal of the solvent afforded 1.18 g (95%) of the imine as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.33 (s, 9H), 7.07 (td, J = 1.5, 7.2 Hz, 1H), 7.36 (tt, J = 0.6, 7.2 Hz, 1H), 7.83 (dd, J = 0.9, 7.8 Hz, 1H), 7.94 (dd, J = 1.8, 7.8 Hz, 1H), 8.41 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 29.8, 58.0, 100.4, 128.5, 128.7, 131.6, 137.9, 139.4, 159.2; IR (neat, cm$^{-1}$) 3059, 2966, 1633; HRMS Calcd for C$_{11}$H$_{14}$N: 287.0170. Found: 287.0173.

$N$-(2-Phenylethynylbenzylidene)-*tert*-butylamine (9). The imine was prepared by the same method used for 7, but employing 2-(2-phenylethynyl)benzaldehyde (0.80 g, 3.88 mmol). Removal of the solvent afforded 1.00 g (97%) of the imine 9 as a yellow oil, which solidified upon cooling: mp 52-53 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.34 (s, 9H), 7.28-7.35 (m, 5H), 7.49-7.54 (m, 3H), 8.07-8.10 (m, 1H), 8.94 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 30.0, 58.0, 86.9, 95.1, 123.3, 124.1,
126.2, 128.7, 128.7, 128.8, 129.9, 131.6, 132.4, 138.0, 154.2; IR (CHCl₃, cm⁻¹) 3060, 2214, 1637; HRMS Calcd for C₁₉H₁₉N: 261.1518. Found: 261.1518.

\( N-(2-\text{Cyclohex-1-enylethynylbenzylidene})-\text{tert-butylamine} \) (17). The imine was prepared by the same method used for 7, but employing 2-(2-cyclohex-1-enylethynyl)benzaldehyde (1.05 g, 5 mmol). Removal of the solvent afforded 1.28 g (96%) of the imine 17 as a yellow oil: \(^1\)H NMR (CDCl₃) \( \delta \) 1.32 (s, 9H), 1.59-1.74 (m, 4H), 2.13-2.20 (m, 2H), 2.22-2.27 (m, 2H), 6.23 (dddd, \( J = 1.8, 1.8, 6.0, 6.0 \) Hz, 1H), 7.29-7.33 (m, 2H), 7.39-7.45 (m, 1H), 7.98-8.05 (m, 1H), 8.82 (s, 1H); \(^1^3\)C NMR (CDCl₃) \( \delta \) 21.6, 22.4, 25.9, 29.3, 29.9, 57.8, 84.2, 97.0, 120.8, 124.5, 125.9, 128.2, 129.7, 132.1, 135.6, 137.6, 154.6; IR (neat, cm⁻¹) 3062, 2200, 1637; HRMS Calcd for C₁₉H₂₃N: 265.1830. Found: 265.1831.

\( N-(2-\text{Cyclohexylethynylbenzylidene})-\text{tert-butylamine} \) (18). The imine was prepared by the same method used for 7, but employing 2-(2-cyclohexylethynyl)benzaldehyde (0.85 g, 4 mmol). Removal of the solvent afforded 1.01 g (95%) of the imine 18 as a yellow oil: \(^1\)H NMR (CDCl₃) \( \delta \) 1.31 (s, 9H), 1.35-1.45 (m, 3H), 1.50-1.63 (m, 3H), 1.73-1.81 (m, 2H), 1.85-1.92 (m, 2H), 2.68 (dddd, \( J = 3.6, 3.6, 12.3, 12.3 \) Hz, 1H), 7.26-7.31 (m, 2H), 7.37-7.43 (m, 1H), 7.98-8.03 (m, 1H), 8.83 (s, 1H); \(^1^3\)C NMR (CDCl₃) \( \delta \) 24.8, 26.0, 29.8, 29.9, 32.7, 57.8, 78.0, 100.2, 124.9, 125.8, 127.9, 129.7, 132.2, 137.8, 154.8; IR (neat, cm⁻¹) 3062, 2224, 1683; HRMS Calcd for C₁₉H₂₅N: 267.1987. Found: 267.1987.

\( N-[4-(\text{Tetrahydropyran-2-yloxy})\text{but-1-ynylbenzylidene}]-\text{tert-butylamine} \) (19). The imine was prepared by the same method used for 7, but
employing 2-[4-[(tetrahydro-2-yl)oxy]but-1-ynyl]benzaldehyde (0.78 g, 3 mmol). Removal of the solvent afforded 0.88 g (94%) of the imine 19 as a yellow oil: $^1$H NMR (CDCl$_3$) δ 1.30 (s, 9H), 1.48-1.65 (m, 4H), 1.68-1.89 (m, 2H), 2.78 (t, $J$ = 7.2 Hz, 2H), 3.48-3.56 (m, 1H), 3.67 (ddd, $J$ = 7.2, 9.6, Hz, 1H), 3.86-3.97 (m, 2H), 4.68 (t, $J$ = 3.0 Hz, 1H), 7.26-7.31 (m, 2H), 7.37-7.42 (m, 1H), 7.97-8.03 (m, 1H), 8.78 (s, 1H); $^{13}$C NMR (CDCl$_3$) δ 19.5, 21.2, 25.5, 29.8, 30.7, 57.7, 62.3, 65.9, 78.8, 92.7, 98.9, 124.4, 125.9, 128.1, 129.7, 132.4, 137.8, 154.5; IR (neat, cm$^{-1}$) 3063, 2229, 1637; HRMS Calcd for C$_{20}$H$_{27}$NO$_2$: 313.2040. Found: 313.2042.

$N$-[2-(3-Hydroxyprop-1-ynyl)benzylidene]-tert-butylamine (20). The imine was prepared by the same method used for 7, but employing 2-(3-hydroxy-prop-1-ynyl)benzaldehyde (1.00 g, 6.25 mmol). Removal of the solvent afforded 1.30 g (96%) of the imine 20 as a tan solid: mp 50-51 °C; $^1$H NMR (CDCl$_3$) δ 1.30 (s, 9H), 4.04 (br s, 1H), 4.45 (s, 2H), 7.23-7.38 (m, 3H), 7.99 (dd, $J$ = 1.8, 7.5 Hz, 1H), 8.01 (s, 1H); $^{13}$C NMR (CDCl$_3$) δ 29.8, 51.0, 58.1, 82.3, 93.6, 123.6, 126.1, 128.7, 129.9, 132.6, 137.6, 155.1; IR (CHCl$_3$, cm$^{-1}$) 3332, 3066, 2969, 1637; HRMS Calcd for C$_{14}$H$_{27}$NO: 215.1310. Found: 215.1310.

$N$-[2-(3-Hydroxy-3-methylbut-1-ynyl)benzylidene]-tert-butylamine (21). The imine was prepared by the same method used for 7, but employing 2-(3-hydroxy-3-methylbut-1-ynyl)benzaldehyde (0.75 g, 4 mmol). Removal of the solvent afforded 0.94 g (97%) of the imine 21 as a viscous yellow oil: $^1$H NMR (CDCl$_3$) δ 1.31 (s, 9H), 1.64 (s, 6H), 2.47 (br s, 1H), 7.27-7.36 (m, 2H),
7.38-7.43 (m, 1H), 8.01-8.04 (m, 1H), 8.77 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 29.8, 31.6, 58.0, 65.7, 79.5, 99.5, 123.4, 126.0, 128.7, 129.7, 132.3, 137.9, 154.3; IR (neat, cm$^{-1}$) 3359, 3063, 2222, 1637; HRMS Calcd for C$_{16}$H$_{21}$NO: 243.1619. Found: 243.1623.

$N$-(2-Triisopropylsilylethylnylbenzylidene)-$\text{tert}$-butylamine (22).

The imine was prepared by the same method used for 7, but employing 2-(2-triisopropylsilylethylnyl)benzaldehyde (0.57 g, 2 mmol). Removal of the solvent afforded 0.66 g (97%) of the imine 22 as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.15 (s, 21H), 1.31 (s, 9H), 7.29-7.38 (m, 2H), 7.49-7.52 (m, 1H), 8.02-8.08 (m, 1H), 8.88 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 11.37, 18.8, 29.9, 57.8, 96.5, 104.2, 124.2, 125.9, 128.7, 129.6, 133.1, 138.2, 154.3; IR (neat, cm$^{-1}$) 3064, 2153, 1702, 1637; HRMS Calcd for C$_{22}$H$_{35}$NSi: 341.2540. Found: 341.2539.

$N$-(6-Bromobenzo[1,3]dioxol-5-ylmethylene)-$\text{tert}$-butylamine (32).

The imine was prepared by the same method used for 7, but employing 2-bromopiperalonal (2.00 g, 8.73 mmol). Removal of the solvent afforded 2.27 g (92%) of the imine 32 as a white solid: mp 73-74 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.29 (s, 9H), 5.99 (s, 2H), 6.98 (s, 1H), 7.52 (s, 1H), 8.50 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 29.8, 57.8, 102.1, 107.8, 112.5, 117.2, 129.5, 147.9, 150.1, 154.2; IR (CHCl$_3$, cm$^{-1}$) 3077, 2963, 1627; HRMS Calcd for C$_{12}$H$_{14}$BrNO$_2$: 283.0208. Found: 283.0205.

$N$-(2-Bromopyridin-3-ylmethylene)-$\text{tert}$-butylamine (35).

The imine was prepared by the same method used for 7, but employing 2-bromo-3-formylpyridine (0.51 g, 2.74 mmol). Removal of the solvent afforded 0.62 g (94%)
of the imine 35 as a yellow oil: \(^1\text{H NMR (CDCl}_3\text{) }\delta 1.28 (s, 9H), 7.27 (dd, } J = 4.8, 7.8 \text{ Hz, 1H)}), 8.25 (dd, } J = 1.8, 7.5 \text{ Hz, 1H), 8.34 (dd, } J = 0.9, 4.5 \text{ Hz, 1H), 8.48 (s, 1H)}; \(^{13}\text{C NMR (CDCl}_3\text{) }\delta 29.6, 58.5, 123.2, 132.9, 136.9, 144.0, 151.1, 153.2; IR \text{ (neat, cm}^{-1}\text{) } 3043, 2968, 1633, 1576; \text{ HRMS Calcd for } C_{10}H_{14}BrN_2: 240.0262. \text{ Found: 240.0262.}

\text{N-(2-Bromocyclopent-1-enylmethylene)-tert-butylamine (38). The imine was prepared by the same method used for 7, but employing 2-bromocyclopentene-1-carboxaldehyde (0.75 g, 4.31 mmol). Removal of the solvent afforded 0.89 g (90%) of the imine 38 as a dark yellow oil: } \(^1\text{H NMR (CDCl}_3\text{) }\delta 1.22 (s, 9H), 1.97 (\text{quintet, 2H), 2.59 (tt, } J = 2.1, 7.5 \text{ Hz, 2H), 2.79 (tt, } J = 2.4, 7.5 \text{ Hz, 2H), 8.18 (s, 1H); }^{13}\text{C NMR (CDCl}_3\text{) }\delta 21.6, 29.8, 31.1, 41.6, 57.7, 127.9, 139.1, 151.8; IR \text{ (neat, cm}^{-1}\text{) } 2965, 1630; \text{ HRMS Calcd for } C_{10}H_{14}BrN: 229.0466. \text{ Found: 229.0460.}

\text{N-(1-Bromo-3,4-dihydronaphthalen-2-ylmethylene)-tert-butylamine (41). The imine was prepared by the same method used for 7, but employing 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde (0.77 g, 3.26 mmol). Removal of the solvent afforded 0.85 g (89%) of the imine 41 as a viscous yellow oil: } \(^1\text{H NMR (CDCl}_3\text{) }\delta 1.31 (s, 9H), 2.81-2.83 (m, 4H), 7.16 (dd, } J = 1.8, 6.9 \text{ Hz, 1H), 7.22-7.31 (m, 2H), 7.79 (dd, } J = 1.8, 7.2 \text{ Hz, 1H), 8.61 (s, 1H); }^{13}\text{C NMR (CDCl}_3\text{) }\delta 25.3, 27.7, 30.0, 58.1, 126.8, 127.3, 127.6, 128.6, 129.1, 134.2, 135.9, 138.3, 157.0; IR \text{ (neat, cm}^{-1}\text{) } 3063, 2965, 1612; \text{ HRMS Calcd for } C_{15}H_{18}BrN: 291.0623. \text{ Found: 290.0548 (M-H).}
N-[(Z)-3-iodo-3-phenyallylidene]-tert-butylamine (43). The imine was prepared by the same method used for 7, but employing Z-3-iodo-3-phenyl-2-propenal (0.60 g, 2.33 mmol). Removal of the solvent afforded 0.64 g (87%) of the imine 43 as a yellow solid: mp 81-83 °C; ¹H NMR (CDCl₃) δ 1.29 (s, 9H), 6.77 (d, J = 7.8 Hz, 1H), 7.32-7.35 (m, 3H), 7.56-7.60 (m, 2H), 8.15 (d, J = 7.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 29.7, 58.4, 113.6, 128.5, 128.8, 129.6, 134.9, 142.0, 161.4; IR (CHCl₃, cm⁻¹) 3078, 2967, 1614; HRMS Calcd for C₁₃H₁₅N: 313.0328. Found: 313.0332.

General Procedure for the Copper-Catalyzed Cyclization of Iminoalkynes. DMF (5 mL), the imine (0.25 mmol), and Cul (5 mg, 0.025 mmol), were placed in a 2 dram vial. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

3-Phenylisoquinoline (10). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 51 mg (100%) of the indicated compound with
spectral properties identical to those previously reported\textsuperscript{27}: mp 102-103 °C (lit.\textsuperscript{27} mp 101-102 °C).

**3-(Cyclohex-1-enyl)isoquinoline** (23). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 42 mg (81%) of the indicated compound as a yellow solid: mp 114-115 °C (hexanes/EtOAc); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 1.67-1.75 (m, 2H), 1.81-1.89 (m, 2H), 2.29-2.36 (m, 2H), 2.54-2.60 (m, 2H), 7.02 (tt, \(J = 2.4, 3.6\) Hz, 1H), 7.48 (dt, \(J = 0.6, 14.4\) Hz, 1H), 7.57 (s, 1H), 7.63 (dd, \(J = 1.2, 6.9\) Hz, 1H), 7.74 (d, \(J = 8.1\) Hz, 1H), 7.89 (d, \(J = 8.1\) Hz, 1H), 9.18 (s, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 22.3, 23.1, 26.1, 26.2, 114.2, 126.4, 126.8, 127.6, 128.4, 130.3, 135.7, 136.7, 151.7, 152.5 (one sp\textsuperscript{2} carbon missing due to overlap); IR (CHCl\textsubscript{3}, cm\textsuperscript{-1}) 3060, 2919, 1621, 1574; MS m/z (rel intensity) 209 (100, M\textsuperscript{+}), 208 (89), 194 (42), 180 (51). Anal. Calcd for C\textsubscript{15}H\textsubscript{15}N: C, 86.09; H, 7.23; N, 6.69. Found: C, 86.03; H, 7.30; N, 6.73.

**3-Cyclohexylisoquinoline** (24). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 49 mg (93%) of the indicated compound as a yellow oil, which solidified upon cooling: mp 40-41 °C (hexanes/EtOAc); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 1.25-1.67 (m, 6H), 1.89 (dt, \(J = 2.7, 12.6\) Hz, 2H), 2.06 (dd, \(J = 1.5, 12.9\) Hz, 2H), 2.84 (tt, \(J = 3.3, 11.7\) Hz, 1H), 7.45 (s, 1H), 7.50 (ddd, \(J = 1.2, 6.9, 8.1\) Hz, 1H), 7.62 (td, \(J = 1.2, 6.9\) Hz, 1H), 7.74 (d, \(J = 8.1\) Hz, 1H), 7.90 (d, \(J = 8.4\) Hz, 1H), 9.19 (s, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 26.3, 26.8, 33.2, 46.2, 116.2, 126.3, 126.4, 127.3, 127.5, 130.2, 136.7, 151.9, 160.2; IR (CHCl\textsubscript{3}, cm\textsuperscript{-1}) 3055, 2926, 1628, 1585; HRMS Calcd for C\textsubscript{15}H\textsubscript{17}N: 211.1356. Found: 211.1361.
3-[2-(Tetrahydropyran-2-yloxy)ethyl]isoquinoline (25). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 53 mg (83%) of the indicated compound as a yellow oil: \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 1.40-1.60 (m, 4H), 1.61-1.82 (m, 2H), 3.23 (t, \( J = 7.2 \) Hz, 2H), 3.42-3.48 (m, 1H), 3.76 (ddd, \( J = 3.3, 8.1, 11.7 \) Hz, 1H), 3.87 (ddd, \( J = 6.9, 9.6, 16.5 \) Hz, 1H), 4.18 (ddd, \( J = 6.9, 9.6, 16.8 \) Hz, 1H), 4.62 (ddd, \( J = 2.7, 2.7, 2.7 \) Hz, 1H), 7.52 (ddd, \( J = 1.2, 6.9, 9.3 \) Hz, 1H), 7.55 (s, 1H), 7.63 (ddd, \( J = 1.2, 6.6, 9.3 \) Hz, 1H), 7.74 (d, \( J = 8.1 \) Hz, 1H), 7.91 (d, \( J = 7.8 \) Hz, 1H), 9.19 (s, 1H); \( ^{13}C \) NMR (CDCl\(_3\)) \( \delta \) 19.6, 25.5, 30.7, 38.5, 62.3, 67.0, 98.9, 119.2, 126.2, 126.6, 127.3, 127.6, 130.3, 136.5, 152.1, 152.6; IR (CHCl\(_3\), \( \text{cm}^{-1} \)) 3054, 2942, 1629, 1588; HRMS Calcd for C\(_{16}\)H\(_{19}\)NO\(_2\): 257.1416. Found: 257.1415.

**General Procedure for the Palladium and Copper-Catalyzed Formation of Isoquinolines and Pyridines from Terminal Acetylenes.**

Et\(_3\)N (2 mL), PdCl\(_2\)(PPh\(_3\))\(_2\) (7 mg, 0.01 mmol), the imine (0.5 mmol), the terminal acetylene (0.6 mmol) and Cul (1 mg, 0.005 mmol) were placed in a 2 dram vial. The vial was flushed with nitrogen and heated in an oil bath at 55 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. For the reactions with imine 7, the reaction mixture was cooled, the precipitates were filtered off and washed with ether, and the solvent was removed under reduced pressure. For the reactions with imines 32, 35, 37, and 39, the reaction mixture was cooled, the solvent was removed under reduced pressure, the
precipitates were filtered off and washed with ether, and the solvent was removed under reduced pressure. The residue obtained was transferred to a 2 dram vial and DMF (5 mL) and Cul (10 mg, 0.05 mmol) were added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

3-Phenylisoquinoline (10). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 94 mg (91%) of the indicated compound, whose spectral data were identical with that reported above.

3-(Cyclohex-1-enyl)isoquinoline (23). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 85 mg (81%) of the indicated compound, whose spectral data were identical with that reported above.

3-Cyclohexylisoquinoline (24). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 93 mg (88%) of the indicated compound, whose spectral data were identical with that reported above.

3-[2-(Tetrahydropyran-2-yloxy)ethyl]isoquinoline (25). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 122 mg
(95%) of the indicated compound, whose spectral data were identical with that reported above.

3-(Diethoxymethyl)isoquinoline (29). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 97 mg (84%) of the indicated compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.25 (dt, $J = 0.6$, 13.5 Hz, 6H), 3.67 (dddt, $J = 0.6$, 7.2, 7.8, 16.5 Hz, 4H), 5.67 (s, 1H), 7.54 (dddd, $J = 1.2$, 1.2, 8.1, 8.1 Hz, 1H), 7.64 (dddt, $J = 1.2$, 1.2, 6.9, 6.9 Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.90-7.93 (m, 2H), 9.23 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 15.3, 62.0, 102.4, 117.7, 127.2, 127.5, 127.5, 128.4, 130.5, 136.2, 151.5, 152.2; IR (neat, cm$^{-1}$) 3056, 2975, 1629, 1587; HRMS Calcd for C$_{14}$H$_{17}$NO$_2$: 231.1259. Found: 232.1338 (M+H).

4-(3-Isoquinolinyl)butanenitrile (30). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 85 mg (87%) of the indicated compound as an off-white solid: mp 104-105 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 2.18 (pentet, $J = 7.2$ Hz, 2H), 2.36 (t, $J = 7.8$ Hz, 2H), 3.04 (t, $J = 7.2$ Hz, 2H), 7.48 (s, 1H), 7.53 (ddd, $J = 1.2$, 6.9, 9.3 Hz, 1H), 7.64 (dd, $J = 1.2$, 6.9, 9.3 Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 9.17 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 16.6, 25.3, 36.4, 118.9, 119.7, 126.2, 126.9, 127.4, 127.6, 130.7, 136.4, 152.6, 152.8; IR (CHCl$_3$, cm$^{-1}$) 3054, 2946, 1627, 1586; HRMS Calcd for C$_{13}$H$_{12}$N$_2$: 196.1000. Found: 196.1001.

3-[3-(3-Isoquinolinyl)propyl]isoquinoline (31). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 42 mg (56%) of the indicated compound as a yellow solid: mp 116-117 °C (hexanes/EtOAc); $^1$H NMR
(CDCl₃) δ 2.37 (pentet, J = 8.1 Hz, 2H), 3.05 (t, J = 8.4 Hz, 4H), 7.48 (s, 2H), 7.51 (ddd, J = 1.2, 6.9, 9.3 Hz, 2H), 7.62 (ddd, J = 1.2, 6.9, 9.6 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 9.19 (br s, 2H); ¹³C NMR (CDCl₃) δ 30.1, 37.8, 118.3, 126.2, 126.4, 127.2, 127.5, 130.3, 136.6, 152.2, 155.3; IR (CHCl₃, cm⁻¹) 3054, 2946, 1627, 1586; HRMS Calcd for C₁₂H₁₈N₂: 298.1470. Found: 298.1469.

7-Cyclohexyl-1,3-dioxolo[4,5-g]isoquinoline (33). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 97 mg (76%) of the indicated compound as a yellow solid: mp 93-94 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.20-1.61 (m, 5H), 1.71-1.77 (m, 1H), 1.85 (dt, J = 3.0, 12.3 Hz, 2H), 1.97-2.02 (m, 2H), 2.74 (tt, J = 3.3, 8.1 Hz, 1H), 6.01 (s, 2H), 6.95 (s, 1H), 7.09 (s, 1H), 7.25 (s, 1H), 8.89 (s, 1H); ¹³C NMR (CDCl₃) δ 26.3, 33.3, 62.3, 67.1, 98.9, 101.4, 102.3, 103.0, 116.1, 124.3, 135.1, 147.7, 149.7, 150.8, 159.3; IR (CHCl₃, cm⁻¹) 3029, 2923, 1601, 1584, 1482, 1453; HRMS Calcd for C₁₆H₁₇NO₂: 255.1259. Found: 255.1254.

7-[2-(Tetrahydropyran-2-yloxy)ethyl]-1,3-dioxolo[4,5-g]isoquinoline (34). The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 122 mg (81%) of the indicated compound as a yellow oil: ¹H NMR (CDCl₃) δ 1.38-1.79 (m, 6H), 3.12 (t, J = 6.9 Hz, 2H), 3.38-3.45 (m, 1H), 3.69-3.84 (m, 2H), 4.06-4.15 (m, 1H), 4.57-4.59 (m, 1H), 6.01 (s, 2H), 6.94 (s, 1H), 7.08 (s, 1H), 7.34 (s, 1H), 8.87 (s, 1H); ¹³C NMR (CDCl₃) δ 19.6, 25.5, 30.7, 38.3, 62.3, 67.1, 98.9, 101.5, 102.2, 103.0, 119.0, 124.4, 134.9, 147.9, 149.8, 150.9,
7-Phenyl-1,6-naphthyridine (36). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 88 mg (85%) of the indicated compound as a yellow solid: mp 135-136 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 7.39-7.45 (m, 2H), 7.48-7.53 (m, 2H), 8.13-8.17 (m, 2H), 8.23 (d, $J = 8.1$ Hz, 1H), 8.31 (s, 1H), 9.04 (br s, 1H), 9.30 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 117.9, 122.3, 122.7, 127.3, 129.0, 129.2, 135.6, 138.9, 151.4, 152.7, 155.1, 155.2; IR (CDCl$_3$, cm$^{-1}$) 3048, 1618, 1594, 1558; HRMS Calcd for C$_{14}$H$_{10}$N$_2$: 206.0844. Found: 206.0840.

7-n-Butyl-1,6-naphthyridine (37). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 67 mg (72%) of the indicated compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 0.91 (t, $J = 7.5$ Hz, 3H), 1.38 (sextet, $J = 7.5$ Hz, 2H), 1.77 (quintet, $J = 7.5$ Hz, 2H), 2.95 (t, $J = 7.5$ Hz, 2H), 7.39 (dd, $J = 4.2$, 8.4 Hz, 1H), 7.69 (s, 1H), 8.19 (dd, $J = 0.9$, 8.4 Hz, 1H), 8.99 (d, $J = 2.7$ Hz, 1H), 9.16 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.0, 22.5, 31.9, 38.0, 119.6, 121.7, 121.9, 135.6, 151.1, 152.4, 154.8, 160.4; IR (neat, cm$^{-1}$) 3051, 2942, 1604, 1481, 1456; HRMS Calcd for C$_{12}$H$_{14}$N$_2$: 186.1157. Found: 186.1159.

6,7-Dihydro-5H[2]-3-phenylpyridine (39). The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford 68 mg (69%) of the indicated compound with $^1$H spectral properties identical to those previously reported$^{26}$: mp 49-50 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 2.13 (quintet, $J = 7.5$ Hz, 2H), 2.95 (t, $J = 7.2$ Hz, 4H), 7.35-7.41 (m, 1H), 7.42-7.48 (m, 2H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.69 (s, 1H), 8.13 (d, $J = 8.1$ Hz, 1H), 8.23 (d, $J = 8.1$ Hz, 1H), 8.31 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 117.9, 122.3, 122.7, 127.3, 129.0, 129.2, 135.6, 138.9, 151.4, 152.7, 155.1, 155.2; IR (CDCl$_3$, cm$^{-1}$) 3048, 1618, 1594, 1558; HRMS Calcd for C$_{14}$H$_{10}$N$_2$: 206.0844. Found: 206.0840.
0.3 Hz, 1H), 7.94-7.98 (m, 2H), 8.54 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 25.2, 30.1, 32.8, 116.9, 127.0, 128.5, 128.7, 138.8, 140.1, 145.5, 154.7, 155.5; IR (CHCl$_3$, cm$^{-1}$) 3067, 2950, 1611, 1556; HRMS Calcd for C$_{14}$H$_{13}$N: 195.1048. Found: 194.0965 (M-H).

6,7-Dihydro-5H[2]-3-(cyclohex-1-enyl)pyridine (40). The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford 55 mg (55%) of the indicated compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.62-1.69 (m, 2H), 1.74-1.81 (m, 2H), 2.07 (quintet, $J$ = 7.5 Hz, 2H), 2.22-2.25 (m, 2H), 2.47-2.49 (m, 2H), 2.88 (q, $J$ = 6.9 Hz, 4H), 6.56-6.59 (m, 1H), 7.24 (s, 1H), 8.38 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 22.3, 23.0, 25.2, 26.0, 26.4, 30.1, 32.8, 115.2, 127.5, 136.9, 137.9, 144.5, 154.1, 157.2; IR (CHCl$_3$, cm$^{-1}$) 3059, 2854, 1602, 1554, 1477; HRMS Calcd for C$_{14}$H$_{13}$N: 199.1361. Found: 199.1361.

2-n-Butyl-5,6-dihydrobenzo[f]isoquinoline (42). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 55 mg (46%) of the indicated compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 0.96 (t, $J$ = 7.5 Hz, 3H), 1.42 (sextet, $J$ = 7.5 Hz, 2H), 1.75 (quintet, $J$ = 7.8 Hz, 2H), 2.80-2.92 (m, 6H), 7.24-7.36 (m, 3H), 7.44 (s, 1H), 7.75-7.82 (m, 1H), 8.39 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.1, 22.6, 25.1, 28.7, 32.4, 38.2, 116.5, 124.2, 127.2, 128.6, 129.0, 129.3, 132.3, 138.4, 142.0, 148.5, 161.3; IR (neat, cm$^{-1}$) 3061, 2933, 1603, 1544, 1483; HRMS Calcd for C$_{17}$H$_{19}$N: 237.1517. Found: 237.1508.
2,4-Diphenylpyridine (43). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 66 mg (57%) of the indicated compound as a yellow oil with spectral properties identical to those previously reported.

**Total synthesis of Decumbenine B**

*N-(Benzo[1,3]dioxol-5-ylmethylene)-tert-butylamine.* To a mixture of piperonal (2.00 g, 13.3 mmol) and H₂O (2 mL) was added tert-butylamine (26.6 mmol, 2 equiv). The mixture was then stirred under a nitrogen atmosphere at room temperature for 12 h. The excess tert-butylamine was removed under reduced pressure and the resulting mixture was extracted with ether. The combined organic layers were then dried (Na₂SO₄) and filtered. Removal of the solvent afforded 2.65 g (97%) of the imine as a white solid: mp 44-45 °C; ¹H NMR (CDCl₃) δ 1.27 (s, 9H), 5.97 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 7.10 (dd, J = 1.5, 8.1 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 8.15 (s, 1H); ¹³C NMR (CDCl₃) δ 29.9, 57.0, 101.4, 106.6, 108.0, 123.9, 132.2, 148.3, 149.5, 154.3; IR (CHCl₃, cm⁻¹) 3060, 2214, 1637; HRMS Calcd for C₁₂H₁₅NO₂: 205.1100. Found: 205.1103.

*N-(4-iodobenzo[1,3]dioxol-5-ylmethylene)-tert-butylamine (49).* N-(4-iodobenzo[1,3]dioxol-5-ylmethylene)-tert-butylamine was prepared according to a modified literature procedure.²¹ To a solution of N-(benzo[1,3]dioxol-5-ylmethylene)-tert-butylamine (1.03 g, 5.00 mmol) in 40 mL of THF at -78 °C was added 5.25 mmol of n-BuLi (2.5 M in hexanes) dropwise over a
five minute period. The solution was stirred for 30 min at -78 °C and a solution of I₂ (2.68 g, 7.5 mmol) in 15 mL of THF was added dropwise. The resulting solution was warmed to room temperature and was stirred for 2 h. The reaction mixture was then quenched with water, extracted with ether, washed with saturated aqueous Na₂S₂O₃, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. Recrystallization from hexanes/EtOAc afforded 0.77 g (70%) of the desired compound as an off-white solid: mp 126-127 °C; ¹H NMR (CDCl₃) δ

1.29 (s, 9H), 6.05 (s, 2H), 6.61 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 8.32 (s, 1H); ¹³C NMR (CDCl₃) δ 29.9, 57.8, 77.1, 100.9, 108.6, 122.7, 131.2, 147.6, 149.4, 157.4; IR (CHCl₃, cm⁻¹) 3062, 2965, 1596; HRMS Calcd for C₁₂H₁₄N₂O₂: 331.0069. Found: 331.0064.

(5-Iodobenzo[1,3]dioxol-4-yl)methanol. To a solution of 2,3-(methylenedioxy)benzaldehyde (1.50 g, 10.0 mmol) in 5 mL CH₂Cl₂ was added NaBH₄ (0.47 g, 12.5 mmol) in MeOH (5 mL). The reaction mixture was stirred for 2 h at room temperature, quenched with water, extracted with CH₂Cl₂, dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure to afford 1.52 g of the desired alcohol as a colorless oil: ¹H NMR (CDCl₃) δ 2.36 (br s, 1H), 4.64 (s, 2H), 5.93 (s, 2H), 6.73-6.85 (m, 3H); ¹³C NMR (CDCl₃) δ 60.0, 101.1, 108.2, 121.2, 121.8, 122.4, 145.1, 147.4. To a mixture of this alcohol and AgO₂CCF₃ (2.21 g, 10.0 mmol) in 15 mL of CHCl₃ was added a solution of iodine (2.54 g, 10.0 mmol) in 80 mL of CHCl₃. The reaction mixture was stirred for 24 h and then filtered. The filtrate was washed with saturated aqueous NaHCO₃, brine, dried
(MgSO₄), and filtered. Removal of the solvent afforded a yellow oil, which was dissolved in ether. Addition of hexanes precipitated 1.58 g (57%) of the desired alcohol as a yellow solid: mp 96-97 °C; ¹H NMR (CDCl₃) δ 2.20 (br s, 1H), 4.69 (s, 2H), 5.99 (s, 2H), 6.53 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H); ¹³C NMR (CDCl₃) δ 63.4, 88.3, 101.8, 110.2, 124.3, 132.1, 146.6, 148.2; IR (CHCl₃, cm⁻¹) 3358, 2891, 1460; HRMS Calcd for C₉H₇O₂: 277.9444. Found: 277.9442.

(5-Ethynylbenzo[1,3]dioxol-4-yl)methanol (50). To a solution of (5-iodobenzo[1,3]dioxol-4-yl)methanol (0.56 g, 2.0 mmol) and (trimethylsilyl)acetylene (0.24 g, 2.4 mmol) in Et₂NH (10 mL) was added PdCl₂(PPh₃)₂ (28 mg, 2 mol %). The mixture was stirred for 5 min and Cul (4 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The crude silyl acetylene was dissolved in 30 mL of MeOH, and K₂CO₃ (0.55 g, 4 mmol) was added. The mixture was then stirred for 1 h at room temperature. The mixture was washed with saturated aqueous NaHCO₃, extracted with CH₂Cl₂, dried (Na₂SO₄), and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 2:1 hexanes/EtOAc to afford 0.30 g (98%) of the desired compound as a brown solid: mp 64-65 °C; ¹H NMR (CDCl₃) δ 2.50 (br t, J = 5.7 Hz, 1H), 3.20 (s, 1H), 4.77 (d, J = 5.4 Hz, 2H), 5.98 (s, 2H), 6.68 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H); ¹³C NMR (CDCl₃) δ 58.1, 79.9, 81.4,
101.7, 108.0, 114.7, 124.1, 127.6, 146.0, 148.3; IR (CHCl₃, cm⁻¹) 3401, 3286, 2099, 1466; HRMS Calcd for C₁₀H₇O₂: 176.0474. Found: 176.0474.

**Decumbenine B (46).** DMF (5 mL), Pd(OAc)₂ (3 mg, 0.013 mmol), Na₂CO₃ (26 mg, 0.25 mmol), and N-(4-iodobenzo[1,3]dioxol-5-ylmethylene)-tert-butylamine (0.083 g, 0.25 mmol) were placed in a 2 dram vial. The contents were then stirred for 1 minute and (5-ethynylbenzo[1,3]dioxol-4-yl)methanol (42 mg, 0.28 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100°C for 48 h. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column using 1:1 hexanes/EtOAc to afford 42 mg (52%) of the indicated compound with spectral properties identical to those previously reported: mp 221-222 °C (lit. mp 222-224 °C).

**3,4-Diphenylisoquinoline (51).** DMF (5 mL), Pd(dba)₂ (7 mg, 0.013 mmol), PPh₃ (7 mg, 0.025 mmol), Na₂CO₃ (26 mg, 0.25 mmol), and iodobenzene (153 mg, 0.75 mmol) were placed in a 2 dram vial. The contents were then stirred for 1 minute and the appropriate imine (0.25 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for 9 h. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH₄Cl, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure and
the residue was chromatographed using 5:1 hexanes/EtOAc to afford 59 mg (84%) of the indicated compound with spectral properties identical to those previously reported\textsuperscript{30}: mp 154-155 °C (lit.\textsuperscript{30} mp 155-156 °C).

4-iodo-3-phenylisoquinoline (54). To a mixture of iodine (190 mg, 0.75 mmol) and NaHCO\textsubscript{3} (63 mg, 0.75 mmol) in CH\textsubscript{3}CN (1 mL) was added a solution of N-(2-phenylethynylbenzylidene)-\textit{tert}-butylamine (65 mg, 0.25 mmol) in CH\textsubscript{3}CN (1 mL). The resulting mixture was stirred at room temperature for 6 h. Saturated aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (25 mL) was added and the product was extracted with Et\textsubscript{2}O, dried (Na\textsubscript{2}SO\textsubscript{4}), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column using 10:1 hexanes/EtOAc to afford 46 mg (55%) of the indicated compound as a dark brown solid. Filtration through charcoal gave a yellow solid: mp 84-85 °C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) 7.42-7.54 (m, 3H), 7.61-7.67 (m, 2H), 7.70 (ddd, \( J = 0.9, 6.9, 9.0 \) Hz, 1H), 7.85 (ddd, \( J = 1.5, 6.9, 9.9 \) Hz, 1H), 7.98 (dd, \( J = 0.3, 8.1 \) Hz, 1H), 8.25 (dd, \( J = 0.6, 8.4 \) Hz, 1H), 9.19 (s, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \( \delta \) 98.2, 128.0, 128.1, 128.4, 129.9, 132.3, 132.5, 138.7, 143.8, 152.1, 157.2 (one sp\textsuperscript{2} carbon missing due to overlap); IR (CHCl\textsubscript{3}, cm\textsuperscript{-1}) 3055, 1630, 1549; HRMS Calcd for C\textsubscript{19}H\textsubscript{13}O\textsubscript{4}N: 330.9858. Found: 330.9852.

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Chemicals Co., Ltd. for donation of the palladium salts, and Merck and Co., Inc. for an Academic Development Award in Chemistry.

References


15. For a recent leading reference, see: (a) Monteiro, N.; Arnold, A.; Balme, G. 


CHAPTER 3. SYNTHESIS OF ISOINDOLO[2,1-a]INDOLES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKYNES

A paper to be submitted to the Journal of Organic Chemistry

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Abstract

A wide variety of substituted isoindolo[2,1-a]indoles have been prepared via annulation of internal alkynes by imines derived from o-iodoanilines in the presence of a palladium catalyst. This methodology provides an extremely efficient route for the synthesis of these tetracyclic heterocycles from readily available starting materials. The mechanism of this interesting annulation process appears to involve (1) oxidative addition of the aryl iodide to Pd(0), (2) alkyne insertion, (3) addition of the resulting vinylic palladium intermediate to the C-N double bond of the imine, (4) either electrophilic palladation of the resulting σ-palladium intermediate onto the adjacent aromatic ring derived from the internal alkyne, or oxidative addition of the neighboring aryl carbon-hydrogen bond, and (5) reduction of the tetracyclic product and Pd(0). A variety of internal acetylenes have been employed in this annulation process in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring.
Introduction

The development of efficient and selective synthetic transformations is a major challenge in organic synthesis. Consequently, tandem (domino) processes have been extensively investigated as they are among the most versatile reactions for the efficient, stereocontrolled synthesis of complex organic molecules. It is not surprising, therefore, that transition metal-catalyzed alkyne annulation processes have received considerable attention for the synthesis of a variety of complex carbo- and heterocycles due to the synthetic efficiency of this methodology. For example, the palladium-catalyzed annulation of internal alkynes has been employed by Larock and co-workers for the synthesis of indoles, benzofurans, benzopyrans, isocoumarins, indenones, isoquinolines, α-pyrones, and polycyclic aromatic hydrocarbons.

Considerable attention has been directed towards the synthesis of compounds containing the indole nucleus, a structural subunit of a wide variety of biologically active natural products. However, the synthesis of functionalized indoles still presents a major challenge in organic synthesis. Isoindolo[2,1-a]indoles are a class of these functionalized indoles that have been synthesized by employing classical synthetic organic and palladium-mediated methodologies.

Various photochemical approaches to this ring system have been reported. For example, the synthesis of isoindoles 2 by irradiation of phthalimides 1, followed by dehydration, has been reported (eq 1). In addition, isoindole 4 has been synthesized in low yield by the irradiation of iodide 3 (eq 2).
Other reports of the synthesis of these indoles have included acid- and base-catalyzed rearrangements and ring expansion reactions. For example, the synthesis of a mixture of isoindole 5 in 34% yield and indole 6 in 11% yield has been reported from the acid-catalyzed rearrangement of a phthalimidine derivative (eq 3). In addition, these same researchers have reported the synthesis of isoindole 5 in low yield from the base-catalyzed rearrangement of vinylic bromide 7 (eq 4).
The synthesis of indole 4 has also been reported in low yield from the sequence of transformations shown in eq 5. Finally, isoindole 8 has been synthesized as a single example in 57% yield via a thermal ring expansion (eq 6). However, pyrrolophenanthridinediol 9 and indole 10 were also isolated in 12% and 8% yields, respectively from this reaction.
In addition to the photochemical and rearrangement routes already discussed, radical routes to the isoindole nucleus have been reported. For example, the intramolecular radical cyclization of indole 11 employing $n$-Bu$_3$SnH and AIBN has been reported to give isoindole 12 in 35% yield (eq 7). In addition, isoindole 14 has been synthesized in low yield from indole 13 by employing a radical ipso-substitution reaction (eq 8).

Palladium-based methodology has also been employed in the synthesis of isoindolo[2,1-a]indole derivatives. The synthesis of 6-oxo-6H-isoindolo[2,1-a]indoles has been accomplished in yields of 7-47% by the intramolecular dehydrogenation of 1-arylindoles with Pd(OAc)$_2$ (eq 9). However, the yields from this process are relatively low, and the use of 0.5 equiv of Pd(OAc)$_2$ greatly
limits the synthetic utility. In addition, the yields from this synthesis do not exceed 50%, suggesting that the process actually requires stoichiometric amounts of palladium salts.

\[ 0.5 \text{Pd(OAc)}_2, \text{HOAc} \quad 110^\circ \text{C} \]

\[ \text{R} = \text{H, Me, Cl} \]

The synthesis of this class of indoles has been expanded, however, by employing additional palladium-catalyzed cyclization methodology. For example, the palladium-catalyzed cyclization of indole 3 to isoindole 4 has been reported in 80% yield (eq 10), in addition to the synthesis of isoindole 11 in 86% yield (eq 11) and isoindole 4 in 72% yield by employing catalytic amounts of Pd(PPh$_3$)$_4$ (eq 12). In addition to these examples, the synthesis of isoindole 15, containing an acetamide moiety, has been synthesized in 74% yield by employing palladium-catalyzed methodology (eq 13). The synthesis of 15 is of note due to the fact that it has been shown to display a high binding affinity for the peripheral benzodiazepine receptor, which is linked to the production of neurosteroids.

\[ 3 \xrightarrow{10\% \text{Pd(OAc)}_2, 20\% \text{PPh}_3} 4 \quad \text{2 K}_2\text{CO}_3, 1 \text{Et}_4\text{NCl, reflux} \]

(10)
The synthesis of isoindole 12 in 70% yield from the palladium-catalyzed cyclization of iodide 16 (eq 14), and the tetrahydroisoindole derivative 18 from vinylic bromide 17 in 60% yield has also been reported (eq 15). Finally, isoindoles 19 have been synthesized by in yields ranging from 25-87% by employing catalytic amounts of Pd(PPh3)4 (eq 16).

\[ \text{cat. Pd(PPh3)4, KOAc} \]

\[ \text{DMA, } 130 ^\circ \text{C, 10 h} \]

\[ \text{14} \]

\[ \text{cat. Pd(PPh3)4, KOAc} \]

\[ \text{DMA, } 130 ^\circ \text{C, 36 h} \]

\[ \text{4} \]

\[ \text{cat. Pd(PPh3)4, KOAc} \]

\[ \text{DMA, } 160 ^\circ \text{C, 6 h} \]

\[ \text{15} \]
The photochemical, rearrangement, and radical routes for the synthesis of these complex heterocycles all suffer the disadvantage of affording low yields of the tetracyclic products. In addition, the inclusion of additional functionality into the products has not been investigated. Efficient palladium-catalyzed cyclization methodology has been reported for the synthesis of these heterocycles. However, no reports of highly functionalized products, or indoles containing functional groups other than a carbonyl at C-6 of the isoindole[2,1-a]indole structure have appeared.

Due to our continuing interest in the palladium-catalyzed annulation of internal alkynes, we have investigated the reaction of internal alkynes and imines derived from o-iodoanilines and aldehydes. Herein, we report that this annulation methodology very efficiently constructs the isoindolo[2,1-a]indole skeleton from readily prepared imines and internal acetylenes.
Results and Discussion

The palladium-catalyzed reaction of imine 21 and diphenylacetylene was chosen as the model system for our initial investigation of this annulation process. We anticipated that imine 21 might undergo a reaction with an internal alkyne in the presence of a palladium catalyst to produce the highly substituted quinoline derivative 22 (eq 17). However, when reaction conditions were employed that have been used in much of our previous alkyne annulation chemistry (1 equiv of the aryl imine, 2.0 equiv of the acetylene, 5 mol % of Pd(OAc)$_2$, 1 equiv of Na$_2$CO$_3$, and 1 equiv of LiCl in DMF at 100 °C),$^{3a}$ none of the anticipated quinoline derivative was observed. Instead, isoindole 23 was isolated in 85% yield after an 8 h reaction time (eq 18). This was a rather surprising result, and we therefore concentrated on defining the scope and limitations of this intriguing isoindole synthesis.

\[
\begin{align*}
&\text{21} \quad + \quad \text{Ph} \equiv \text{Ph} \quad \xrightarrow{\text{cat. Pd(0) base}} \quad \text{22} \\
&\text{(17)}
\end{align*}
\]
Since the reaction of imine 21 and diphenylacetylene proceeded in high yield and a short reaction time under the reaction conditions that were initially employed, we proceeded to investigate the annulation of 21 with alkynes of differing functionality to expand the scope of this isoindole synthesis. Many of the alkynes that were employed, however, failed to give as good yields as the reactions that were run with diphenylacetylene. For example, the reaction of imine 21 and 1-phenyl-1-butyne under the reaction conditions that were developed for the diphenylacetylene annulation, afforded none of the desired indole 24 (eq 19). Therefore, several optimization reactions were run in order to improve this reaction (Table 1).
### Table 1. Synthesis of Indole 24 by the Pd-Catalyzed Annulation of Internal Acetylenes (eq 19).  

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<td>Na$_2$CO$_3$ (1)</td>
<td>n-Bu$_4$NCl</td>
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<td>65</td>
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<td>63</td>
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<td>n-Bu$_4$NCl</td>
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<td>81$^c$</td>
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</tbody>
</table>

$^a$All reactions were run with 0.5 mmol of the imine, 2.0 mmol of 1-phenyl-1-butyne, and 1 equiv of the chloride source in 10 mL of DMF at 100 °C unless otherwise noted. $^b$1.2 Equiv of 1-phenyl-1-butyne were used. $^c$1.2 Equiv of 1-phenyl-1-butyne and 5 mL of DMF were used.
By employing $n$-Bu$_4$NCl as the chloride source, instead of LiCl, indole 24 was obtained in 65% yield after a 72 h reaction time (entry 1). Upon increasing the amount of Na$_2$CO$_3$ to 2 equiv, virtually no increase in yield or decrease in the reaction time was observed (entry 3). Also, no increase in yield was observed by employing i-Pr$_2$NEt as the base (entry 4). However, by increasing the amount of i-Pr$_2$NEt to 2 equiv with 1 equiv of $n$-Bu$_4$NCl, the yield increased to 78% and the reaction time decreased significantly (entry 5). The yield was not increased, however, by employing 3 equiv of i-Pr$_2$NEt (entry 6). By reducing the amount of the alkyne to 1.2 equiv, indole 24 was isolated in 77% yield (entry 7). Finally, by reducing the amount of alkyne and increasing the concentration of the reaction mixture, the desired product was obtained in 81% yield (entry 8).

As a consequence of the results reported in Table 1, the reaction of imine 21 and diphenylacetylene was reinvestigated (Table 2). By employing i-Pr$_2$NEt as the base, the desired isoindole was obtained in an 85% yield (entry 2). However, as in the reaction with 1-phenyl-1-butyne, reducing the amount of alkyne to 1.2 equiv increased the yield to 94% (entry 3). Upon reducing the amount of alkyne and solvent as in Table 1, the yield was reduced to 85%.

The results of these optimization studies led to the use of three general reaction procedures for the synthesis of the isoindoles. Procedure A: 0.5 mmol of the aryl imine, 2.0 equiv of the acetylene, 5 mol % of Pd(OAc)$_2$, 1 equiv of Na$_2$CO$_3$, and 1 equiv of LiCl in 10 mL of DMF at 100 °C. Procedure B: 0.5 mmol of the aryl imine, 1.2 equiv of the acetylene, 5 mol % of Pd(OAc)$_2$, 1 equiv of i-Pr$_2$NEt, and 1 equiv of $n$-Bu$_4$NCl in 5 mL of DMF at 100 °C. Procedure C: 0.5 mmol of the aryl
Table 2. Synthesis of Indole 23 by the Pd-Catalyzed Annulation of Diphenylacetylene.*

<table>
<thead>
<tr>
<th>entry</th>
<th>base (equiv)</th>
<th>chloride source</th>
<th>time (h)</th>
<th>% isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na₂CO₃ (1)</td>
<td>LiCl</td>
<td>8</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr₂NEt (2)</td>
<td>n-Bu₄NCl</td>
<td>12</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr₂NEt (2)</td>
<td>n-Bu₄NCl</td>
<td>12</td>
<td>94(^b)</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr₂NEt (2)</td>
<td>n-Bu₄NCl</td>
<td>10</td>
<td>85(^c)</td>
</tr>
</tbody>
</table>

*All reactions were run with 0.5 mmol of the imine, 2.0 equiv of diphenylacetylene, and 1 equiv of the chloride source in 10 mL of DMF at 100 °C unless otherwise noted. \(^b\)1.2 Equiv of diphenylacetylene were used. \(^c\)1.2 Equiv of diphenylacetylene and 5 mL of DMF were used.

Imine, 1.2 equiv of the acetylene, 5 mol % of Pd(OAc)₂, 1 equiv of i-Pr₂NEt, and 1 equiv of n-Bu₄NCl in 10 mL of DMF at 100 °C. The procedure used for these reactions is dependent upon the alkyne that is employed, as one procedure may not give any of the desired indole. For example, alkyl-substituted acetylenes afford better yields when procedure B is employed and diaryl acetylenes afford better yields when procedure C is employed. The other substituted alkynes (ester, hydroxyl) afford better yields when procedure A is employed. The isoindoles that have been synthesized are shown in Table 3.

<table>
<thead>
<tr>
<th>entry</th>
<th>imine</th>
<th>alkyne</th>
<th>procedure, time (h)</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph=N=Ph</td>
<td>Ph−≡−Ph</td>
<td>A, 8</td>
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<td>85</td>
</tr>
<tr>
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<td>Ph=N=Ph</td>
<td>Ph−≡−Ph</td>
<td>B, 10</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>Ph−≡−Ph</td>
<td>C, 12</td>
<td>23</td>
<td>94</td>
</tr>
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<td>4</td>
<td>Ph=N=Ph</td>
<td>Ph−≡−Et</td>
<td>A, 72</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ph=N=Ph</td>
<td>Ph−≡−Et</td>
<td>B, 36</td>
<td>24</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>Ph=N=Ph</td>
<td>Ph−≡−Et</td>
<td>C, 36</td>
<td>24</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>Ph=N=Ph</td>
<td>Ph−≡−n-Bu</td>
<td>B, 24</td>
<td>25</td>
<td>81</td>
</tr>
<tr>
<td>entry</td>
<td>imine</td>
<td>alkyne</td>
<td>procedure, time (h)</td>
<td>product</td>
<td>% yield</td>
</tr>
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<td>-------------</td>
<td>---------------------</td>
<td>----------------</td>
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<tr>
<td>8</td>
<td>Ph—≡—CO₂Et</td>
<td>A, 4</td>
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<td>9</td>
<td>Ph—≡—CH₂OH</td>
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<td><img src="image" alt="Product 27" /></td>
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<tr>
<td>10</td>
<td>Ph—≡—CH₂OMe</td>
<td>B, 12</td>
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<td><img src="image" alt="Product 28" /></td>
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Table 3. (continued)

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<th>entry</th>
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<th>alkyne</th>
<th>procedure, time (h)</th>
<th>product</th>
<th>% yield</th>
</tr>
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<tr>
<td>11</td>
<td>Ph = (CH₂)₄OH</td>
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<td>12</td>
<td>Me</td>
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<td>13</td>
<td>MeO = n-Bu</td>
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<td><img src="image" alt="Product 31" /></td>
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<td>alkyne</td>
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<td>product</td>
<td>% yield</td>
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<tr>
<td>14</td>
<td>(\text{F}_3\text{C} \equiv n\text{-Bu})</td>
<td>(\text{B}, 18)</td>
<td>(\text{B}, 18)</td>
<td>(\text{32})</td>
<td>95</td>
</tr>
<tr>
<td>15</td>
<td>(\text{EtO}_2\text{C} \equiv n\text{-Bu})</td>
<td>(\text{B}, 18)</td>
<td>(\text{B}, 18)</td>
<td>(\text{33})</td>
<td>74</td>
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<tr>
<td>16</td>
<td>(\text{N} \equiv n\text{-Bu})</td>
<td>(\text{B}, 10)</td>
<td>(\text{B}, 10)</td>
<td>(\text{34})</td>
<td>93</td>
</tr>
<tr>
<td>entry</td>
<td>imine</td>
<td>alkyne</td>
<td>procedure, time (h)</td>
<td>product</td>
<td>% yield</td>
</tr>
<tr>
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<tr>
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<td>B, 19</td>
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<td>18</td>
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<td>C, 12</td>
<td><img src="image6" alt="Product 36" /></td>
<td>93</td>
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### Table 3. (continued)

<table>
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<tr>
<th>entry</th>
<th>imine</th>
<th>alkyne</th>
<th>procedure, time (h)</th>
<th>product</th>
<th>% yield</th>
</tr>
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<tr>
<td>19</td>
<td><img src="image1.png" alt="Imine Image" /></td>
<td><img src="image2.png" alt="Alkyne Image" /></td>
<td>C, 18</td>
<td><img src="image3.png" alt="Product Image" /></td>
<td>83</td>
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</table>

*Procedure A: 0.5 mmol of the aryl imine, 2.0 equiv of the acetylene, 5 mol % of Pd(OAc)$_2$, 1 equiv of Na$_2$CO$_3$, and 1 equiv of LiCl in 10 mL of DMF were heated at 100 °C for the indicated time. Procedure B: 0.5 mmol of the aryl imine, 1.2 equiv of the acetylene, 5 mol % of Pd(OAc)$_2$, 2 equiv of i-Pr$_2$NEt, and 1 equiv of n-Bu$_4$NCl in 5 mL of DMF were heated at 100 °C for the indicated time. Procedure C: 1 equiv of the aryl imine, 1.2 equiv of the acetylene, 5 mol % of Pd(OAc)$_2$, 2 equiv of i-Pr$_2$NEt, and 1 equiv of n-Bu$_4$NCl in 10 mL of DMF were heated at 100 °C for the indicated time.*
The reaction of imine 21 with a variety of functionalized alkynes has afforded the desired indoles in good to excellent yields. For example, the reaction with diphenylacetylene gave indole 23 in 94% yield by employing procedure C (entry 3). Also, the reaction of 21 with alkyl-substituted alkynes afforded the desired heterocycles in excellent yields by employing procedure B (entries 5 and 7). The annulation with ethyl phenylpropiolate afforded 26 in 80% yield (entry 8).

The reaction of 3-phenyl-2-propyn-1-ol gave 27 in only 51% yield (entry 9). The low yield associated with this alkyne can possibly be explained by a directive effect of the hydroxyl substituent on the alkyne, which has been observed previously in analogous indole chemistry and the palladium-catalyzed hydroarylation of propargylic alcohols. This effect appears to direct alkyne insertion so that the palladium adds to the least hindered end of the alkyne (eq 18). Consequently, the tetracyclic product cannot be formed from this vinylpalladium intermediate, which would undergo unknown side reactions, although no other products were isolated from this reaction (see the latter mechanistic discussion).

\[
\begin{align*}
\text{R} & \quad \text{X} \\
\text{Pd-OH} & \quad \text{Pd-OH} \\
\text{R} & \quad \text{R}
\end{align*}
\]

(eq 18)
In an attempt to avoid the directive effect of the propargylic alcohol, 1-phenyl-3-methoxy-1-propyne was subsequently employed in the annulation with imine 21. However, it appears that the effect of the methyl ether is still significant, as only a low yield of indole 28 was observed (46%, entry 10). 6-Phenyl-5-hexyn-1-ol, which has an additional three carbon spacer between the triple bond and the free hydroxyl substituent, was also employed in the reaction with imine 21. A significant increase in yield was observed from this alkyne annulation (71%, entry 11) when compared to the propargylic alcohol or its methyl ether, although some effect of the heteroatom may still be operating, since the yield was lower than in the annulation in which 1-phenyl-1-hexyne was employed (compare entries 7 and 11).

We have also investigated the regiochemistry of ring closure onto the aryl group of the acetylene (entries 12-15). This has been done by employing alkynes which bear substituents meta to the ethynyl substituent. In the case of the aryl acetylene bearing a methyl group, a single regioisomer 30 was obtained in 84% yield (entry 12). Also, a single regioisomer 31 was isolated in 78% yield from the annulation using an aryl acetylene bearing an electron-donating methoxy group (entry 13). By 1H NMR spectral analysis, regioisomer 30 was obtained, which has the methyl substituent in the 9-position of the isoindole. However, indole 31 has the electron-donating methoxy substituent in the 7-position. The excellent regioselectivity of this ring closure, as well as the reversal of regioselectivity upon switching from the electron-donating methoxy group to the relatively neutral methyl group were rather surprising, so we therefore investigated the use of alkynes bearing electron-withdrawing substituents.
When alkynes bearing electron-withdrawing substituents were employed with imine 21, single regioisomers were also obtained. For example, indole 32 was obtained in which the trifluoromethyl substituent appears in the 9-position, as had been observed with the alkyne bearing the methyl group (entry 14). Surprisingly, the alkyne bearing the electron-withdrawing ester reacted in such a manner as to place the ester functionality in the 7-position, as had been observed with the alkyne bearing the electron-donating methoxy group (entry 15).

From these results, it appears that substituents on the aryl ring of the alkyne are able to control the regioselectivity of ring closure by chelation of the palladium in the σ-palladium intermediate that is formed during the reaction (see the latter mechanistic discussion). For example, products were isolated in which ring closure had occurred to place the oxygen-containing alkoxy or ester functionalities in the 7-position. However, when alkynes were employed that contained trifluoromethyl or methyl substituents, products were isolated with these substituents in the 9-position, presumably due to steric interactions that inhibit ring closure and thus place these groups in the 7-position. Nevertheless, it does appear that by the appropriate choice of functionality, it is possible to exclusively prepare one isoindole isomer.

In addition to the previous examples, ring closure onto heterocyclic rings has also been investigated. For example, 5-pyrimidyl-1-hexyne afforded a 93% yield of the desired tetracyclic indole in a short reaction time (entry 16). Also, a thienyl-
substituted acetylene also undergoes this annulation process to afford heterocycle 35 in 84% yield (entry 17).

Finally, the annulation of functionalized imines also affords the isoindoles in good yields. For example, the annulation of imine 36 with diphenylacetylene afforded indole 37 in 93% yield (entry 18). This example not only demonstrates the ease of introduction of additional functionality into the tetracyclic structure, but it also shows the chemoselectivity of the annulation. Imine 38 bearing an electron-withdrawing methyl ester has also been employed with diphenylacetylene to afford isoindole 39 in good yield (entry 19).

As mentioned previously, the anticipated product from the annulation of imine 21 and diphenylacetylene was the highly substituted quinoline derivative 22 (eq 17). To our surprise, none of this heterocycle was observed and tetracyclic indole 23 was isolated as the only product in 85% yield. From a mechanistic standpoint, these two heterocycles can be formed from two different possible ring closure pathways as illustrated in Scheme 1. Following reduction of Pd(OAc)$_2$ to the actual catalyst Pd(0), oxidative addition of the aryl iodide to Pd(0), and coordination and subsequent insertion of the acetylene, either a 5-exo or 6-endo addition of the vinylpalladium intermediate across the adjacent carbon-nitrogen double bond can occur. The $\sigma$-palladium intermediate resulting from the 5-exo mode cyclization pathway proceeds to form the observed tetracyclic products, and the 6-endo pathway might be expected to form the anticipated quinoline derivative. In this
palladium-catalyzed process, however, the 5-exo pathway, which forms the tetracyclic products, occurs exclusively.

**Scheme 1**

Numerous examples have been reported in the literature in which palladium intermediates can cyclize via exo or endo pathways in Heck-type reactions. Although the exo mode cyclizations have generally been observed to be the dominant ring-closure pathway when substrates are employed that can cyclize via either process, various examples of the less favored endo-mode pathway have been reported. Preliminary data suggests that by slightly altering the reaction conditions employed in this annulation process, it is possible to promote the formation of quinoline derivatives through the 6-exo cyclization pathway (eq 19).
However, a significant amount of the tetracyclic product has also generally been observed. Work on this process is continuing.

\[ \text{Ph} - \text{Ph} + 2 \text{Ph} \equiv \text{Ph} \xrightarrow{10\% \text{Pd(OAc)}_2, 2 \text{n-Bu}_4\text{NCI}} \text{5.5 NaOAc, 10 mL DMF} \xrightarrow{24 \text{h}, 100 \degree \text{C}} \]

Based on the previous discussion, we propose a mechanism for this remarkable isoindole synthesis involving (1) reduction of Pd(OAc)$_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent insertion of the acetylene, (4) a 5-exo addition of the vinylpalladium intermediate across the carbon-nitrogen double bond, (5) either electrophilic palladation of the $\sigma$-palladium intermediate onto the adjacent aromatic ring (path A), or oxidative addition of the neighboring aryl carbon-hydrogen bond of the aromatic ring to the $\sigma$-palladium intermediate to form a Pd(IV) intermediate (path B), and subsequent elimination of HI by base, and (6) regeneration of the Pd(0) catalyst by reductive elimination to form the isoindole as shown in Scheme 2.
Likewise, we propose a mechanism for formation of the quinoline heterocycles involving (1) reduction of Pd(OAc)$_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent insertion of the acetylene, (4) a 6-endo addition of the vinylpalladium intermediate across the carbon-nitrogen double bond, (5) beta hydride elimination to form the quinoline, and (6) regeneration of the Pd(0) catalyst by reductive elimination of HPdI, as shown in Scheme 3.
Conclusion

We have developed an efficient, palladium-catalyzed synthesis of isoindolo[2,1-a]indole heterocycles from readily available starting materials. A wide variety of aryl acetylenes in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring undergo this process in moderate to excellent yields with high regioselectivity. In addition, preliminary results indicate that the formation of highly substituted quinoline heterocycles may be possible by slightly altering the reaction conditions employed.
Experimental

General Procedures. All $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic KMnO$_4$ solution [3 g of KMnO$_4$ + 20 g of K$_2$CO$_3$ + 5 mL of NaOH (5%) + 300 mL of H$_2$O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na$_2$CO$_3$, K$_2$CO$_3$, NaOAc, NaHCO$_3$, LiCl, DMF, THF, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh$_3$ was donated by Kawaken Fine Chemicals Co. Ltd. 2-Iodoaniline, benzaldehyde, 4-chlorobenzaldehyde, methyl 4-aminobenzoate, diphenylacetylene, ethyl phenylpropiolate, 1-phenyl-1-hexyne, methyl propargyl ether, 1-hexyne, 5-hexyn-1-ol, iodobenzene, 2-iodothiophene, 5-bromopyrimidine, 3-bromotoluene, 3-iodoanisole, 3-iodobenzotrifluoride, Et$_3$N, and i-Pr$_2$NEt were purchased from Aldrich Chemical Co., Inc. 3-Phenyl-2-propyn-1-ol, ethyl 3-
iodobenzoate, and $n$-Bu$_4$NCl were purchased from Lancaster Synthesis, Inc. 1-Phenyl-1-butyne was purchased from Farchan Chemical Co. Methyl 3-iodo-4-aminobenzoate was prepared according to a previous literature procedure.$^{25}$ The following starting materials were prepared as indicated.

**General Procedure for the Synthesis of the Aryl Alkynes.** To a solution of the iodo- or bromoarene (10.0 mmol) and terminal alkyne (12.0 mmol) in Et$_3$N (40 mL) was added PdCl$_2$(PPh$_3$)$_2$ (140 mg, 2 mol %). The mixture was then stirred for 5 min and Cul (20 mg, 1 mol %) was added. The resulting mixture was heated under a nitrogen atmosphere at 50 °C. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the pure alkynes.

**Alkynes Prepared**

**1-Phenyl-3-methoxy-1-propyne.** The acetylene was prepared by employing iodobenzene (2.04 g, 10 mmol) and methyl propargyl ether (0.84 g, 12 mmol). Column chromatography on silica gel using 20:1 hexanes/EtOAc afforded 1.39 g (95%) of the desired compound as a yellow oil with spectral properties identical to those previously reported.$^{26}$
6-Phenyl-5-hexyn-1-ol. The acetylene was prepared by employing iodobenzene (2.04 g, 10 mmol) and 5-hexyn-1-ol (1.18 g, 12 mmol). Column chromatography on silica gel using 2:1 hexanes/EtOAc afforded 1.70 g (98%) of the desired compound as a yellow oil: $^1$H NMR (CDCl$_3$) δ 1.63-1.80 (m, 5H), 2.45 (t, $J = 6.6$ Hz, 2H), 3.70 (t, $J = 6.3$ Hz, 2H), 7.24-7.29 (m, 3H), 7.36-7.41 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 19.3, 25.1, 32.0, 62.5, 81.0, 90.0, 124.0, 127.7, 128.3, 131.6.

1-(3-Methyiphenyl)-1-hexyne. The acetylene was prepared by employing 3-bromotoluene (1.71 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol) at 90 °C. Column chromatography on silica gel using hexanes afforded 1.70 g (99%) of the desired compound as a yellow oil: $^1$H NMR (CDCl$_3$) δ 0.96 (t, $J = 7.2$ Hz, 3H), 1.44-1.54 (m, 2H), 1.56-1.65 (m, 2H), 2.32 (s, 3H), 2.42 (t, $J = 6.9$ Hz, 2H), 7.08 (d, $J = 7.2$ Hz, 1H), 7.15-7.24 (m, 3H); $^{13}$C NMR (CDCl$_3$) δ 13.7, 19.2, 21.3, 22.1, 31.0, 80.7, 90.1, 124.0, 128.2, 128.4, 128.7, 132.3, 137.9.

1-(3-Methoxyphenyl)-1-hexyne. The acetylene was prepared by employing 3-iodoanisole (2.34 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol). Column chromatography on silica gel using 25:1 hexanes/EtOAc afforded 1.88 g (100%) of the desired compound as a yellow oil with spectral properties identical to those previously reported.$^{27}$

1-(3-Trifluoromethylphenyl)-1-hexyne. The acetylene was prepared by employing 3-iodobenzotrifluoride (2.72 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol). Column chromatography on silica gel using hexanes afforded 2.26 g (100%) of the desired compound as a yellow oil: $^1$H NMR (CDCl$_3$) δ 0.96 (t, $J = 7.2$ Hz, 3H), 1.44-1.54 (m, 2H), 1.56-1.65 (m, 2H), 2.32 (s, 3H), 2.42 (t, $J = 6.9$ Hz, 2H), 7.08 (d, $J = 7.2$ Hz, 1H), 7.15-7.24 (m, 3H); $^{13}$C NMR (CDCl$_3$) δ 13.7, 19.2, 21.3, 22.1, 31.0, 80.7, 90.1, 124.0, 128.2, 128.4, 128.7, 132.3, 137.9.
Hz, 3H), 1.41-1.65 (m, 4H), 2.42 (t, J = 6.9 Hz, 2H), 7.39 (dd, J = 7.8, 7.8 Hz, 1H),
7.52 (d, J = 13.8 Hz, 1H), 7.54 (d, J = 13.5 Hz, 1H), 7.65 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$
13.7, 19.1, 22.1, 30.7, 79.3, 92.3, 123.9 (q, $^1$$J_{CF}$ = 272.6 Hz), 124.1 (q, $^3$$J_{CF}$ = 3.9
Hz), 125.1, 128.4 (q, $^4$$J_{CF}$ = 3.8 Hz), 128.7, 130.8 (q, $^2$$J_{CF}$ = 32.6 Hz), 134.7.

2-(1-Hexynyl)benzoic acid ethyl ester. The acetylene was prepared
by employing ethyl 3-iodobenzoate (2.76 g, 10.0 mmol) and 1-hexyne (0.99 g,
12.0 mmol). Column chromatography on silica gel using 20:1 hexanes/EtOAc
afforded 2.16 g (94%) of the desired compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$
0.93 (t, J = 7.2 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.42-150 (m, 2H), 1.53-1.63 (m, 2H)
2.39 (t, J = 6.9 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 7.32 (ddd, J = 0.3, 7.8, 7.8 Hz, 1H),
7.53 (ddd, J = 1.5, 1.5, 6.3 Hz, 1H), 7.91 (ddd, J = 1.2, 1.2, 7.8 Hz, 1H), 8.05 (dd, J
= 1.5, 1.5 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 13.7, 14.4, 19.1, 22.1, 30.8, 61.1, 79.8, 91.5,
124.6, 128.3, 128.5, 130.7, 132.7, 135.7, 166.1.

1-(5-Pyrimidyl)-1-hexyne. The acetylene was prepared by employing 5-
bromopyrimidine (1.59 g, 10 mmol) and 1-hexyne (0.99 g, 12 mmol). Column
chromatography on silica gel using 15:1 hexanes/EtOAc afforded 1.53 g (96%) of
the desired compound as a dark yellow oil with spectral properties identical to
those previously reported.$^{28}$

1-(2-Thienyl)-1-hexyne. The acetylene was prepared by employing 2-
iodothiophene (2.10 g, 10 mmol) and 1-hexyne (0.99 g, 12 mmol). Column
chromatography on silica gel using 25:1 hexanes/EtOAc afforded 1.64 g (100%) of
the desired compound as a dark yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 0.96 (t, J = 7.2 Hz,
Imines Prepared

**Benzylidene(2-iodophenyl)amine (21).** A mixture of 2-iodoaniline (2.19 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), and p-toluenesulfonic acid monohydrate (1 crystal) in benzene (40 mL) was refluxed with the aid of a Dean-Stark apparatus to remove the water produced. The reaction was monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The oily residue was dissolved in a minimal amount of 100% ethanol and cooled. The resulting solid was collected to afford 2.15 g (70%) of the imine 21 as an off-white solid: mp 56-57 °C; $^1$H NMR (CDCl$_3$) $\delta$ 6.94 (td, $J = 1.5$, 7.8 Hz, 1H), 7.02 (dd, $J = 1.5$, 8.1 Hz, 1H), 7.38 (td, $J = 1.2$, 7.5 Hz, 1H), 7.48-7.55 (m, 3H), 7.93 (dd, $J = 1.2$, 7.8 Hz, 1H), 7.99-8.02 (m, 2H), 8.31 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 95.0, 118.6, 127.2, 129.0, 129.3, 129.5, 131.9, 135.9, 139.2, 153.1, 161.1; IR (CHCl$_3$, cm$^{-1}$) 3052, 3001, 1626, 1573; HRMS Calcd for C$_{13}$H$_{10}$N: 306.9858. Found: 306.9855.

**4-Chlorobenzylidene(2-iodophenyl)amine (36).** The imine was prepared by the same method used for imine 21 by employing 2-iodoaniline (2.19 g, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol). Crystallization from
100% ethanol afforded 2.46 g (72%) of the imine 36 as a yellow solid: mp 44-45 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 6.94 (td, \(J = 0.9, 5.7\) Hz, 1H), 7.00 (dd, \(J = 1.2, 6.0\) Hz, 1H), 7.37 (td, \(J = 0.9, 6.0\) Hz, 1H), 7.47 (dt, \(J = 1.5, 6.6\) Hz, 2H), 7.90-7.93 (m, 3H), 8.26 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 95.0, 118.3, 127.4, 129.2, 129.4, 130.3, 134.3, 137.9, 139.2, 152.7, 159.5; IR (CHCl\(_3\), cm\(^{-1}\)) 3056, 2997, 1628, 1569; HRMS Calcd for C\(_{13}\)H\(_9\)ClIN: 340.9468. Found: 340.9472.

4-Benzylideneamino-3-iodobenzoic acid methyl ester (38). The imine was prepared by the same method used for imine 21 by employing methyl 3-iodo-4-aminobenzoate (4.27 g, 15.4 mmol) and benzaldehyde (2.45 g, 23.1 mmol). Crystallization from 100% ethanol afforded 1.46 g (40%) of the imine 38 as an off-white solid: mp 64-65 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.93 (s, 3H), 7.00 (d, \(J = 8.1\) Hz, 1H), 7.45-7.57 (m, 3H), 7.98 (dd, \(J = 1.5, 6.3\) Hz, 2H), 8.04 (dd, \(J = 1.5, 8.1\) Hz, 1H), 8.30 (s, 1H), 8.5 (d, \(J = 1.2\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 52.4, 93.6, 118.2, 128.5, 129.0, 129.4, 131.0, 132.3, 135.5, 140.5, 157.2, 162.0, 165.6; IR (CHCl\(_3\), cm\(^{-1}\)) 3060, 2949, 1720, 1631, 1585; HRMS Calcd for C\(_{15}\)H\(_{12}\)INO\(_2\): 364.9913. Found: 364.9921.

**General Procedure for the Palladium-Catalyzed Formation of Isoindolo[2,1-a]indoles.** Procedure A: DMF (10 mL), Pd(OAc)\(_2\) (6 mg, 0.027 mmol), LiCl (21 mg, 0.5 mmol), Na\(_2\)CO\(_3\) (56 mg, 0.5 mmol), and the alkyne (1.0 mmol) were placed in a 4 dram vial. Procedure B: DMF (5 mL), Pd(OAc)\(_2\) (6 mg, 0.027 mmol), n-Bu\(_4\)NCl (139 mg, 0.5 mmol), i-Pr\(_2\)NEt (130 mg, 1.0 mmol), and the alkyne (0.6 mmol) were placed in a 2 dram vial. Procedure C: DMF (10 mL),
Pd(OAc)$_2$ (6 mg, 0.027 mmol), $n$-Bu$_4$NCl (139 mg, 0.5 mmol), $i$-Pr$_2$NEt (130 mg, 1.0 mmol), and the alkyne (1.2 mmol) were placed in a 4 dram vial. The chemicals for procedures A-C were mixed and the appropriate imine (0.5 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature, diluted with 30 ml of ether, washed with 45 mL (Procedures A and C) or 30 mL (Procedure B) of saturated aqueous NH$_4$Cl, dried (Na$_2$SO$_4$), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

**Compounds Prepared**

**6,11-Diphenylisoindolo[2,1-a]indole** (Compound 23, Table 3, entry 3). The reaction was run using procedure C and was chromatographed using 25:1 hexanes/EtOAc to afford 168 mg (94%) of the indicated compound as a white solid: mp 168-169 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 6.20 (s, 1H), 7.02 (dt, $J$= 0.6, 8.1 Hz, 1H), 7.16 (ddddd, $J$= 1.5, 7.2, 7.2, 22.2 Hz, 2H), 7.25-7.49 (m, 9H), 7.63 (t, $J$ = 7.5 Hz, 2H), 7.87-7.94 (m, 4H); $^{13}$C NMR (CDCl$_3$) $\delta$ 64.5, 109.8, 110.3, 120.3, 120.5, 121.1, 122.4, 124.1, 126.5, 127.3, 127.7, 128.4, 128.6, 128.9, 129.3, 129.5, 131.9, 132.0, 133.7, 135.1, 138.9, 139.5, 147.5; IR (CHCl$_3$, cm$^{-1}$) 3065, 3028, 1602,
152; MS m/z (rel intensity) 358 (28, M+1), 357 (100, M*), 356 (26), 280 (78). Anal. Calcd for C_{27}H_{25}N: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.39; H, 5.61; N, 3.94.

11-Ethyl-6-phenylisoindolo[2,1-a]indole (Compound 24, Table 3, entry 5). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 126 mg (81%) of the indicated compound as a white solid: mp 144-145 °C (hexanes/EtOAc); 'H NMR (CDCl_{3}) δ 1.50 (t, J = 7.5 Hz, 3H), 3.18 (q, J = 7.5 Hz, 2H), 6.14 (s, 1H), 6.97 (dd, J = 1.8, 7.8 Hz, 1H), 7.06-7.16 (m, 2H), 7.22-7.26 (m, 4H), 7.35-7.47 (m, 4H), 7.75 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H); ^{13}C NMR (CDCl_{3}) δ 15.9, 18.1, 64.3, 109.9, 110.1, 119.1, 119.8, 120.9, 121.7, 124.1, 126.8, 127.2, 128.4, 128.5, 129.1, 132.5, 132.8, 133.6, 139.1, 139.4, 147.2; IR (CHCl_{3}, cm^{-1}) 3057, 2926, 1611, 1451; HRMS Calcd for C_{23}H_{19}N: 309.1518. Found: 309.1516. Anal. Calcd for C_{23}H_{19}N: C, 89.28; H, 6.19; N, 4.53. Found: C, 88.95; H, 6.47; N, 4.66.

11-n-Butyl-6-phenylisoindolo[2,1-a]indole (25). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 137 mg (81%) of the indicated compound as a white solid: mp 135-136 °C (hexanes/EtOAc); 'H NMR (CDCl_{3}) δ 1.04 (t, J = 7.5 Hz, 3H), 1.56 (sextet, J = 7.5 Hz, 2H), 1.86 (quintet, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 6.14 (s, 1H), 6.93 (dd, J = 0.9, 7.5 Hz, 1H), 7.09 (dddd, J = 1.2, 7.2, 7.2, 17.7 Hz, 2H), 7.18-7.24 (m, 4H), 7.33-7.44 (m, 4H), 7.71 (dd, J = 0.6, 8.1 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H); ^{13}C NMR (CDCl_{3}) δ 14.3, 22.9, 24.5, 33.5, 64.3, 108.3, 110.0, 119.1, 119.9, 120.9, 121.6, 124.1, 126.8, 127.2, 128.3, 128.4, 129.1, 132.5, 133.1, 133.5, 139.4, 139.5, 147.2;
Ethyl 6-phenylisoindolo[2,1-a]indole-11-carboxylate (26). The reaction was run using procedure A and was chromatographed using 7:1 hexanes/EtOAc to afford 141 mg (80%) of the indicated compound as a white solid: mp 181-182 °C (hexanes/EtOAc); \(^1H\) NMR (CDCl\(_3\)) \(\delta\) 1.57 (t, \(J = 7.2\) Hz, 3H), 4.55 (q, \(J = 7.2\) Hz, 2H), 6.02 (s, 1H), 6.90 (d, \(J = 8.1\) Hz, 1H), 7.06-7.13 (m, 3H), 7.24 (dt, \(J = 0.9, 14.4\) Hz, 2H), 7.30-7.37 (m, 4H), 7.49 (dt, \(J = 0.6, 14.7\) Hz, 1H), 8.28 (d, \(J = 8.1\) Hz, 1H), 8.78 (d, \(J = 7.5\) Hz, 1H); \(^13C\) NMR (CDCl\(_3\)) \(\delta\) 14.9, 60.0, 64.9, 99.9, 104.4, 122.0, 122.9, 123.4, 125.7, 127.2, 128.8, 129.3, 130.7, 131.2, 133.1, 137.5, 148.3, 148.6, 165.8 (two sp\(^2\) carbons missing due to overlap); IR (CHCl\(_3\), cm\(^{-1}\)) 3056, 2980, 1688, 1559; HRMS Calcd for C\(_{24}\)H\(_{19}\)NO\(_2\): 353.1416. Found: 353.1416.

11-Hydroxymethyl-6-phenylisoindolo[2,1-a]indole (27). The reaction was run using procedure A and was chromatographed using 1:1 hexanes/EtOAc to afford 80 mg (51%) of the indicated compound as a white solid: mp 182-183 °C (hexanes/EtOAc); \(^1H\) NMR (CDCl\(_3\)) \(\delta\) 1.59 (br s, 1H), 5.20 (s, 2H), 6.12 (s, 1H), 6.92 (d, \(J = 7.8\) Hz, 1H), 7.10 (dddd, \(J = 1.2, 6.9, 6.9, 19.5\) Hz, 2H), 7.15-7.22 (m, 2H), 7.25, (dd, \(J = 0.9, 5.4\) Hz, 2H), 7.28-7.35 (m, 3H), 7.41 (td, \(J = 1.8, 8.1\) Hz, 1H), 7.76 (d, \(J = 7.5\) Hz, 1H), 7.92 (d, \(J = 7.5\) Hz, 1H); \(^13C\) NMR (CDCl\(_3\)) \(\delta\) 56.2, 64.6, 106.6, 110.2, 119.7, 120.0, 121.8, 122.1, 124.0, 127.2, 127.6, 128.5, 128.6, 129.2, 131.5,
11-Methoxymethyl-6-phenylisoindolo[2,1-a]indole (28). The reaction was run using procedure B and was chromatographed using 10:1 hexanes/EtOAc to afford 75 mg (46%) of the indicated compound as a white solid: mp 144-145 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 3.53 (s, 3H), 5.03 (s, 2H), 6.12 (s, 1H), 6.94 (dd, $J = 0.3, 7.8$ Hz, 1H), 7.11 (dddd, $J = 1.2, 7., 7.2, 21.6$ Hz, 2H), 7.19 (dd, $J = 3.6, 7.5$ Hz, 2H), 7.25-7.27 (m, 2H), 7.33-7.36 (m, 3H), 7.43 (td, $J = 2.4, 8.1$ Hz,1H), 7.78 (dd, $J = 0.6, 7.8$ Hz, 1H), 7.93 (d, $J = 7.8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 57.6, 64.5, 65.3, 103.8, 110.2, 119.90, 119.94, 121.9, 122.0, 124.0, 127.2, 127.5, 128.5, 128.6, 129.2, 131.8, 132.9, 133.4, 138.83, 141.9, 147.4; IR (CHCl$_3$, cm$^{-1}$) 3055, 2923, 1612, 1451; HRMS Calcd for C$_{22}$H$_{17}$NO: 311.1310. Found: 311.1307.

11-(4-Hydroxybutyl)-6-phenylisoindolo[2,1-a]indole (29). The reaction was run using procedure B and was chromatographed using 1:1 hexanes/EtOAc to afford 127 mg (72%) of the indicated compound as a white solid: mp 136-137 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 1.61 (br s, 1H), 1.73-1.82 (m, 2H), 1.89-1.99 (m, 2H), 3.16 (t, $J = 7.2$ Hz, 2H), 3.71 (t, $J = 6.6$ Hz, 2H), 6.13 (s, 1H), 6.93 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.08 (dddd, $J = 1.2, 7.2, 7.2, 15.9$ Hz, 2H), 7.17-7.26 (m, 4H), 7.31-7.43, (m, 4H), 7.68 (dd, $J = 1.2, 6.9$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 24.4, 27.3, 32.7, 63.1, 64.2, 107.6, 110.1, 119.2, 119.8, 120.8, 121.7, 124.1, 126.9, 127.2, 128.3, 128.4, 129.1, 132.4, 133.0, 133.5, 139.3, 139.6,
11-n-Butyl-9-methyl-6-phenylisoindolo[2,1-a]indole (30). The reaction was run using procedure B and was chromatographed using 50:1 hexanes/EtOAc to afford 142 mg (81%) of the indicated compound as a yellow solid: mp 122-124 °C (hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.08 (t, \(J = 7.2\) Hz, 3H), 1.61 (sextet, \(J = 7.5\) Hz, 2H), 1.90 (quintet, \(J = 7.2\) Hz, 2H), 2.51 (s, 3H), 3.18 (t, \(J = 7.5\) Hz, 2H), 6.11 (s, 1H), 6.95 (dd, \(J = 1.2, 6.9\) Hz, 1H), 7.05-7.17 (m, 4H), 7.20-7.25 (m, 2H), 7.32-7.40 (m, 3H), 7.65 (s, 1H), 7.74 (dd, \(J = 0.6, 7.2\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 14.4, 21.8, 22.9, 24.5, 33.5, 64.1, 108.2, 110.0, 119.0, 119.9, 121.5, 121.6, 123.8, 127.2, 127.7, 128.3, 129.1, 132.7, 133.2, 133.6, 138.2, 139.6, 139.7, 144.6; IR (CDCl\(_3\), cm\(^{-1}\) ) 3058, 2954, 1620, 1452; HRMS Calcd for C\(_{25}\)H\(_{23}\)NO: 353.1780. Found: 353.1787.

11-n-Butyl-7-methoxy-6-phenylisoindolo[2,1-a]indole (31). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 144 mg (78%) of the indicated compound as a white solid: mp 153-154 °C (hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.99 (t, \(J = 7.5\) Hz, 3H), 1.52 (sextet, \(J = 7.5\) Hz, 2H), 1.81 (quintet, \(J = 7.5\) Hz, 2H), 3.08 (t, \(J = 7.5\) Hz, 2H), 3.88 (s, 3H), 6.08 (s, 1H), 6.75 (dd, \(J = 2.4, 8.4\) Hz, 1H), 6.89 (dddd, \(J = 0.9, 0.9, 0.9, 8.1\) Hz, 1H), 7.04 (dddd, \(J = 1.2, 6.9, 6.9, 22.2\) Hz, 2H), 7.10 (d, \(J = 8.4\) Hz, 1H), 7.14-7.20 (m, 2H), 7.28-7.36 (m, 4H), 7.65 (dddd, \(J = 0.9, 0.9, 0.9, 7.8\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 14.4, 22.9, 24.5, 33.5, 55.7, 63.8, 106.7, 108.5, 110.0, 112.3, 119.1,
120.0, 121.7, 124.7, 127.2, 128.3, 129.1, 133.1, 133.6, 133.8, 139.3, 139.6, 139.8, 160.2; IR (CHCl₃, cm⁻¹) 3043, 2925, 1626, 1456; HRMS Calcd for C₂₆H₂₃NO: 367.1936. Found: 367.1936.

The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 193 mg (95%) of the indicated compound as a yellow solid: mp 139-140 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.01 (t, J = 7.2 Hz, 3H), 1.52 (sextet, J = 7.5 Hz, 2H), 1.83 (quintet, J = 7.5 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 6.23 (s, 1H), 6.90 (dd, J = 1.2, 6.3 Hz, 1H), 7.09 (ddddd, J = 1.5, 7.2, 7.2, 14.1 Hz, 2H), 7.15 (d, J = 1.8 Hz, 1H), 7.17 (d, J = 4.2 Hz, 1H), 7.29-7.37 (m, 4H), 7.46 (dd, J = 0.6, 8.1 Hz, 1H), 7.70 (dd, J = 1.5, 6.9 Hz, 1H), 7.96 (s, 1H); ¹³C NMR (CDCl₃) δ 14.2, 22.8, 24.4, 33.3, 64.1, 109.7, 110.1, 117.4 (q, ³JCF = 2.8 Hz), 119.4, 120.3, 122.3, 123.6 (q, ⁴JCF = 2.7 Hz), 124.2 (q, ¹JCF = 204.1 Hz), 124.4, 127.1, 128.7, 129.3, 130.0 (q, ²JCF = 24.2 Hz), 133.0, 133.2, 133.5, 137.9, 138.4, 150.3; IR (CHCl₃, cm⁻¹) 3049, 2926, 1455, 1438; HRMS Calcd for C₂₆H₂₂F₃N: 405.1704. Found: 405.1705.

Ethyl 11-n-butyl-6-phenylisoindolo[2,1-a]indole-7-carboxylate (33). The reaction was run using procedure B and was chromatographed using 10:1 hexanes/EtOAc to afford 151 mg (74%) of the indicated compound as a yellow solid: mp 120-121 °C (hexanes/EtOAc); ¹H NMR (CDCl₃) δ 1.02 (t, J = 7.5 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.53 (sextet, J = 7.5 Hz, 2H), 1.84 (quintet, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 4.44 (q, J = 7.2 Hz, 2H), 6.15 (s, 1H), 6.90 (ddd, J = 0.9, 0.9,
8.1 Hz, 1H), 7.07 (dddd, J = 1.2, 7.2, 7.2, 14.7 Hz, 2H), 7.15-7.18 (m, 2H), 7.26 (d, J = 8.1 Hz, 1H), 7.31-7.36 (m, 3H), 7.68 (dddd, J = 1.5, 6.6 Hz, 1H), 7.90 (dd, J = 1.5, 8.1 Hz, 1H), 8.41 (d, J = 1.2 Hz, 1H); ^13C NMR (CDCl₃) δ 14.3, 14.5, 22.8, 24.4, 33.4, 61.3, 64.3, 109.3, 110.1, 119.4, 120.2, 121.8, 122.1, 123.9, 127.2, 128.2, 128.6, 129.2, 131.0, 132.9, 133.1, 133.5, 138.4, 138.7, 151.5, 166.4; IR (CDCl₃, cm⁻¹) 3056, 2967, 1720, 1437; HRMS Calcd for C₂₃H₂₁N₃: 339.1736. Found: 339.1738.

**Compound 34** (Table 3, entry 16). The reaction was run using procedure B and was chromatographed using 1:1 hexanes/EtOAc to afford 158 mg (93%) of the indicated compound as an off-white solid: mp 200-201 °C (hexanes/EtOAc); ^1H NMR (CDCl₃) δ 0.99 (t, J = 7.2 Hz, 3H), 1.49 (sextet, J = 7.5 Hz, 2H), 1.82 (quintet, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 6.17 (s, 1H), 6.96 (dddd, J = 3.6, 3.6, 7.8, 7.8 Hz, 1H), 7.13 (dddd, J = 1.2, 1.2, 8.1, 8.1 Hz, 2H), 7.19 (dd, J = 3.6, 7.5 Hz, 2H), 7.35-7.38 (m, 3H), 7.71 (dddd, J = 3.3, 3.3, 11.1, 11.1 Hz, 1H), 9.00 (s, 1H), 9.04 (s, 1H); ^13C NMR (CDCl₃) δ 14.2, 22.8, 24.9, 33.2, 64.6, 110.7, 112.4, 120.0, 120.5, 123.2, 125.5, 127.2, 129.0, 129.3, 132.1, 133.5, 134.1, 135.9, 147.8, 156.0, 173.6; IR (CHCl₃, cm⁻¹) 3028, 2953, 1495, 1456; HRMS Calcd for C₂₅H₂₁N₃: 409.2042. Found: 409.2048.

**Compound 35** (Table 3, entry 17). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 144 mg (84%) of the indicated compound as an off-white solid: mp 104-105 °C (hexanes/EtOAc); ^1H NMR (CDCl₃) δ 1.01 (t, J = 7.2 Hz, 3H), 1.50 (sextet, J = 7.5 Hz, 2H), 1.85 (quintet, J
= 7.2 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 6.07 (s, 1H), 6.86-6.89 (m, 2H), 7.04 (dddd, J = 1.5, 6.9, 6.9, 13.8 Hz, 2H), 7.20 (dddd, J = 4.2, 4.2, 4.2, 6.3 Hz, 2H), 7.27 (d, J = 4.8 Hz, 1H), 7.30-7.37 (m, 3H), 7.62 (dddd, J = 0.6, 0.6, 0.6, 8.1 Hz, 1H); \({}^{13}\)C NMR (CDCl\(_{3}\)) \(\delta\) 14.3, 22.9, 24.9, 32.8, 63.2, 105.8, 109.3, 118.9, 120.0, 121.5, 121.7, 127.1, 128.3, 128.4, 129.2, 132.5, 133.0, 134.5, 136.7, 138.6, 151.1; IR (CHCl\(_3\), cm\(^{-1}\)) 3041, 2925, 1552, 1454; HRMS Calcd for C\(_{23}\)H\(_{21}\)NS: 343.1395. Found: 343.1395.

**11-Phenyl-6-(3-chlorophenyl)isoindolo[2,1-a]indole (37).** The reaction was run using procedure C and was chromatographed using 25:1 hexanes/EtOAc to afford 182 mg (93%) of the indicated compound as a white solid: mp 165-166 °C (hexanes/EtOAc); \(^1\)H NMR (CDCl\(_{3}\)) \(\delta\) 6.11 (s, 1H), 6.99 (dd, J = 1.2, 7.2 Hz, 1H), 7.13-7.39 (m, 9H), 7.47 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 2H), 7.86-7.93 (m, 4H); \(^{13}\)C NMR (CDCl\(_{3}\)) \(\delta\) 63.7, 110.0, 110.2, 120.5, 120.6, 121.2, 122.5, 123.9, 126.6, 127.8, 128.6, 128.7, 129.0, 129.5, 129.5, 131.8, 132.0, 133.6, 134.4, 134.9, 137.5, 139.3, 147.0; IR (CHCl\(_3\), cm\(^{-1}\)) 3051, 3016, 1602, 1489; HRMS Calcd for C\(_{27}\)H\(_{18}\)ClN: 391.1128. Found: 391.1121.

**Methyl 6,11-diphenylisoindolo[2,1-a]indole-2-carboxylate (39).** The reaction was run using procedure C and was chromatographed using 15:1 hexanes/EtOAc to afford 172 mg (83%) of the indicated compound as a white solid: mp 170-171 °C (hexanes/EtOAc); \(^1\)H NMR (CDCl\(_{3}\)) \(\delta\) 3.90 (s, 3H), 6.22 (s, 1H), 6.95 (d, J = 8.7 Hz, 1H), 7.21-7.47 (m, 9H), 7.60 (t, J = 7.5 Hz, 2H), 7.77-7.88 (m, 4H), 8.55 (d, J = 1.8 Hz, 1H); \(^{13}\)C NMR (CDCl\(_{3}\)) \(\delta\) 51.9, 64.5, 109.8, 110.9, 121.3, 122.2,
123.3, 123.8, 124.1, 126.9, 128.2, 128.5, 128.7, 129.1, 129.3, 129.5, 131.2, 131.6, 134.1, 136.0, 138.4, 140.7, 147.3, 168.2; IR (CDCl₃, cm⁻¹) 3063, 2947, 1711, 1621, 1437; HRMS Calcd for C₂₉H₂₁NO₂: 415.1572. Found: 415.1574.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donation of the palladium salts, and Merck and Co., Inc. for an Academic Development Award in Chemistry.

References


3270.

18. Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T.


20. Kozikowski, A. P.; Ma, D.; Brewer, J.; Sun, S.; Costa, E.; Romeo, E.; Guidotti, A.


GENERAL CONCLUSION

In this dissertation, the scope and limitations of several palladium-catalyzed processes have been presented. Specifically, the scope of the palladium-catalyzed internal alkyne methodology that has been employed by Larock and co-workers for the synthesis of a variety of carbo- and heterocycles has been expanded by employing tert-butylimines derived from α-iodobenzaldehydes and 3-halo-2-alkenals for the synthesis of isoquinolines and pyridines. In addition, imines derived from α-iodoanilines have been employed for the synthesis of isoindolo[2,1-a]indoles.

Chapter 1 describes the synthesis of a variety of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[f]isoquinoline, pyridine, and pyridine heterocycles by the palladium-catalyzed annulation of internal alkynes. These heterocycles have been synthesized in moderate to excellent yields by employing mild reaction conditions and short reaction times. Also, during the development of this annulation methodology, an interesting isoquinoline synthesis was discovered when trimethylsilyl-substituted acetylenes were employed. A mechanism involving desilylation of the acetylene and subsequent palladium-catalyzed coupling and cyclization of the intermediate iminoalkynes is proposed for this annulation process.

Chapter 2 describes in detail, a related terminal acetylene annulation process that was discovered during the development of the internal alkyne methodology presented in chapter 1. It was subsequently discovered that, in addition to trimethylsilyl-substituted alkynes, terminal acetylenes could also be
employed in this palladium-catalyzed coupling and cyclization process. Also, a palladium-catalyzed coupling of the tert-butylimines of o-iodobenzaldehydes and 3-halo-2-alkenals with terminal acetylenes and subsequent copper-catalyzed cyclization of the intermediate iminoalkynes were employed for the synthesis of a variety of isoquinolines and pyridines. Finally, the effectiveness of this palladium-catalyzed terminal acetylene annulation methodology was demonstrated by the total synthesis of the isoquinoline natural product decumbenine B.

Chapter 3 presents the synthesis of a variety of substituted isoindolo[2,1-a]indoles via annulation of internal aryl acetylenes with imines derived from o-iodoanilines. This methodology very efficiently constructs these tetracyclic indoles in good to excellent yields by employing mild reaction conditions, readily prepared imines, and a variety of internal alkynes which contain either phenyl or heterocyclic rings. In addition, preliminary results indicate that the formation of highly substituted quinoline heterocycles may be possible by slightly altering the reaction conditions employed.
APPENDIX A. CHAPTER 1 \(^1\text{H}\) AND \(^{13}\text{C}\) NMR SPECTRA
Table 2, Compound 5
Table 2, Compound 5
Table 2, Compound 20

MeO\[\text{N-Bu}\]MeO

I

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 ppm
Table 2, Compound 20
Table 2, Compound 26
Table 2, Compound 26
Table 2, Compound 30
Table 2, Compound 30
Table 2, Compound 33

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</tbody>
</table>

Structural Diagram: [Image of molecular structure]

The peak at 7.0 ppm is assigned to the nitrogen atom. The peak at 1.0 ppm is assigned to the tert-butyl group.
Table 2, Compound 33

![](image)
Table 2, Compound 38
Table 2, Compound 38
Table 2, Compound 42
Table 2, Compound 45

Me\[\equiv\text{N}\]\text{-t-Bu}

Ph\text{-I}
Table 2, Compound 45
Table 2, Compound 49
Table 2, Compound 49
Table 2, Compound 8
Table 2, Compound 9
Table 2, Compound 9
Table 2, Compound 10
Table 2, Compound 10

| ppm | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|---|---|---|---|---|---|---|---|---|

CH$_2$OH

Ph

/dat2/data/krr/nmr/krr412ac.fid/l/pdata/1 unknown Thu Jan 7 16:59:13 1999
Table 2, Compound 11
Table 2, Compound 11
Table 2, Compound 12

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</table>
Table 2, Compound 12
Table 2, Compound 13

![Chemical Structure: C≡C-Ph](image)

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<th>5.0</th>
<th>4.0</th>
<th>3.0</th>
<th>2.0</th>
<th>1.0</th>
<th>0.0 ppm</th>
</tr>
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</table>

C=C-Ph

Table 2, Compound 13
Table 2, Compound 13
Table 2, Compounds 14 and 15
Table 2, Compounds 14 and 15
Table 2, Compounds 16 and 17
Table 2, Compounds 16 and 17
Table 2, Compound 21

MeO
MeO
Ph
Ph

-giga/data/krr/nmr/krr264ah.fid/1/pdata/1  unknown Wed Sep 18 12:29:50 1996
Table 2, Compound 21
Table 2, Compound 22

\[
\text{MeO} \quad \text{MeO} \\
\text{Ph} \quad \text{CO}_2\text{Et}
\]
Table 2, Compound 22
Table 2, Compound 23
Table 2, Compound 23
Table 2, Compound 24
Table 2, Compound 24
Table 2, Compound 25
Table 2, Compound 25

MeO

MeO

Ph

Me
Table 2, Compound 27
Table 2, Compound 27

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![NMR Spectrogram](image-url)
Table 2, Compound 28
Table 2, Compound 28
Table 2, Compound 29
Table 2, Compound 29
Table 2, Compound 31

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217
Table 2, Compound 31
Table 2, Compound 32
Table 2, Compound 32
Table 2, Compound 34
Table 2, Compound 34
Table 2, Compound 35
Table 2, Compound 35
Table 2, Compound 36
Table 2, Compound 36
Table 2, Compound 37
Table 2, Compound 37

CH$_2$OH
Table 2, Compound 39
Table 2, Compound 39
Table 2, Compound 40

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 ppm
Table 2, Compound 40
Table 2, Compound 41

CH2OH
Table 2, Compound 41
Table 2, Compound 43
Table 2, Compound 43
Table 2, Compound 44
Table 2, Compound 44

<table>
<thead>
<tr>
<th>Compound Structure</th>
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<td>![Structure Image]</td>
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### Table 2

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Unknown Sat Feb 21 21:25:38 1998
Table 2. Compound 46

[Chemical structure image]
Table 2, Compound 46
Table 2, Compound 47
Table 2, Compound 48
Table 2, Compound 48

![NMR spectrum of Compound 48](https://example.com/nmr_spectrum.png)
Table 2, Compound 51
Table 2, Compound 51

Ph
Ph

CH₂OH
APPENDIX B. CHAPTER 2 $^1$H AND $^{13}$C NMR SPECTRA
Table 3, Compound 9
Table 3, Compound 9
Table 3, Compound 17
Table 3, Compound 17
Table 3, Compound 18
Table 3, Compound 18
Table 3, Compound 19

[Chemical structure diagram]

I-Bu
(\text{CH}_2)_2\text{OTHP}

/dat2/data/krr/nmr/krr646ah.fld/1/pdata/1  unknown  Thu Jul 30 20:10:00 1998
Table 3, Compound 19

(\text{CH}_2\text{OTHP})

\begin{tabular}{c}
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132.413 \\
129.659 \\
128.122 \\
125.861 \\
124.444 \\
98.884 \\
92.685 \\
78.822 \\
65.849 \\
62.322 \\
57.734 \\
30.658 \\
29.838 \\
25.485 \\
21.165 \\
19.487
\end{tabular}
Table 3, Compound 20
Table 3, Compound 20
Table 3, Compound 21
Table 3: Compound 21

\[
\text{CH}_2\text{OH} \quad \text{N} \quad \text{Bu}
\]
Table 3, Compound 22

\[ \text{Si(Pr)}_3\]

\[
\begin{aligned}
\text{N} & \quad \text{t-Bu} \\
\text{Si(Pr)}_3 & 
\end{aligned}
\]
Table 3, Compound 22
Table 6, Compound 23
Table 6, Compound 24

This image contains a chemical structure and a graph representing the nuclear magnetic resonance (NMR) spectrum of Compound 24. The spectrum shows peaks at various chemical shifts, with the corresponding ppm values indicated on the x-axis. The structure of Compound 24 is shown below the spectrum.
Table 6, Compound 24
Table 6, Compound 25

![Chemical Structure](https://example.com/structure.png)
Table 6, Compound 25

\[(\text{CH}_2\text{O})_{26}\text{THP}\]
Table 6, Compound 29
Table 6, Compound 29
Table 6, Compound 30

(CH₂)₃CN
Table 6, Compound 30
Table 6, Compound 33
Table 6, Compound 34
Table 6, Compound 34
Table 6, Compound 35
Table 6, Compound 35

![Chemical Structure]

Table 6, Compound 35
Table 6, Compound 36
Table 6, Compound 36
Table 6, Compound 37
Table 6, Compound 39
Table 6, Compound 39

Chemical shift (ppm)
Table 6, Compound 40
Table 6, Compound 40

180 160 140 120 100 80 60 40 20 ppm
Table 6, Compound 42
Compound 49
Compound 50
Compound 50
Table 6, Compound 54

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</table>

[Image of a chemical structure with labels: Ph]

For more information, see the file `/dat2/data/krr/nmr/krr516ah.fid/1/pdata/1` from an unknown source on Mon Jan 25 13:12:11 1999.
APPENDIX C. CHAPTER 3 $^1$H AND $^{13}$C NMR SPECTRA
Table 3, Compound 21
Table 3, Compound 21
Table 3, Compound 36
Table 3, Compound 36
Table 3, Compound 38
Table 3, Compound 38

MeO₂C

N → Ph

I
Table 3, Compound 23
Table 3, Compound 23
Table 3, Compound 24
Table 3, Compound 24
Table 3, Compound 25
Table 3, Compound 25
Table 3, Compound 26
Table 3, Compound 27
Table 3, Compound 28
Table 3, Compound 29

\[
\text{(CH}_2\text{)}_4\text{OH}
\]

Ph

Wed Mar 17 14:11:17 1999

0.0 ppm
Table 3, Compound 29
Table 3, Compound 30

Ph

N

Me

n-Bu

3.0 2.0 1.0

9.0 8.0 7.0 6.0 5.0 4.0
Table 3, Compound 30
Table 3, Compound 31
Table 3, Compound 31
Table 3, Compound 32
Table 3, Compound 33
Table 3, Compound 34
Table 3, Compound 34
Table 3, Compound 35

[Chemical structure diagram]

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</tbody>
</table>

Ph

n-Bu
Table 3, Compound 35
Table 3, Compound 37
Table 3, Compound 37
Table 3, Compound 39
Table 3, Compound 39
ACKNOWLEDGMENTS

I must begin this section with a sincere word of thanks to my major professor, Richard C. Larock, for his patience, excellent guidance, and financial support throughout the course of this work. Also, I have to acknowledge his willingness to listen to many of my crazy ideas, and to always offer advice as to how those ideas should be carried out.

I have met so many people during my years at Iowa State that have helped me through a number of things, and others that made the time here extremely memorable. I know for a fact that this degree would not have been possible without the assistance of a few certain people. The immense help that I received from Dr. Xiaojun Han from our start at ISU (and also during our last year at SIU) in course work and lab work in the early days, as well as the many of those memorable discussions, will always be appreciated and remembered. Dr. Mitchell Refvik pulled me through numerous tough times by offering advice in so many areas, and telling me some of the most interesting jokes I have ever heard. Without his help, I definitely would not have made it through. I cannot end this dissertation without thanking him for all of the great times that we had while he was here at Iowa State. I also must thank Melanie Refvik (are you wearing them now?) for keeping Mitch and I in line, as well as Kirsten and Samantha for teaching me so many things. Finally, I cannot forget some of the times that I had with Dr. Dan Gregory. I must thank Dan for the trips to Minnesota (although my foot still hurts when I think about them), removing my screen, helping me move, listening to David Allen Coe and Kern River, and burning rubber in the Monz.
This dissertation could not end without a few words about the infamous lunchroom crowd. Some of the most memorable discussions I ever had at Iowa State, or anywhere else, came from the lunchroom. Some of the things that I heard during that time will never be forgotten (although I wish I could forget some things). For those discussions I have to thank Dr. Mitchell (Michelena) Refvik, Dr. Dan (G-Roy) Gregory, Nate (Big Daddy) Classen, and Steve (Lance) Gagnier. A special thanks goes to Nate for taking it like a man in the lunchroom and Steve for letting me take his money at golf.

During the last year and a half of this degree, Jack Hunter has helped me immensely. I have to thank him for taking me to and from the airport, Saturday lunches, page numbering and thesis help, and again, many memorable discussions. I have also had numerous enlightening discussions, which sometimes included chemistry, with Dan Emrich, that I must thank him for. I must also thank Dan for being the racy person that he is. I also must thank Marino Campo for teaching me some things that I did not need to know. Finally, I would like to thank all other members of the Larock group, past and present, that I have had the pleasure to work with.

Many thanks go to my parents who have supported me throughout the completion of my degrees. I would definitely not have made it through without their unending support, which means a great deal. When I look back at some of the things that have happened to all three of us throughout the years, I can only laugh.

Finally, I have to thank my wife, Julie, for being there through a little bit of everything. Her support and help over these many years, and especially the last
three here in Iowa, have meant more than she will ever know. Actually, I still
cannot believe that she still puts up with me. I know she has spent many lonely
nights waiting for me to complete this degree. For her patience and understanding,
I have only one thing to say, WE DID IT!