Palladium and electrophilic cyclization approaches to carbo- and heterocyclic compounds

Dawei Yue
Iowa State University

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Palladium and electrophilic cyclization approaches to carbo- and heterocyclic compounds

by

Dawei Yue

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

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
Richard C. Larock, Major Professor
Daniel Armstrong
William Jenks
George Kraus
Victor Lin

Iowa State University
Ames, Iowa

2004
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Dawei Yue

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

For the Major Program
To my parents and my wife,

for their love, patience, support and encouragement.
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</tr>
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GENERAL INTRODUCTION

Palladium-catalyzed organic transformations have become indispensable for many common and state-of-art syntheses. In recent years, a variety of palladium-based methods have been developed which demonstrate palladium's ability to produce a wide range of carbo- and heterocycles. These reactions have proven to be general in scope and exhibit a high degree of regio- and stereospecificity. Palladium catalysts have also been shown to be tolerant of considerable functionality and are not generally moisture or air sensitive.

Electrophilic cyclization has been widely used in organic synthesis. However, this type of cyclization has mainly been limited to the cyclization of carbon-carbon double bonds. The cyclization of compounds with carbon-carbon triple bonds is relatively unexplored. Previous work by Cacchi, Flynn, Barluenga and Larock has shown that iodine and other electrophiles can be used for the synthesis of benzo[b]furans, benzo[b]thiophenes, indoles and isoquinolines. This type of cyclization is generally viewed as proceeding through an intramolecular, stepwise electrophilic addition and dealkylation mechanism involving a cationic intermediate. The mild reaction conditions and high efficiency encouraged us to further explore the generality of this synthetic approach to biologically interesting benzo[b]furans, isochromenes and coumestans.

The Larock group has recently discovered new 1,4-palladium migrations from an aryl to an aryl, a vinyl to an aryl, an aryl to an alkyl and an alkyl to an aryl position. Utilizing these novel migrations in synthesis has also been explored. We have investigated the possibility of other types of Pd migration reactions and their synthetic applications. As a result, an unusual 1,4-palladium migration from an aryl to an imidoyl position has been realized and its synthetic applications have also been explored.
Dissertation Organization

This dissertation is composed of four chapters. The chapters presented herein are written 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, acknowledgements, and references.

Chapter 1 describes the synthesis of 2,3-disubstituted benzo[b]furans by palladium catalyzed coupling and electrophilic cyclization of terminal alkynes. This process has proven to be highly efficient. Various electrophiles undergo this process and give high yields of the desired cyclization products.

Chapter 2 presents the synthesis of heterocycles by the electrophilic cyclization reactions of acetylenic aldehydes, ketones and imines. The overall synthetic process involves the coupling of terminal acetylenes with o-haloarencarboxaldehydes and ketones by a palladium/copper-catalyzed coupling reaction, followed by electrophilic cyclization with various electrophiles in the presence of proper nucleophiles.

Chapter 3 examines the synthesis of coumestan and coumestrol by selective electrophilic cyclization, followed by palladium-catalyzed intramolecular carbonylation and lactonization. The biologically interesting coumestan system can be quickly constructed by this very efficient approach.

Chapter 4 serves to expand the scope and synthetic utility of an unusual 1,4-palladium through space migration. The synthesis of various fluoren-9-ones has been accomplished by the palladium-catalyzed intramolecular C-H activation of imines derived from 2-iodoaniline and biarylcarboxaldehydes. This methodology makes use of a novel 1,4-palladium
migration from an aryl position to an imidoyl position to generate the key imidoyl palladium intermediate, which undergoes intramolecular arylation to produce imines of complex polycyclic compounds containing the fluoren-9-one core structure.

Finally, all of the $^1$H and $^{13}$C NMR spectra for the starting materials, the electrophilic cyclization products and the palladium-catalyzed reaction products have been compiled in appendices A-D, following the general conclusions for this dissertation.
CHAPTER 1. SYNTHESIS OF 2,3-DISUBSTITUTED BENZO[b]FURANS BY THE PALLADIUM-CATALYZED COUPLING OF o-IODOANISOLE AND TERMINAL ALKynes, FOLLOWED BY ELECTROPHILIC CYCLIZATION

Based on a paper to be published in the Journal of Organic Chemistry
Dawei Yue and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, IA 50011, USA
larock@iastate.edu

Abstract

2,3-Disubstituted benzo[b]furans are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of o-iodoanisole and terminal alkynes, followed by electrophilic cyclization using I2, Br2, PhSeCl and p-O2NC6H4SCl. Aryl- and vinylic-substituted alkynes undergo electrophilic cyclization in excellent yields. Biologically important furopyridines can be prepared by this approach in high yields.

Introduction

The benzo[b]furan nucleus is prevalent in a wide variety of biologically active natural and unnatural compounds.1 Many 2-arylbenzofuran derivatives are well known to exhibit a broad range of biological activities, such as anticancer,2 antiproliferative,3 antiviral,4 antifungal,5 immunosuppressive,6 antiplatelet,7 antioxidative,8 insecticidal,9 anti-inflammatory,10 antifeedant,11 and cancer preventative activity.12 These compounds are also important calcium blockers13 and phytoestrogens.14 For instance, XH-1415 was the first
reported nonnucleoside-type potent adenosine A₁ agonist\textsuperscript{16} and obovaten is known as an active antitumor agent.\textsuperscript{17}

There has been growing interest in developing a general and versatile synthesis of benzo[\textit{b}]furan derivatives. A number of synthetic approaches to this class of compounds have been introduced in recent years.\textsuperscript{18} One common approach to heterocycles that has been utilized for the synthesis of benzo[\textit{b}]furans,\textsuperscript{19} benzo[\textit{b}]thiophenes,\textsuperscript{20} indoles\textsuperscript{21} and isoquinolines\textsuperscript{22} has been electrophilic cyclization of the corresponding 2-(1-alkynyl)-phenols, -thioanisoles, -anilines and -imines respectively (Scheme 1).

\textbf{Scheme 1}

\[
\begin{align*}
\text{X-Y} & \xrightarrow{1.2 \text{ HC} = \text{CR}} \text{cat. PdCl}_2(\text{PPh}_3)_2 \xrightarrow{\text{cat. Cul, Et}_3\text{N}} \text{X-Y - O-H, S-Me, NMe}_2, \text{CH=N-t-Bu} \\
E^+ & \text{ Br}_2, \text{NBS, I}_2, \text{PhSeCl, } \rho-\text{O}_2\text{NC}_6\text{H}_4\text{SCl}
\end{align*}
\]

Our and other’s recent success in the synthesis of benzo[\textit{b}]thiophenes,\textsuperscript{20} indoles\textsuperscript{21} and isoquinolines\textsuperscript{22} encouraged us to examine the possibility of preparing benzo[\textit{b}]furans by the same strategy involving a palladium/copper-catalyzed alkyne coupling, followed by electrophilic cyclization. Cacchi and co-workers reported an approach to the synthesis of 3-iodobenzo[\textit{b}]furans by a related process involving iodo cyclization (Scheme 2).\textsuperscript{19}
Unfortunately, the protecting and deprotecting steps required to synthesis the alkynylphenol are not particularly attractive synthetically. Some of the alkynylphenols are also relatively unstable. In another paper, Cacchi has demonstrated an analogous cyclization of benzylic ethers to generate furopyridines and reported that the $\alpha$-hydroxyalkynylpyridines are not stable and cyclize spontaneously to give furopyridines (eq 1). We have attempted to make this overall approach more attractive synthetically by examining the preparation and cyclization of the corresponding methyl ethers using a variety of commercially available electrophiles. Herein, we wish to report an efficient approach to 2,3-disubstituted benzo[b]furans and furopyridines involving the palladium/copper-catalyzed coupling of various iodoanisoles and an iodomethoxypyridine and terminal alkynes, followed by electrophilic cyclization.
Results and Discussion

The arylalkynes required for our approach to benzo[b]furans are readily prepared by the Sonogashira coupling\textsuperscript{24} of commercially available o-iodoanisole (5.0 mmol) and terminal alkynes (6.0 mmol) using a catalyst consisting of 2 mol % PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} and 1 mol % CuI in the presence of Et\textsubscript{3}N (12.5 mL) as the solvent at room temperature. The yields of this process range from 70 to 94% and this procedure should readily accommodate considerable functionality.

We first examined the reaction of our alkynes (0.25 mmol in 3 mL of CH\textsubscript{2}Cl\textsubscript{2}) with I\textsubscript{2} (2.0 equiv in 2 mL of CH\textsubscript{2}Cl\textsubscript{2}) under our well established reaction conditions for the synthesis of benzo[b]thiophenes\textsuperscript{20} and indoles\textsuperscript{21} (Scheme 1). We were pleased to see that 2-(phenylethynyl)anisole reacted in less than 3 h at room temperature to afford 3-iodo-2-phenylbenzo[b]furan in an 87% yield (Table 1, entry 1). In order to extend this approach to other benzo[b]furans, we have also looked at a range of other readily available electrophiles. So far, Br\textsubscript{2}, p-O\textsubscript{2}NC\textsubscript{6}H\textsubscript{4}SCl and PhSeCl have been successfully employed in this electrophilic cyclization, providing excellent yields of the desired cyclization products (Table 1, entries 2-4).

The nature of the substituents attached to the triple bond and the arene have a major impact on the success of the reaction. Virtually no difference in the rates of reaction or the overall yields have been observed using a vinylic alkyne and arylalkynes bearing certain types of functionality on the aromatic ring (entries 1-16). However, alkynes bearing a single alkyl group (entries 19, 20 and 25) fail to undergo electrophilic cyclization. Instead, an almost quantitative yield of the product of simple addition of the electrophile to the alkyne triple bond was obtained (entries 19, 20 and 25). In order to form a furan moiety, the
Table 1. Synthesis of benzo[b]furans by electrophilic cyclization.

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<td>29</td>
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All reactions were run with 0.25 mmol of the alkyne, 2 equiv of electrophile in 5 mL of CH₂Cl₂ at 25 °C. *None of the desired cyclization product was observed. *An inseparable mixture was obtained.
oxygen of the methoxy group has to undergo a five \textit{endo-dig} attack on the carbon-carbon triple bond. However, a methoxy group \textit{para} to the triple bond increases the electron density on the distal end of the triple bond (Figure 1) and promotes addition of the electrophile to the triple bond, rather than cyclization (entries 17, 18 and 24).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Methoxy electron-donating effect towards the triple bond}
\end{figure}

The presence of a nitro group in compound 29 decreases the electron density on \( \text{C}_1 \) (Figure 2), and again favors simple addition of the electrophile to the alkyne triple bond (entries 21 and 22). On the other hand, the presence of an electron-withdrawing group, such as a nitro group on the methoxy-substituted arene favors electrophilic cyclization, although a longer reaction time is generally required (entries 11 and 12). The more electron deficient \( \text{C}_2 \) position is more likely to undergo attack by the nucleophilic oxygen of the methoxy group than the \( \text{C}_1 \) position, because of either the resonance effect of the nitro group \textit{para} to the carbon-carbon triple bond (Figure 3) or the inductive effect of the electron-poor arene.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure2.png}
\caption{Nitro electron-withdrawing effect towards the triple bond}
\end{figure}

The trimethylsilyl-substituted alkyne 30 failed to undergo electrophilic cyclization and
provided an inseparable mixture of unidentifiable compounds, which is consistent with Cacchi’s earlier results (entry 23).  

Figure 3. Nitro electron-withdrawing effect towards the triple bond

Compound 21 with both a methoxy and an acetoxy group in positions ortho to the triple bond undergoes electrophilic cyclization onto the methoxy group to produce compound 22 in a 95% yield (entry 14). This should be quite useful for the regioselective synthesis of benzofurans. Thus, the more nucleophilic methoxy group more readily attacks the triple bond, affording the corresponding cyclization product.

We have also investigated the possibility of carrying out double iodocyclizations, which might be quite useful for the quick assembly of systems with extended conjugation. Compounds 23 and 25 undergo iodocyclization to afford double cyclization products in 97% and 60% yields respectively (entries 15 and 16).

While Cacchi reported the successful synthesis of several furopyridines by electrophilic cyclization of o-(benzyloxy)alkynylpyridines, we have examined the cyclization of an o-methoxyalkynylpyridine and found that a methyl group can also be a good leaving group in this reaction. Pyridine derivative 19 was treated with I₂ under our standard electrophilic cyclization conditions to afford the desired furopyridine in a 67% yield. This provides a convenient alternative route to the synthesis of furopyridines, since methoxypyridines are more readily available than (benzyoxy)pyridines in many cases.
Mechanistically, we believe that these cyclizations proceed by *anti* attack of the electrophile and the oxygen of the methoxy group on the alkyne to produce an intermediate A, which undergoes methyl group removal via $S_N2$ displacement by nucleophiles present in the reaction mixture (Scheme 3). In most cases, the nucleophile is presumably the halide remaining in solution.

**Scheme 3**

We believe that this approach to 3-iodobenzo[b]furans and furopyridines should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting iodide functionality into other substituents. For example, the resulting heterocyclic iodides should be particularly useful as intermediates in many palladium-catalyzed processes, like Sonogashira,\(^{24}\) Suzuki,\(^{25}\) and Heck\(^{26}\) cross-coupling processes.

**Conclusions**

We believe that this approach to 3-iodobenzo[b]furans and furopyridines should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting iodide functionality into other substituents. For example, the resulting heterocyclic iodides should be particularly useful as intermediates in many palladium-catalyzed processes, like Sonogashira,\(^{24}\) Suzuki,\(^{25}\) and Heck\(^{26}\) cross-coupling processes.
Experimental Section

General. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 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 a 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.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of ethyl ether, hexanes, ethyl acetate, and CH$_2$Cl$_2$ were purchased from Fisher Scientific Co. 2-Iodoanisole, 2-bromo-1,4-dimethoxybenzene, 1-bromo-2,4-dimethoxybenzene, 2-ido-4-nitroanisole, 2-ido-5-nitroanisole, resorcinol, 4-idoanisole, 1-ido-4-nitrobenzene, phenylacetylene, 1-cyclohexenyl acetylene, 1-octyne, trimethylsilylacetylene, and Et$_3$N were purchased from Aldrich Chemical Co., Inc. The palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd.

General procedure for the palladium/copper-catalyzed formation of o-(1-alkynyl)anisoles. To a solution of Et$_3$N (12.5 mL), PdCl$_2$(PPh$_3$)$_2$ (2 mol %), 5.0 mmol of o-iodoanisole and 6.0 mol of terminal acetylene (stirring for 5 min beforehand), Cul (1 mol %) was added and stirring was continued for another 2 min before flushing with Ar. The flask was then sealed. The mixture was allowed to stir at room temperature for 3-6 h and the
resulting solution was filtered, washed with satd aq NaCl and extracted with diethyl ether (2 x 15 mL). The combined ether fractions were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

**2-(Pheny lethynyl)anisole (1).** The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) δ 3.90 (s, 3H), 6.89 (d, $J= 8.4$ Hz, 1H), 6.93 (t, $J= 7.6$ Hz, 1H), 7.29-7.33 (m, 4H), 7.50 (d, $J= 7.2$ Hz, 1H), 7.55-7.57 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 56.0, 85.9, 93.6, 110.9, 112.6, 120.7, 123.7, 128.2, 128.3, 129.9, 131.8, 133.7, 160.1; IR (neat, cm$^{-1}$) 3058, 2926, 2855, 2226; HRMS calcd for C$_{15}$H$_{12}$O 208.0888, found 208.0894.

**2-[(Cyclohex-1-enyl)ethynyl]anisole (6).** The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) δ 7.05-7.26 (m, 4H), 6.20 (s, 1H), 3.77 (s, 3H), 2.09-2.35 (m, 4H), 1.20-1.67 (m, 4H); IR (neat, cm$^{-1}$) 3048, 2944, 2222; HRMS calcd for C$_{15}$H$_{16}$O 212.1201, found 212.1206.

**1-Methoxy-2-[(4-methoxyphenyl)ethynyl]benzene (9).** The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) δ 3.77 (s, 3H), 3.87 (s, 3H), 6.83-6.93 (m, 4H), 7.26 (t, $J= 8.0$ Hz, 1H), 7.46-7.50 (m, 3H); $^{13}$C NMR (CDCl$_3$) δ 55.4, 55.9, 84.5, 93.6, 110.8, 112.8, 114.0, 115.8, 120.6, 129.6, 133.2, 133.5, 159.6, 159.9; IR (neat, cm$^{-1}$) 2227; HRMS calcd for C$_{16}$H$_{14}$O$_2$ 238.0994, found 238.1000.

**1,4-Dimethoxy-2-(phenylethynyl)benzene (12).** The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) δ 3.76 (s, 3H), 3.86 (s, 3H), 6.80-6.84 (m, 2H), 7.05 (s, 1H), 7.30-7.34 (m, 3H), 7.56 (d, $J= 6.0$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 56.0, 56.7, 85.9, 93.6,
4-Nitro-2-(phenylethynyl)anisole (15). The product was obtained as a yellow oil:

$^1$H NMR (CDCl$_3$) $\delta$ 4.01 (s, 3H), 6.96 (d, $J = 9.2$ Hz, 1H), 7.36-7.38 (m, 3H), 7.56-7.58 (m, 2H), 8.20 (dd, $J = 9.2$, 2.8 Hz, 1H), 8.38 (d, $J = 2.4$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.8, 83.5, 95.6, 110.5, 113.9, 122.7, 125.7, 128.6, 129.1, 129.2, 132.0, 141.3, 164.6; IR (neat, cm$^{-1}$) 3058, 2926, 2855, 2225; HRMS calcd for C$_{15}$H$_{14}$O$_2$ 238.0994, found 238.0999.

5-Nitro-2-(phenylethynyl)anisole (17). The product was obtained as a yellow oil:

$^1$H NMR (CDCl$_3$) $\delta$ 4.01 (s, 3H), 7.37-7.38 (m, 3H), 7.57-7.62 (m, 3H), 7.75 (d, $J = 2.0$ Hz, 1H), 7.83 (dd, $J = 8.4$, 2.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.6, 84.3, 98.6, 105.8, 115.9, 119.9, 122.7, 128.6, 129.3, 132.1, 133.7, 148.2, 160.3; IR (neat, cm$^{-1}$) 3047, 2215; HRMS calcd for C$_{15}$H$_{11}$NO$_3$ 253.0739, found 253.0742.

2-Ethynyl-1-methoxybenzene. The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.32 (s, 1H), 3.89 (s, 3H), 6.87-6.93 (m, 2H), 7.32 (t, $J = 8.4$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 55.9, 80.2, 81.3, 110.7, 111.2, 120.6, 130.4, 134.3, 160.7; IR (neat, cm$^{-1}$) 3058, 2222; HRMS calcd for C$_9$H$_8$O 132.0575, found 132.0577.

2-[(Cyclohex-1-enyl)ethynyl]-1,4-dimethoxybenzene. The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.61-1.70 (m, 4H), 2.14-2.16 (m, 2H), 2.25-2.28 (m, 2H), 3.76 (s, 3H), 3.84 (s, 3H), 6.24-6.26 (m, 1H), 6.80-6.81 (m, 2H), 6.95-6.96 (m, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.7, 22.5, 26.0, 29.4, 55.9, 56.6, 83.0, 95.5, 112.2, 113.6, 115.3, 118.1, 120.9, 135.5, 153.3, 154.4; IR (neat, cm$^{-1}$) 2226; HRMS calcd for C$_{16}$H$_{18}$O$_2$ 242.1307, found 242.1312.
3-Methoxy-6-methyl-2-(phenylethynyl)pyridine (19). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 2.52 (s, 3H), 3.90 (s, 3H), 7.06-7.15 (m, 2H), 7.33-7.36 (m, 3H), 7.61-7.64 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.0, 55.8, 85.7, 93.7, 118.8, 122.9, 123.5, 128.4, 128.9, 132.3, 150.6, 155.3; IR (neat, cm$^{-1}$) 2217; HRMS calcd for C$_{15}$H$_{13}$NO 233.0997, found 233.1002.

2-Acetoxy-2'-methoxy-diphenylacetylene (21). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 2.37 (s, 3H), 3.87 (s, 3H), 6.88 (d, $J$ = 8.7 Hz, 1H), 6.92 (td, $J$ = 7.5, 0.9 Hz, 1H), 7.11 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.20 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.26-7.35 (m, 2H), 7.46 (dd, $J$ = 7.5, 1.8 Hz, 1H), 7.59 (dd, $J$ = 7.5, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.0, 55.8, 88.3, 90.9, 110.9, 112.3, 118.0, 120.6, 122.4, 126.0, 129.4, 130.2, 133.1, 133.7, 151.6, 160.1, 169.1; IR (neat, cm$^{-1}$) 2213, 1770; HRMS calcd for C$_{17}$H$_{14}$O$_3$ 266.0943, found 266.0946.

1,4-Bis[(2-methoxyphenyl)ethynyl]benzene (23). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.91 (s, 6H), 6.88-6.96 (m, 4H), 7.30 (t, $J$ = 7.6 Hz, 2H), 7.48-7.53 (m, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.0, 87.7, 93.4, 110.8, 112.4, 120.7, 123.4, 130.1, 131.7, 133.7, 160.1; IR (neat, cm$^{-1}$) 2210; HRMS calcd for C$_{24}$H$_{18}$O$_2$ 338.1307, found 338.1315.

2,5-Dimethoxy-1,4-di(phenylethynyl)benzene (25). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.90 (s, 6H), 7.04 (s, 2H), 7.32-7.37 (m, 6H), 7.56-7.59 (m, 4H); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.7, 85.9, 95.2, 113.6, 115.9, 123.4, 128.5, 128.6, 131.9, 154.1; IR (neat, cm$^{-1}$) 2227; HRMS calcd for C$_{24}$H$_{18}$O$_2$ 338.1307, found 338.1314.
2,4-Dimethoxy-1-(phenylethynyl)benzene (27). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.79 (s, 3H), 3.87 (s, 3H), 6.46 (d, $J = 6.0$ Hz, 2H), 7.27-7.34 (m, 3H), 7.42 (d, $J = 9.0$ Hz, 1H), 7.54 (d, $J = 9.0$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 55.5, 56.0, 86.0, 92.1, 98.6, 105.0, 105.1, 124.0, 127.9, 128.4, 131.6, 134.5, 161.3, 161.4; IR (neat, cm$^{-1}$) 3058, 2926, 2855, 2227, 1464, 1435, 749; HRMS calcd for C$_{16}$H$_{14}$O$_2$ 238.0994, found 238.1000.

2-(1-Octynyl)anisole (28). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 0.88-0.93 (m, 3H), 1.30-1.34 (m, 4H), 1.46-1.50 (m, 2H), 1.60-1.65 (m, 2H), 2.47 (t, $J = 1.2$ Hz, 2H), 3.87 (s, 3H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.88 (td, $J = 7.5$, 0.9 Hz, 1H), 7.24 (td, $J = 8.1$, 1.8 Hz, 1H), 7.37 (dd, $J = 7.5$, 1.8 Hz, 1H); HRMS calcd for C$_{15}$H$_{20}$O 216.1514, found 216.1519.

1-Methoxy-2-[(4-nitrophenyl)ethynyl]benzene (29). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.92 (s, 3H), 6.92-6.99 (m, 2H), 7.37 (t, $J = 8.4$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 2H), 8.19 (d, $J = 8.8$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.0, 91.6, 91.4, 110.9, 111.4, 120.8, 123.7, 130.8, 131.1, 132.4, 133.9, 147.0, 160.4; HRMS calcd for C$_{15}$H$_{11}$NO$_2$ 253.0739, found 253.0745.

2-(Trimethylsilylethynyl)anisole (30). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 0.08 (s, 9H), 3.68 (s, 3H), 6.64-6.71 (m, 2H), 7.08 (td, $J = 8.4$, 2.0 Hz, 1H), 7.24 (dd, $J = 7.6$, 1.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 0.3, 56.0, 98.6, 101.5, 110.8, 112.5, 120.5, 130.2, 134.4, 160.5.

2,4-Dimethoxy-5-(phenylethynyl)pyrimidine (31). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 4.01 (s, 3H), 4.06 (s, 3H), 7.32-7.35 (m, 3H), 7.51-7.54 (m,
2H), 8.40 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 54.6, 55.2, 80.8, 95.5, 100.2, 122.9, 128.4, 128.6, 131.6, 161.3, 164.2, 170.4; IR (neat, cm$^{-1}$) 2207 cm$^{-1}$; HRMS calcd for C$_{14}$H$_{12}$N$_2$O$_2$ 240.0899, found 240.0901.

3-Methoxy-6-methyl-2-(1-octynyl)pyridine (33). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 0.88 (t, $J$ = 6.8 Hz, 3H), 1.28-1.33 (m, 8H), 1.43-1.48 (m, 2H), 1.61-1.68 (m, 2H), 2.47 (s, 3H), 2.49 (t, $J$ = 7.2 Hz, 2H), 3.85 (s, 3H), 7.04 (dd, $J$ = 19.8, 8.7 Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.2, 19.9, 22.8, 23.5, 28.6, 29.2, 29.2, 29.3, 31.9, 56.0, 77.1, 95.7, 118.5, 122.7, 133.0, 150.1, 154.8; IR (neat, cm$^{-1}$) 2217; HRMS calcd for C$_{17}$H$_{25}$NO 259.1936, found 259.1941.

3-Iodo-2-phenylbenzo[b]furan (2). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.28-7.51 (m, 7H), 8.16-8.19 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 61.3, 111.4, 122.1, 123.7, 125.9, 127.7, 128.7, 129.4, 130.2, 132.7, 153.2, 154.1; IR (neat, cm$^{-1}$) 3058, 1450; HRMS calcd for C$_{14}$H$_9$IO 319.9698, found 319.9700.

**General procedure for the iodo- and bromocyclizations.** To a solution of 0.25 mmol of the alkyne and 3 mL of CH$_2$Cl$_2$, 2 equiv of I$_2$ or Br$_2$ dissolved in 2 mL of CH$_2$Cl$_2$ was added gradually. The reaction mixture was flushed with Ar and allowed to stir at room temperature for the desired time. The excess I$_2$ or Br$_2$ was removed by washing with satd aq Na$_2$S$_2$O$_3$. The mixture was then extracted by diethyl ether (2 x 10 mL). The combined ether layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

3-Iodo-2-phenylbenzo[b]furan (2). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.28-7.51 (m, 7H), 8.16-8.19 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 61.3, 111.4, 122.1, 123.7, 125.9, 127.7, 128.7, 129.4, 130.2, 132.7, 153.2, 154.1; IR (neat, cm$^{-1}$) 3058, 1450; HRMS calcd for C$_{14}$H$_9$IO 319.9698, found 319.9700.
3-Bromo-2-phenylbenzo[b]furan (3). The product was obtained as a colorless oil:

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.36-7.52 (m, 7H), 8.24-8.34 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 105.1, 122.4, 123.9, 125.5, 125.8, 128.8, 129.0, 129.9, 133.3, 137.9, 138.4, 139.4; IR (neat, cm\(^{-1}\)) 3026; HRMS calcd for C\(_{14}\)H\(_9\)BrO 217.9837, found 217.9840.

2-(Cyclohex-1-enyl)-3-iodobenzo[b]furan (7). The product was obtained as a yellow oil: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.66-1.70 (m, 2H), 1.77-1.79 (m, 2H), 2.25-2.29 (m, 2H), 2.59-2.64 (m, 2H), 6.77-6.79 (m, 2H), 7.24-7.28 (m, 2H), 7.35-7.38 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.9, 22.7, 25.9, 26.9, 59.1, 111.0, 121.7, 123.3, 125.2, 128.2, 132.0, 132.2, 153.5, 155.3; HRMS calcd for C\(_{14}\)H\(_{13}\)IO 324.0011, found 324.0020.

3-Iodo-2-(4-methoxyphenyl)benzo[b]furan (10). The product was obtained as a yellow oil: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.84 (s, 3H), 6.99 (d, \(J = 8.0\) Hz, 2H), 7.28-7.31 (m, 2H), 7.39-7.45 (m, 2H), 8.10 (d, \(J = 8.8\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 55.5, 59.7, 111.2, 114.1, 121.7, 122.8, 123.6, 125.4, 129.2, 132.8, 153.4, 153.9, 160.5; HRMS calcd for C\(_{15}\)H\(_{11}\)IO 349.9803, found 349.9810.

3-Iodo-5-methoxy-2-phenylbenzo[a]furan (13). The product was obtained as a yellow oil: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.89 (s, 3H), 6.88 (s, 1H), 6.94 (d, \(J = 8.5\) Hz, 1H), 7.36 (d, \(J = 8.8\) Hz, 1H), 7.41 (t, \(J = 7.2\) Hz, 1H), 7.48 (t, \(J = 7.6\) Hz, 2H), 8.14 (d, \(J = 7.2\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 56.2, 61.3, 104.1, 112.1, 114.9, 127.6, 128.7, 129.4, 130.3, 133.3, 149.0, 154.0, 156.9; IR (neat, cm\(^{-1}\)) 3058, 2926, 2855, 2227, 1464, 1435, 749; HRMS calcd for C\(_{15}\)H\(_{11}\)IO 349.9804, found 349.9810.

3-Iodo-5-nitro-2-phenylbenzo[a]furan (16). The product was obtained as a yellow oil: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.50-7.58 (m, 4H), 8.15-8.18 (m, 2H), 8.27 (dd, \(J = 12.0, 3.2\) Hz,
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$^1$H NMR (CDCl$_3$) $\delta$ 8.37 (d, $J = 3.2$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 60.9, 111.9, 118.7, 121.5, 127.8, 128.9, 129.0, 130.4, 133.6, 144.9, 156.5, 157.0; IR (neat, cm$^{-1}$) 3058, 2926; HRMS calcd for C$_{14}$H$_{18}$INO$_3$ 364.9549, found 364.9551.

3-Iodo-6-nitro-2-phenylbenzo[b]furan (18). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.50-7.56 (m, 4H), 8.18-8.21 (m, 2H), 8.23 (dd, $J = 8.4$, 2.0 Hz, 1H), 8.39 (d, $J = 2.0$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 60.6, 107.8, 119.5, 122.1, 128.0, 129.0, 129.0, 130.7, 138.5, 146.1, 152.6, 158.4; IR (neat, cm$^{-1}$) 3058, 2926; HRMS calcd for C$_{14}$H$_{18}$INO$_3$ 364.9549, found 364.9552.

3-Iodo-5-methyl-2-phenylfuro[3,3-b]pyridine (20). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 2.73 (s, 3H), 7.14 (d, $J = 8.4$ Hz, 1H), 7.46-7.54 (m, 3H), 7.62 (d, $J = 8.4$ Hz, 1H), 8.21-8.24 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 24.7, 64.4, 118.5, 120.6, 127.8, 128.8, 129.9, 130.0, 145.8, 148.9, 156.0, 156.2; IR (neat, cm$^{-1}$) 1775; HRMS calcd for C$_{14}$H$_{10}$INO, 334.9808, found 334.9809.

2-(2-Acetoxyphenyl)-3-iodobenzo[b]furan (22). The product was obtained as a yellow oil: mp 218 °C (dec); $^1$H NMR (CDCl$_3$) $\delta$ 2.21 (s, 3H), 7.25 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.32-7.40 (m, 3H), 7.44-7.53 (m, 3H), 7.82 (dd, $J = 7.8$, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.3, 65.4, 111.4, 122.1, 123.3, 123.7, 123.8, 126.0, 126.1, 131.2, 131.7, 131.9, 148.8, 152.3, 154.6, 169.4; IR (neat, cm$^{-1}$) 1771; HRMS calcd for C$_{16}$H$_{11}$IO$_3$, 377.9753, found 377.9758.

2,2'-(1,4-Phenylene)-bis[3-iodobenzo[b]furan] (24). The product was obtained as a white solid: mp 256-257 °C; $^1$H NMR (CDCl$_3$) $\delta$ 7.34-7.42 (m, 4H), 7.47-7.53 (m, 4H),
8.36 (s, 4H); $^{13}$C NMR (CDCl$_3$) $\delta$ 62.3, 111.5, 122.2, 123.9, 126.3, 127.5, 130.7, 132.8, 152.5, 154.2; HRMS calcd for C$_{22}$H$_{12}$I$_2$O$_2$ 561.8927. Found 561.8934.

3,7-Diiodo-2,6-diphenylbenzoo[1,2-b:4,5-b']difuran (26). The product was obtained as a white solid: mp $>$300 °C (dec); HRMS calcd for C$_{22}$H$_{12}$I$_2$O$_2$ 561.8927. Found 561.8933.

5-(1,2-Diiodo-2-phenylethenyl)-2,4-dimethoxypyrimidine (32). The product was obtained as yellow oil and ready to decompose.

2-(1,2-Diiodo-n-1-decenyl)-6-methyl-3-methoxy-pyridine (34): The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 0.88-0.92 (m, 3H), 1.25-1.44 (m, 10 H), 1.65-1.70 (m, 2H), 2.50 (s, 3H), 2.72-2.77 (m, 1H), 2.84-2.89 (m, 1H), 3.86 (s, 3H), 7.10 (dd, $J$ = 13.5, 8.4 Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.3, 22.9, 23.7, 28.5, 28.6, 29.4, 29.7, 32.1, 49.1, 56.1, 91.0, 107.4, 120.1, 124.1, 149.5, 149.7, 151.9; IR (neat, cm$^{-1}$) 1715; HRMS calcd for C$_{15}$H$_{21}$I$_2$NO 484.9713. Found 484.9720.

General procedure for the $p$-O$_2$NC$_6$H$_4$SCl and PhSeCl cyclizations. To a solution of 0.25 mmol of the alkyne and CH$_2$Cl$_2$ (5 mL), 0.375 mmol of $p$-O$_2$NC$_6$H$_4$SCl or PhSeCl was added. The mixture was flushed with Ar and allowed to stir at 25 °C for 2-6 h. The reaction mixture was washed with 20 mL of water and extracted with diethyl ether. The combined ether layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum to yield the crude product, which was further purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-Phenyl-3-(phenylselenyl)benzo[b]furan (4). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.13-7.17 (m, 3H), 7.22 (t, $J$ = 4.0 Hz, 1H), 7.27-7.32 (m, 4H), 7.43
(t, J = 7.6 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 8.19-8.21 (m, 2H); 
\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 99.9, 111.4, 121.4, 123.6, 125.4, 126.4, 128.0, 128.7, 129.4, 129.5, 130.3, 131.6, 132.1, 154.3, 157.4; IR (neat, cm\(^{-1}\)) 3058, 2926; HRMS calcd for C\(_{20}\)H\(_{14}\)OSe 350.0211, found 350.0220.

3-p-Nitrophenylsulfenyl-2-phenylbenzo\([b]\)furan (5). The product was obtained as a yellow oil: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.22 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.35-7.46 (m, 5H), 7.60 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 7.2 Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 102.1, 111.9, 120.1, 124.1, 124.4, 125.9, 126.0, 127.6, 128.9, 129.3, 130.1, 130.1, 145.6, 146.4, 154.2, 158.6; IR (neat, cm\(^{-1}\)) 3058, 2926; HRMS calcd for C\(_{20}\)H\(_{13}\)NO\(_3\)S 347.0617, found 347.0622.

2-(Cyclohex-1-enyl)-3-(phenylselenyl)benzofuran (8). The product was obtained as a yellow oil: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.64-1.66 (m, 2H), 1.72-1.74 (m, 2H), 2.19-2.21 (m, 2H), 2.50-2.51 (m, 2H), 6.09-6.10 (m, 1H), 7.10-7.15 (m, 5H), 7.28-7.31 (m, 2H), 7.76-7.78 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.9, 23.0, 25.9, 30.4, 114.0, 122.2, 124.7, 125.0, 126.0, 129.3, 131.7, 132.0, 133.3, 138.4, 142.0, 152.1; IR (neat, cm\(^{-1}\)) 3025; HRMS calcd for C\(_{20}\)H\(_{16}\)OSe 354.0523, found 354.0533.

2-(4-Methoxyphenyl)-3-(phenylselenyl)benzo\([b]\)furan (11). The product was obtained as a yellow oil: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.82 (s, 3H), 6.95 (d, J = 8.0 Hz, 2H), 7.11-7.23 (m, 4H), 7.26-7.53 (m, 3H), 7.48-7.53 (dd, J = 8.4 Hz, 7.6 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 55.1, 98.0, 111.2, 114.1, 121.1, 123.0, 123.5, 125.0, 126.3, 129.1, 129.5, 131.8, 132.3, 154.1, 157.7, 160.6; HRMS calcd for C\(_{21}\)H\(_{16}\)O\(_2\)Se 380.0317, found 380.0328.
5-Methoxy-2-phenyl-3-(phenylselenyl)benzo[b]furan (14). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.75 (s, 3H), 6.90-6.93 (m, 2H), 7.12-7.17 (m, 3H), 7.29 (d, $J$ = 8.0 Hz, 2H), 7.36-7.44 (m, 4H), 7.18 (d, $J$ = 2.0 Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.0, 99.6, 103.3, 112.0, 114.5, 126.4, 127.9, 128.6, 129.3, 129.4, 129.5, 130.4, 131.6, 132.9, 149.2, 156.7, 158.2; IR (neat, cm$^{-1}$) 3058, 2926, 2855, 2227, 1464, 1435, 749; HRMS calcd for C$_{21}$H$_{16}$SeO$_2$ 380.0317, found 380.0328.

Acknowledgements

We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health and the National Science Foundation for partial support of this research and Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for donations of palladium salts.

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Catalyzed Cross-Coupling Reactions; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: 
CHAPTER 2. AN EFFICIENT SYNTHESIS OF HETEROCYCLES BY ELECTROPHILIC CYCLIZATION OF ACETYLENIC ALDEHYDES, KETONES AND IMINES

Based on a communication to be submitted to Organic Letters and a paper to be published in the Journal of Organic Chemistry

Dawei Yue, Nicola Della Ca* and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, IA 50011, USA

larock@iastate.edu

Abstract

Highly substituted 1H-isochromenes and 1,2-dihydroisoquinolines can be prepared in high yields at room temperature by reacting o-(1-alkynyl)arenecarboxaldehydes, ketones and the corresponding imines with I₂, p-O₂NC₆H₄SCl or PhSeBr and various alcohols or carbon-based nucleophiles.

Introduction

The electrophilic cyclization of functionally-substituted alkenes has provided an extremely useful route for the synthesis of a wide variety of heterocyclic and carbocyclic compounds, which have often proven useful as intermediates in the synthesis of natural products and pharmaceuticals. The analogous chemistry of alkynes has been far less studied, although it would appear to be a very promising route to an extraordinary range of useful, functionally-substituted heterocycles and carbocycles. Our recent work has indicated that benzothiophenes, isoquinolines and isocoumarins can be easily synthesized.
by the electrophilic cyclization of appropriate functionally-substituted alkynes using iodine-,
sulfur- and selenium-containing electrophiles under exceptionally mild reaction conditions
(Scheme 1). Others have recently reported a number of analogous, very useful iodine-
promoted cyclizations of functionally-substituted alkynes.⁶

**Scheme 1**

![Scheme 1 diagram](image)

\[
\begin{align*}
X-Y &= \text{O-H, S-Me, NMe}_2, \text{CH=N-t-Bu} \\
E^+ &= \text{Br}_2, \text{NBS, I}_2, \text{PhSeCl, } \rho-O_2NC_6H_4SCl
\end{align*}
\]

Recently, Yamamoto reported an interesting cyclization of acetylenic aldehydes to 1-
alkoxy-1\(^H\)-isochromenes catalyzed by palladium.⁷ The Pd(II) salt employed was claimed to
exhibit a dual role as both a Lewis acid and a transition-metal catalyst (eq 1).

![Equation 1](image)

\[
\text{(1)}
\]

In a more recent study, the analogous preparation of 1\(^H\)-isochromenes has been
achieved upon reaction of bis(pyridine)iodonium tetrafluoroborate (IPy\(_2\)BF\(_4\)) and HBF\(_4\) with
the same acetylenic carbonyl precursors in the presence of various nucleophiles (eq 2).⁸

![Equation 2](image)

\[
\text{(2)}
\]
The use of expensive IPy$_2$BF$_4$ together with B(OMe)$_3$ or toxic, strongly acidic HBF$_4$, and the relatively complicated stepwise procedure employed make this approach a bit unwieldy synthetically. Furthermore, the scope of this cyclization has yet to be reported.

We simultaneously found that this three component reaction$^9$ proceeds smoothly by using various electrophiles, such as I$_2$, $p$-O$_2$NC$_6$H$_4$SCl and PhSeBr, to generate the corresponding iodine-, sulfur- and selenium-substituted heterocycles in high yields under very mild reaction conditions. Herein, we wish to report a much more efficient and convenient approach to these types of heterocycles involving electrophilic cyclization using a range of electrophiles and nucleophiles.

**Results and Discussion**

Our initial studies were aimed at finding optimal reaction conditions for the electrophilic cyclization of the o-(1-alkynyl)benzaldehydes. Our investigation began with the reaction of o-(phenylethynyl)benzaldehyde (1), methanol and I$_2$ (Table 1). The reaction was first attempted using 0.25 mmol of o-(phenylethynyl)benzaldehyde (1), 1.2 equiv of methanol, 1.0 equiv of K$_2$CO$_3$ and 1.2 equiv of I$_2$ in CH$_2$CI$_2$ at room temperature. Iodocyclization proceeded smoothly and provided an 88 % yield of the desired product 2. Other solvents, such as CH$_3$CN and DMF, were also investigated and proved to be far less effective. KHCO$_3$ and NEt$_3$ were also investigated as bases. While KHCO$_3$ provided a slightly lower yield of the desired product than K$_2$CO$_3$, NEt$_3$ proved to be ineffective and none of the desired product was detected. Although CH$_2$Cl$_2$ is not a good solvent for K$_2$CO$_3$, the presence of K$_2$CO$_3$ was crucial for a clean, high yielding reaction. K$_2$CO$_3$ is presumed to neutralize the by-product HI of the electrophilic cyclization, which can also react with the
acetylenic aldehyde and generate the corresponding pyrilium salt.\textsuperscript{10} Increasing the amount of methanol from 1.2 equiv to using MeOH as the solvent resulted in a lower yield. 1.2 Equiv of I\textsubscript{2} has proven to be enough to achieve a high yield. Further increasing the amount of I\textsubscript{2} did not give better yields.

**Table 1.** Iodocyclization of 2-(phenylethynyl)benzaldehyde

<table>
<thead>
<tr>
<th>solvent</th>
<th>MeOH (equiv)</th>
<th>I\textsubscript{2} (equiv)</th>
<th>base (equiv)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>1.2</td>
<td>1.2</td>
<td>K\textsubscript{2}CO\textsubscript{3} (1.0)</td>
<td>88</td>
</tr>
<tr>
<td>CH\textsubscript{3}CN</td>
<td>1.2</td>
<td>1.2</td>
<td>K\textsubscript{2}CO\textsubscript{3} (1.0)</td>
<td>40</td>
</tr>
<tr>
<td>DMF</td>
<td>1.2</td>
<td>1.2</td>
<td>K\textsubscript{2}CO\textsubscript{3} (1.0)</td>
<td>trace</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>1.2</td>
<td>1.2</td>
<td>KHCO\textsubscript{3} (1.0)</td>
<td>70</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>2.0</td>
<td>2.5</td>
<td>K\textsubscript{2}CO\textsubscript{3} (1.0)</td>
<td>80</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>2.0</td>
<td>2.5</td>
<td>K\textsubscript{2}CO\textsubscript{3} (2.0)</td>
<td>78</td>
</tr>
<tr>
<td>MeOH</td>
<td>-</td>
<td>2.5</td>
<td>K\textsubscript{2}CO\textsubscript{3} (2.0)</td>
<td>68</td>
</tr>
</tbody>
</table>

Based on the above optimization efforts, the combination of 1.2 equiv of nucleophile, 1.0 equiv of K\textsubscript{2}CO\textsubscript{3}, 1.2 equiv of I\textsubscript{2} and using CH\textsubscript{2}Cl\textsubscript{2} as the solvent at room temperature gave the best results. This procedure has been used as our standard reaction conditions for subsequent electrophilic cyclizations. To test the generality of this chemistry, acetylenic aldehydes bearing different substituents on the carbon-carbon triple bond were synthesized in high yields by the palladium/copper-catalyzed coupling of o-bromobenzaldehyde and the corresponding terminal alkynes.\textsuperscript{11} The resulting acetylenic aldehydes were then allowed to react under our standard electrophilic cyclization conditions to afford the corresponding 1H-
isochromene products in good to excellent yields. The results are summarized in Table 2. Alkynes bearing an aromatic ring, as well as alkyl and vinylic substituents, all react well with methanol and ethanol to provide the desired iodocyclization products in good yields (entries 1, 2, 7 and 10). Interestingly, not only alcohols, but also electron-rich aromatic compounds, such as N,N-dimethylaniline and phenol, can be used as nucleophiles, affording iodocyclization products in generally good to excellent yields (entries 3, 4, 8 and 11). On the other hand, anisole and 1,4-dimethoxybenzene did not react as nucleophiles and provided unidentifiable products. In all cases where we have run comparable reactions, the reactions with readily available, inexpensive I$_2$ have given higher yields than the process using the expensive iodonium salt and HBF$_4$ used by Barluenga.$^8$

To further explore the scope of this cyclization, commercially available sulfur and selenium electrophiles have also been used in this process and have been found to provide decent yields of the desired cyclization products using both methanol and N,N-dimethylaniline as nucleophiles (entries 5, 6, 9 and 12). The reactions with I$_2$ and p-O$_2$NC$_6$H$_4$SCl were completed in a shorter period of time and gave higher yields of products than those with PhSeBr.

Besides the benzaldehyde derivatives, ketone 16 has also been allowed to react with I$_2$ under our reaction conditions (entry 13). This reaction proceeded smoothly to provide a 90% yield of a 5-exo-dig cyclization product, rather than the six-membered ring ether formed by the electrophilic cyclization of analogous benzaldehyde derivatives. The use of K$_2$CO$_3$ provides very mild basic conditions and avoids the acid-initiated, partial decomposition of this cyclization product described in Barluenga’s paper.$^8$
Table 2. Electrophilic cyclization of acetylenic aldehydes, ketones and imines

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>nucleophile</th>
<th>electrophile</th>
<th>product</th>
<th>% isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="alkyne1.png" alt="Image" /></td>
<td>MeOH</td>
<td>I₂</td>
<td><img src="product1.png" alt="Image" /></td>
<td>2</td>
</tr>
<tr>
<td>2</td>
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<td>EtOH</td>
<td>I₂</td>
<td><img src="product2.png" alt="Image" /></td>
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</tr>
<tr>
<td>3</td>
<td><img src="alkyne3.png" alt="Image" /></td>
<td>NMe₂</td>
<td>I₂</td>
<td><img src="product3.png" alt="Image" /></td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td><img src="alkyne4.png" alt="Image" /></td>
<td>OH</td>
<td>I₂</td>
<td><img src="product4.png" alt="Image" /></td>
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<td>---</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>MeOH</td>
<td>PhSeBr</td>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>MeOH</td>
<td>$p$-NO$_2$C$_6$H$_4$SCl</td>
<td>7</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>MeOH</td>
<td>I$_2$</td>
<td>9</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>MeOH</td>
<td>I$_2$</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>MeOH</td>
<td>$p$-NO$_2$C$_6$H$_4$SCl</td>
<td>11</td>
<td>73</td>
</tr>
<tr>
<td>No.</td>
<td>Structure 1</td>
<td>Structure 2</td>
<td>Reaction</td>
<td>Yield</td>
<td></td>
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<tr>
<td>-----</td>
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<td>------------</td>
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<tr>
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<td><img src="image" alt="Structure 2" /></td>
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<tr>
<td>11</td>
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<td><img src="image" alt="Structure 2" /></td>
<td>I₂</td>
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<tr>
<td>12</td>
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<td><img src="image" alt="Structure 2" /></td>
<td>p-NO₂C₆H₄SCl</td>
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<td><img src="image" alt="Structure 2" /></td>
<td>MeOH</td>
<td>90</td>
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</tr>
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</table>
The reactions were run under the following conditions, unless otherwise specified. While stirring a solution of 2.5 mL of CH$_2$Cl$_2$ containing 0.25 mmol of the alkyne, 0.30 mmol of the nucleophile and 0.25 mmol of K$_2$CO$_3$, 0.30 mmol of electrophile were added and the resulting mixture was further stirred at room temperature until the total disappearance of the starting material as indicated by TLC analysis. The reaction was run on a 1.0 mmol scale; the 0.25 mmol scale reaction provides an 88% yield of compound 2. A 25% yield of O-nucleophile trapping product was also observed. The yields were determined by $^1$H NMR spectroscopic analysis due to the apparent instability of the products.
Iminoalkyne 18 has also been allowed to react under our usual cyclization conditions in the hope that after attack of the nucleophile, the reaction might provide biologically interesting dihydroisoquinoline derivatives. However, for some reason, a large amount of an unidentifiable salt was generated when MeOH was used as the trapping agent. Only about 25 % of the desired cyclization product was observed upon $^1$H NMR spectroscopic analysis (entry 14). On the other hand, using $N,N$-dimethylaniline as the nucleophile under the same reaction conditions gave a 60 % yield of the desired iodocyclization product (entry 15).

Interestingly, when we followed the stepwise procedure described in Barluenga’s paper, we were unable to get high yields of the desired iodocyclization products. Instead, an unreactive solid, presumed to be the pyrilium salt, was generated. Based on this observation, a possible mechanism is proposed in Scheme 2. We believe that these cyclizations proceed by *anti* attack of the electrophile and the carbonyl on the alkyne to produce a pyrilium intermediate. Before it forms an insoluble precipitate, the pyrilium intermediate is immediately trapped by the nucleophile present in the reaction mixture.
Conclusions

We believe that this approach to heterocycles should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting halogen, sulfur and selenium functionalities into other substituents. For instance, the resulting heterocyclic iodides should be particularly useful intermediates in many palladium-catalyzed processes, such as Sonogashira, Suzuki, Stille, and Heck cross couplings.

Experimental Section

General. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 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 a 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.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of ethyl ether, hexanes, ethyl acetate, and CH$_2$Cl$_2$ were purchased from Fisher Scientific Co. 2-Bromobenzaldehyde, 2-iodoacetophenone, phenylacetylene, 1-cyclohexenyl acetylene, 1-hexyne, PhSeCl, PhSeBr, $p$-O$_2$NC$_6$H$_4$SCl, PhNMe$_2$, phenol and Et$_3$N were purchased from Aldrich Chemical Co., Inc. The palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd.
Starting materials. The 2-(1-alkynyl)benzaldehydes were prepared by the Sonogashira coupling of 2-bromobenzaldehyde with various terminal alkynes. The same procedure was used to prepare 2-(phenylethynyl)acetophenone. All commercially available compounds were used as received.

General procedure for the synthesis of 4-iodo-1H-isochromenes. Into a solution of the 2-(1-alkynyl)benzaldehyde, K₂CO₃ (1.0 equiv) and the nucleophile (1.2 equiv) in CH₂Cl₂ (0.25 mmol), I₂ (1.2 equiv) was added and the solution was stirred at room temperature until the total disappearance of the starting material as determined by TLC analysis. The reaction mixture was then quenched with satd aq Na₂S₂O₃ (5.0 mL) and water (5.0 mL). The resulting solution was extracted by diethyl ether. The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude product was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford pure compounds.

4-Iodo-1-methoxy-3-phenyl-1H-isochromene (2). The product was obtained as a yellow oil: ¹H NMR (CDCl₃) δ 3.71 (s, 3H), 6.12 (s, 1H), 7.34 (d, J = 7.0 Hz, 1H), 7.42 (t, J = 7.0 Hz, 1H), 7.54-7.57 (m, 4H), 7.72-7.74 (m, 3H); ¹³C NMR (CDCl₃) δ 55.9, 73.7, 99.8, 125.3, 127.0, 127.7, 127.8, 129.2, 129.6, 129.8, 129.9, 131.2, 137.2, 151.6; IR (neat, cm⁻¹) 3039, 2936, 1052; HRMS calcd for C₁₆H₁₃IO₂ 363.9960, found 363.9964.

1-n-Butoxy-4-iodo-3-phenyl-1H-isochromene (3). The product was obtained as a yellow oil: ¹H NMR (CDCl₃) δ 0.95 (t, J = 7.3 Hz, 3H), 1.38-1.50 (m, 2H), 1.62-1.72 (m, 2H), 3.76-3.84 (m, 1H), 4.00-4.04 (m, 1H), 6.13 (s, 1H), 7.21 (dd, J = 7.4, 1.0 Hz, 1H), 7.35
(td, $J = 7.4, 1.1$ Hz, 1H), 7.43-7.50 (m, 4H), 7.61-7.66 (m, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.2, 19.6, 31.9, 68.9, 74.0, 99.1, 125.6, 127.8, 128.0, 128.2, 129.5, 129.9, 130.0, 130.2, 131.8, 137.8, 152.2; IR (neat, cm$^{-1}$) 3063, 3032, 2956, 2931, 2870, 1594, 1483; HRMS calcd for C$_{19}$H$_{18}$I$_2$O$_2$ 406.0430, found 406.0438.

1-(4-Dimethylaminophenyl)-4-iodo-3-phenyl-1H-isochromene (4). The product was obtained as a white solid (mp = 51 °C, dec): $^1$H NMR (CDCl$_3$) $\delta$ 3.02 (s, 6H), 6.21 (s, 1H), 6.74-6.77 (m, 3H), 7.24-7.36 (m, 7H), 7.53-7.58 (m, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 40.4, 72.9, 80.6, 112.1, 124.8, 126.2, 127.5, 128.3, 128.9, 129.2, 129.4, 130.4, 131.5, 133.4, 136.7, 150.6, 154.6; IR (neat, cm$^{-1}$) 3046, 1612, 1524; HRMS calcd for C$_{23}$H$_{20}$INO 454.0668, found 454.0660.

1-(4-Hydroxyphenyl)-4-iodo-3-phenyl-1H-isochromene (5). The product was obtained as an orange syrup: $^1$H NMR (CDCl$_3$) $\delta$ 5.50 (br s, 1H), 6.23 (s, 1H), 6.82 (d, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 8.7$ Hz, 2H), 7.23-7.25 (m, 3H), 7.34-7.36 (m, 4H), 7.53-7.55 (m, 2H), 7.63 (d, $J = 7.7$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 73.2, 80.2, 115.3, 124.8, 127.6, 127.7, 128.5, 129.0, 129.3, 129.9, 130.2, 130.9, 131.1, 133.3, 136.6, 154.5, 155.9; IR (neat, cm$^{-1}$) 3569, 3044, 1174; HRMS calcd for C$_{23}$H$_{20}$INO 426.0117, found 426.0119.

1-Methoxy-3-phenyl-4-phenyselenyl-1H-isochromene (6). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.74 (s, 3H), 6.13 (s, 1H), 7.09 (d, $J = 4.8$ Hz, 1H), 7.15 (t, $J = 5.4$ Hz, 2H), 7.23-7.40 (m, 9H), 7.56-7.59 (m, 2H), 7.73 (d, $J = 5.1$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.4, 76.9, 100.4, 125.7, 125.7, 126.6, 127.5, 127.6, 127.9, 128.4, 128.2, 129.3, 129.4, 129.8, 130.0, 131.4, 133.6, 136.4, 157.1; IR (neat, cm$^{-1}$) 3063, 2968, 1021, 960; HRMS calcd for C$_{22}$H$_{18}$O$_2$Se 394.0472, found 394.0479.
1-Methoxy-4-p-nitrophenylsulfenyl-3-phenyl-1H-isochromene (7). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.77 (s, 3H), 6.17 (s, 1H), 7.24-7.27 (m, 2H), 7.35-7.43 (m, 6H), 7.58-7.61 (m, 3H), 8.03 (d, $J = 9.0$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.7, 100.5, 102.6, 123.8, 124.3, 125.6, 126.0, 127.7, 128.1, 128.2, 129.5, 129.9, 130.1, 130.2, 134.7, 145.3, 148.6, 158.8; IR (neat, cm$^{-1}$) 3093, 3065, 2930, 2833, 1594, 1510, 1337; HRMS calcd for C$_{22}$H$_{17}$NO$_4$S 391.0878, found 391.0883.

3-n-Butyl-4-iodo-1-methoxy-1H-isochromene (9). The product was obtained as a pale yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.02 (t, $J = 7.2$ Hz, 3H), 1.43-1.64 (m, 2H), 2.63-2.92 (m, 2H), 3.63 (s, 3H), 5.92 (s, 1H), 7.21 (d, $J = 7.1$ Hz, 1H), 7.34 (td, $J = 7.1$, 1.3 Hz, 1H), 7.43 (td, $J = 7.9$, 1.3 Hz, 1H), 7.54 (d, $J = 7.9$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 13.9, 22.1, 29.3, 36.9, 55.4, 73.3, 99.1, 125.2, 126.6, 126.8, 128.4, 129.5, 130.8, 154.5; IR (neat, cm$^{-1}$) 3029, 2956, 1078; HRMS calcd for C$_{14}$H$_{17}$IO$_2$ 344.0273, found 344.0288.

1-(4-Dimethylaminophenyl)-3-n-butyl-4-iodo-1H-isochromene (10). The product was obtained as a white solid (mp = 51 °C, dec): $^1$H NMR (CDCl$_3$) $\delta$ 0.86 (t, $J = 5.4$ Hz, 3H), 1.22-1.38 (m, 2H), 1.44-1.53 (m, 2H), 2.50-2.80 (m, 2H), 2.97 (s, 6H), 5.99 (s, 1H), 6.66 (d, $J = 5.6$ Hz, 1H), 6.72 (d, $J = 6.4$ Hz, 2H), 7.11 (t, $J = 5.6$ Hz, 1H), 7.19 (d, $J = 6.5$ Hz, 2H), 7.29 (t, $J = 5.7$ Hz, 1H), 7.40 (d, $J = 5.8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.1, 22.5, 30.1, 32.7, 56.1, 63.9, 99.9, 115.6, 122.9, 124.3, 125.4, 126.0, 127.2, 127.3, 129.7, 130.1, 145.2, 148.6; IR (neat, cm$^{-1}$) 3062, 2955, 2926, 2858, 2806, 1736, 1612, 1524; HRMS calcd for C$_{21}$H$_{24}$INO$_4$ 433.0903, found 433.0913.

3-n-Butyl-1-methoxy-4-p-nitrophenylsulfenyl-1H-isochromene (11). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 0.89 (t, $J = 7.3$ Hz, 3H), 1.26-1.39 (m,
2H), 1.57-1.67 (m, 2H), 2.57-2.67 (m, 1H), 2.79-2.89 (m, 1H), 3.64 (s, 3H), 6.04 (s, 1H),
7.20-7.28 (m, 6H), 8.05 (d, J = 6.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 14.1, 22.5, 30.1, 32.7, 56.1,
63.9, 99.9, 122.9, 124.3, 125.4, 126.0, 127.2, 127.4, 129.7, 130.1, 145.2, 148.6; IR (neat,
cm$^{-1}$) 3062, 2955, 1736, 1612, 1524; HRMS calcd for C$_{20}$H$_{21}$NO$_4$S 371.1192, found
371.1199.

3-(Cyclohex-1-enyl)-4-iodo-1-methoxy-1H-isochromene (13). The product was
obtained as a yellow oil: $^1$H NMR (CDCl$_3$) δ 1.72-1.78 (m, 4H), 2.24-2.38 (m, 4H), 3.64 (s,
3H), 5.92 (s, 1H), 6.14 (m, 1H), 7.14 (dd, J = 7.2, 1.3 Hz, 1H), 7.32 (td, J = 7.2, 1.3 Hz, 1H),
7.42 (td, J = 7.7, 1.5 Hz, 1H), 7.53 (dd, J = 7.7, 1.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 21.6, 22.3,
24.9, 26.7, 55.6, 71.9, 99.4, 125.2, 127.0, 127.2, 129.4, 129.6, 131.3, 132.9, 135.2, 153.8; IR
(neat, cm$^{-1}$) 3034, 2926, 1024; HRMS calcd for C$_{16}$H$_{17}$IO$_2$ 368.0273, found 368.0273.

1-(4-Dimethylaminophenyl)-3-(cyclohex-1-enyl)-4-iodo-1H-isochromene (14). The product was
obtained as a yellow oil: $^1$H NMR (CDCl$_3$) δ 1.56-1.66 (m, 4H), 2.03-2.17 (m,
4H), 2.96 (s, 6H), 5.98-5.99 (m, 1H), 6.02 (s, 1H), 6.68-6.72 (m, 3H), 7.12 (t, J = 6.0 Hz,
1H), 7.17 (d, J = 6.4 Hz, 2H), 7.30 (t, J = 5.7 Hz, 1H), 7.45 (d, J = 5.8 Hz, 1H); $^{13}$C NMR
(CDCl$_3$) δ 22.0, 22.6, 25.3, 27.0, 31.2, 57.0, 71.9, 80.5, 112.3, 117.6, 125.1, 127.3, 128.4,
128.8, 129.6, 131.9, 133.2, 133.7, 135.3, 157.6; IR (neat, cm$^{-1}$) 2927, 2855, 1613, 1523;
HRMS calcd for C$_{23}$H$_{24}$INO 457.0903, found 457.0913.

Synthesis of 1,3-dihydro-3-[(E)-1-iodo-1-phenylmethylene]-1-methoxy-1-methylisobenzofuran (17). To a stirred mixture of 2-(phenylethynyl)acetophenone (0.25
mmol), K$_2$CO$_3$ (1.0 equiv) and MeOH (1.2 equiv) in CH$_2$Cl$_2$ (5 mL), I$_2$ (1.2 equiv) was
added and the mixture was stirred until no starting material remained as indicated by TLC
analysis. The reaction mixture was quenched with satd aq Na$_2$S$_2$O$_3$ (5.0 mL) and water (5.0 mL). The mixture was extracted with diethyl ether and the combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford a pale yellow solid (*unstable*): $^1$H NMR (CDCl$_3$) δ 1.73 (s, 3H), 3.01 (s, 3H), 7.23-7.71 (m, 4H), 7.25 (d, $J = 7.2$ Hz, 1H), 7.31-7.45 (m, 3H), 8.82 (d, $J = 6.7$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 25.6, 50.5, 65.9, 110.1, 122.1, 125.5, 127.3, 127.7, 128.9, 130.0, 130.3, 133.8, 141.7, 142.6, 150.9; HRMS calcd for C$_{17}$H$_{13}$IO$_2$ 378.0117, found 378.0121.

**Acknowledgements**

We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health and the National Science Foundation for partial support of this research and Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for donations of palladium salts.

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CHAPTER 3. SYNTHESIS OF COUDESTANS BY SELECTIVE ELECTROPHILIC CYCLIZATION, FOLLOWED BY PALLADIUM-CATALYZED INTRAMOLECULAR CARBONYLATION: AN EFFICIENT SYNTHESIS OF COUMESTROL

Based on a paper to be submitted to the Journal of Organic Chemistry

Dawei Yue and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, IA 50011

larock@iastate.edu

Abstract

Coumestan and coumestrol are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of appropriately substituted o-iodoanisoles and terminal alkynes and selective electrophilic cyclization using I₂, followed by palladium-catalyzed intramolecular carbonylation and subsequent lactonization.

Introduction

Heterocyclic compounds, particularly indole¹ and benzo[b]furan² derivatives, are of interest because they occur widely in nature and have unique biological activities.¹⁻³ Many methods for the synthesis of indoles⁴ and benzo[b]furans⁵ have already been reported. Among them, the cyclization of 2-(1-alkynyl)phenol or 2-(1-alkynyl)aniline derivatives is a powerful method for constructing such ring systems, because of the ready availability of the starting materials and the overall efficiency of this approach.⁴⁻⁵ Recently, we developed a
very efficient method to quickly construct benzo[b]thiophenes, indoles and benzo[b]furans by a palladium/copper-catalyzed coupling of terminal alkynes and appropriate functionally-substituted aryl halides, followed by electrophilic cyclization. Methyl groups on sulfur, nitrogen and oxygen are easily removed by the nucleophiles present in the solution. This approach should have wide applicability, because of the extremely mild reaction conditions and the versatility of the resulting iodoheterocycles.

Phytoestrogens are plant-derived compounds that structurally or functionally mimic mammalian estrogens and therefore are considered to play an important role in the prevention of cancers, heart disease, menopausal symptoms and osteoporosis. Coumestans are a group of plant phenols that show estrogenic activity. Their presence in forage crops has been associated with the disruption of the reproductive performance of livestock. A few coumestans isolated from plants have shown uterotropic activity.

The main coumestans with phytoestrogenic effects are coumestrol and 4'-methoxycoumestrol (Figure 1). Coumestrol was isolated from alfalfa, and strawberry, lucerne and ladino clover by Bickoff et al. in the 1950’s. Since the structure of coumestrol has some resemblance to the well known (E)-4,4'-dihydroxystilbene derivatives, which have potent pharmacological activity, it is not surprising that coumestrol shows estrogenic activity. Coumestrol has higher binding affinities to ERβ than the other phytoestrogen
compounds.\textsuperscript{14} \textit{In vitro} coumestrol has been reported to inhibit bone resorption and to stimulate bone mineralization.\textsuperscript{15} Coumestans are less common in the human diet than isoflavones, yet similar to isoflavones, they are also found in food plants, such as sprouts of alfalfa and mung bean, and they are especially prevalent in clover.\textsuperscript{16} Soy sprouts also show high levels of coumestrol.\textsuperscript{17}

Total syntheses of coumestrol have been reported by several groups using different approaches.\textsuperscript{12d,13,18} However, most of the reported methods required multiple steps and produced only modest yields. Furthermore, a number of naturally occurring coumestan isoflavones have been discovered\textsuperscript{19} and their biological effects are currently under investigation.\textsuperscript{20} Considering the numerous important physiological effects estrogens have on the human body and the potential of phytoestrogens for human health, it is highly desirable to develop more efficient and direct methods for the synthesis of coumestans and derivatives. Utilizing our highly efficient basic approach to benzothiophenes,\textsuperscript{6} indoles,\textsuperscript{7} and benzofurans\textsuperscript{8} developed earlier, we here present a new approach to the synthesis of the coumestan core structure and the synthesis of coumestrol.

\textbf{Results and Discussion}

During our study of the synthesis of benzo[\textit{b}]furans,\textsuperscript{8} we found that compound 1 can be easily cyclized under our iodocyclization conditions to afford compound 2 in a 95\% yield with the acetoxy group still intact (eq 1). The high chemoselectivity of this process allows

\[
\begin{align*}
\text{1} & \quad \overset{\text{AcO}}{\text{AcO}} \quad \overset{\text{I}_2/\text{CH}_2\text{Cl}_2 \quad 95\%}{\text{OMe}} \\
\text{2} & \quad \overset{\text{1OAc}}{\text{OAc}} \\
\end{align*}
\]
selective cyclization onto either end of the alkyne by careful choice of the protecting group on the oxygen functionality.

Based on this result, we set out the following strategy for the synthesis of coumestan (Scheme 1). By using our iodocyclization, compound 1 can be easily cyclized to compound 2, which could produce the coumestan ring system by either a one pot carbonylation and lactonization or a stepwise approach. Compound 1 can be easily synthesized by a Sonogashira reaction between arenes 3 and 4. Compounds 3 and 4 can in turn be synthesized from 2-iodoanisole and 2-iodophenol respectively. Using the same basic methodology (Scheme 2), coumestrol might be synthesized by carbonylation and subsequent lactonization of iodobenzofuran 6, which should be easily synthesized from
diarylacetylene 5 by electrophilic cyclization using iodine. Compound 5 should be easily synthesized from arenes 7 and 8, which might be prepared from the same resorcinol derivative 9.

**Synthesis of the coumestan ring system**

Commercially available 2-iodoanisole and 2-iodophenol were used as the starting materials for the synthesis of coumestan. The Sonogashira coupling of 2-iodoanisole with trimethylsilylacetylene catalyzed by 2 mol % of PdCl₂(PPh₃)₂ in the presence of 1 mol % of CuI and 1.5 equiv of Et₃N in DMF, followed by desilylation using n-Bu₄NF (TBAF) in THF, gave compound 3 in a 95% overall yield for the two steps. In the meanwhile, 2-iodophenol was acetylated to give compound 4 in essentially a quantitative yield.

**Scheme 3**

Reagents, conditions and yields: i, 1.2 equiv of trimethylsilylacetylene, 2 mol % of PdCl₂(PPh₃)₂, 1 mol % of CuI, 1.5 equiv of Et₃N, DMF, 60 °C, 2 h, 96%; ii, 1.0 equiv of TBAF, THF, 25 °C, 99%; iii, 1.2 equiv of AcCl, 2 equiv of Et₃N, THF, 0 °C, 1 h, >99%; iv, 1.2 equiv of 3, 2.0 mol % of PdCl₂(PPh₃)₂, 1.0 mol % of CuI, 2.0 equiv of Et₃N, DMF, 60 °C, 2 h, 95%; v, 1.2 equiv of I₂, CH₂Cl₂, 25 °C, 12 h, 95%.
Under the same Sonogashira coupling conditions used above, compound 3 reacted with 4 and afforded a 95% yield of compound 1. Compound 1 was treated with iodine at 25 °C to produce compound 2 in a 95% yield after 12 h (Scheme 3).

Compound 2 was then treated with a palladium catalyst and 1 atm of CO in the hope that we might affect carbonylation and lactonization in one step. A brief optimization of the reaction conditions showed that when 2 mol % of PdCl2(PPh3)2 was used as the catalyst, 2.0 equiv of K2CO3 was used as the base and DMF was used as the solvent, both carbonylation and lactonization proceeded smoothly under a balloon of CO at 60 °C, affording almost a quantitative yield of coumestan after 6 h (eq 2). Coumestan was identified based on a comparison with previously reported data.18c,22

\[
\begin{align*}
\text{OAc} & \quad \text{1 atm CO, 2.0 K}_2\text{CO}_3 \\
\text{2 mol % PdCl}_2\text{(PPh}_3\text{)}_2 & \quad \text{DMF/60 °C, 6 h} \\
\end{align*}
\]

>98%

**Synthesis of coumestrol**

(a) Synthesis of the substituted phenylacetylene derivative (Scheme 4)

Commercially available 4-bromoresorcinol was selectively tosylated and the resulting phenol was converted into the methyl ether in two steps in a 79% overall yield. The Sonogashira coupling21 of aryl bromide 9 with 1.2 equiv of trimethylsilylacetylene, followed by desilylation with n-Bu4NF, provided compound 8 in an 88% overall yield.

2,4-Diacetoxyiodobenzene (7) was prepared in almost a quantitative yield by acetylation of 4-iodoresorcinol, which was synthesized by the iodination of resorcinol using ICl. Our usual Sonogashira coupling reaction conditions were ineffective for the coupling
Reagents, conditions and yields: i, 1.1 equiv of TsCl, 3.0 equiv of K₂CO₃, acetone, reflux, 21 h; then 2.0 equiv of Mel, reflux, 3 h, 79%; ii, 1.2 equiv of trimethylsilylacetylene, 2 mol % of PdCl₂(PPh₃)₂, 1 mol % of CuI, 1.5 equiv of Et₃N, DMF, 100 °C, 6 h, 89%; iii, 1.0 equiv of TBAF, THF, 25 °C, 10 min, 99%; iv, 1.0 equiv of ICl, Et₂O, 25 °C, 1 h, 70%; v, 2.5 equiv of AcCl, 5.0 equiv of Et₃N, THF, 0 °C, 1 h, >98%.

A large amount of the homocoupling product of acetylene 8 was obtained. A brief optimization of the Sonogashira coupling showed that using i-Pr₂NH as the base and DMF as the solvent at 60 °C provided the best yield of acetylene 5 (eq 3, Table 1). The desired coupling product 5 was obtained in a 95% yield in 1 h.

Table 1. Sonogashira coupling of terminal alkyne 8 and halide 7.
(b) Iodocyclization

Using our standard iodocyclization conditions, compound 5 was successfully cyclized to benzofuran 6 in a 98% yield in 12 h, although the reaction time is substantially longer than our usual iodocyclization reactions and 2.5 equiv of I$_2$ were used (eq 4). The reaction was incomplete and a large amount of starting material was recovered when only 1.2 equiv of I$_2$ were used.

\[
\begin{array}{c}
\text{OMe} & \text{AcO} \\
\text{TsO} & \equiv \\
\text{V} & \text{X} & \text{V} & \text{X} \\
\text{0Ac} & \text{0Ac}
\end{array}
\xrightarrow{2.5 \text{ I}_2} \quad
\begin{array}{c}
\text{CH}_2\text{Cl}_2, 25^\circ\text{C}, 12 \text{ h} \\
\text{TsO} & \equiv \\
\text{V} & \text{X} & \text{V} & \text{X} \\
\text{0Ac} & \text{0Ac}
\end{array}
\]

(c) Carbonylation and lactonization

Under the optimal conditions for carbonylation and subsequent lactonization for coumestan, compound 13 was converted to coumestrol 11 in only a 20% yield, together with a 60% yield of the coumestrol tosylate 10 (eq 5). The tosyl derivative was further converted to coumestrol in a quantitative yield by using 1.1 equiv of TBAF in DMF under reflux for 2 h (eq 6). A separate experiment showed that without further purification, the mixture of coumestrol (11) and tosyl derivative 10 could be converted to coumestrol in a 75% yield using 1.2 equiv of TBAF in DMF under reflux in 4 h.
Conclusions

A general synthetic method has been developed for the synthesis of coumestan and its derivatives under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of o-iodoanisole derivatives and terminal alkynes and their selective electrophilic cyclization using I₂, followed by palladium-catalyzed intramolecular carbonylation and lactonization. Biologically interesting coumestrol has been synthesized in a 75% overall yield in three steps from the corresponding diarylacetylene derivative.

Experimental Section

General. ¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 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 a basic KMnO₄ solution [3 g of KMnO₄ + 20 g of K₂CO₃ + 5 mL of NaOH (5%) + 300 mL of H₂O]. 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.
**Reagents.** All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of THF, DMF, diethyl ether, ethyl acetate and hexanes were purchased from Fisher Scientific Co. \(n\)-Bu\(_4\)NF was purchased from Lancaster Synthesis, Inc. 2-Iodophenol, 2-iodoanisole, 4-bromoresorcinol, resorcinol, Mel, TsCl, AcCl, \(i\)-Pr\(_2\)NH and Et\(_3\)N were obtained from Aldrich Chemical Co., Inc.

**4-Iodoresorcinol.** This compound was prepared according to a literature procedure.\(^{18d}\) A solution of resorcinol (2.75 g, 25.0 mmol) and ICl (4.0 g, 25.0 mmol) in dry Et\(_2\)O (25 mL) was stirred at room temperature for 1 h. Water (50 mL) and Na\(_2\)SO\(_3\) (1.0 g) were added to the mixture and the aqueous phase was then extracted with Et\(_2\)O. The combined organic solution was washed successively with water and satd aq NaCl, dried over anhydrous Na\(_2\)SO\(_4\) and evaporated. The residue was purified by silica gel chromatography [AcOH-CHCl\(_3\) (1:9)] and alumina chromatography [hexane-AcOEt (2:1)] to afford 4-iodoresorcinol as colorless oil (4.13 g, 70%): \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.21 (br s, 2H), 6.27 (dd, \(J=\) 8.2, 2.8 Hz, 1H), 6.54 (d, \(J=\) 2.8 Hz, 1H), 7.46 (d, \(J=\) 8.6 Hz, 1H); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 21.3, 127.7, 129.3, 130.2, 130.9, 133.7, 133.9, 134.9, 138.2, 146.1, 192.7. The spectral properties were identical to those previously reported.\(^{18d}\)

**2-Acetoxy-2'-methoxy-diphenylacetylene (1).** A mixture of 2-ethynylanisole (6.00 mmol), 2-iodophenyl acetate (5.00 mmol), CuI (0.06 mmol) and PdCl\(_2\)(PPh\(_3\))\(_2\) (0.12 mmol) in a mixture of Et\(_3\)N (2.0 equiv) and DMF (50 mL) was heated at 60 °C for 2 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with Et\(_2\)O and the combined extracts were washed successively with water and satd aq NaCl. The organic solution was dried over anhydrous Na\(_2\)SO\(_4\) and evaporated. The residue was purified by flash chromatography on silica gel with hexane-
AcOEt as eluent to give 1 (96%) as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 2.37 (s, 3H), 3.87 (s, 3H), 6.88 (d, $J$ = 8.7 Hz, 1H), 6.92 (td, $J$ = 7.5, 0.9 Hz, 1H), 7.11 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.20 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.26-7.35 (m, 2H), 7.46 (dd, $J$ = 7.5, 1.8 Hz, 1H), 7.59 (dd, $J$ = 7.5, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.0, 55.8, 88.3, 90.9, 110.9, 112.3, 118.0, 120.6, 122.4, 126.0, 129.4, 130.2, 133.1, 133.7, 151.6, 160.1, 169.1; IR (neat) 1771 cm$^{-1}$; HRMS calcd for C$_{17}$H$_{14}$O$_3$ 266.0946, found 266.0943.

2-(2-Acetoxyphenyl)-3-iodobenzofuran (2). A solution of 1 (2.50 mmol) in dry CH$_2$Cl$_2$ (10 mL) was stirred at room temperature for 1 min. 2.5 Equiv of I$_2$ was added and the resulting mixture was allowed to stir at 25 $^\circ$C for 12 h. Satd aq Na$_2$S$_2$O$_3$ (5 mL) was added to the mixture, which was further stirred for 2 min. The resulting mixture was then extracted with Et$_2$O. The combined organic solution was washed successively with water and satd aq NaCl, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was successively purified by flash chromatography on silica gel using hexane-AcOEt as eluent to afford 2 as a yellow oil (95%): $^1$H NMR (CDCl$_3$) $\delta$ 2.21 (s, 3H), 7.25 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.32-7.40 (m, 3H), 7.44-7.53 (m, 3H), 7.82 (dd, $J$ = 7.8, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.3, 65.4, 111.4, 122.1, 123.3, 123.7, 123.8, 126.0, 126.1, 131.2, 131.7, 131.9, 148.8, 152.3, 154.6, 169.4; IR (CH$_2$Cl$_2$) 1771 cm$^{-1}$; HRMS calcd for C$_{16}$H$_{11}$IO$_3$ 377.9758, found 377.9753.

2-Methoxyphenylacetylene (3). The product was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.32 (s, 1H), 3.89 (s, 3H), 6.87-6.93 (m, 2H), 7.32 (t, $J$ = 8.4 Hz, 1H), 7.46 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 55.9, 80.2, 81.3, 110.7, 111.2, 120.6, 130.4, 134.3,
2,4-Diacetoxy-2'-methoxy-4'-tosyloxy-diphenylacetylene (5). A mixture of 2-ethynyl-4-tosyloxy-anisole (5.00 mmol), 2,4-diacetoxy-1-iodobenzene (6.00 mmol), CuI (0.06 mmol) and PdCl\(_2\)(PPh\(_3\))\(_2\) (0.12 mmol) in a mixture of i-Pr\(_2\)NH (6.00 mmol) and DMF (25 mL) was heated at 60 °C for 1 h. Water was added to the mixture, which was extracted with Et\(_2\)O and the combined extracts were washed with water and satd aq NaCl. The organic solution was dried over Na\(_2\)SO\(_4\) and evaporated. The residue was purified by flash chromatography on silica gel using hexane-AcOEt as the eluent to give 1 (96%) as a yellow solid: mp 234-236 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.29 (s, 3H), 2.34 (s, 3H), 2.44 (s, 3H), 3.78 (s, 3H), 6.49 (dd, \(J = 8.4, 2.4\) Hz, 1H), 6.59 (d, \(J = 2.0\) Hz, 1H), 6.97 (d, \(J = 2.4\) Hz, 1H), 7.01 (dd, \(J = 8.4, 2.4\) Hz, 1H), 7.30-7.33 (m, 3H), 7.54 (d, \(J = 8.4\) Hz, 1H), 7.72 (d, \(J = 8.0\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.0, 21.3, 21.9, 56.1, 88.6, 89.6, 106.1, 111.4, 114.4, 115.2, 116.4, 119.4, 128.8, 130.0, 132.2, 133.4, 134.0, 145.8, 150.7, 151.1, 152.0, 160.8, 168.4, 168.8; IR (neat, cm\(^{-1}\)) 1770, 1768; HRMS calcd for C\(_9\)H\(_8\)O\(_13\)S 494.1041, found 494.1036.

2-(2,4-Diacetoxyphenyl)-3-iodo-6-(tosyloxy)benzo[\(\mathbf{b}\)]furan (6). A solution of 5 (2.50 mmol) in dry CH\(_2\)Cl\(_2\) (10 mL) was stirred at room temperature for 1 min. 2.5 Equiv of I\(_2\) was added and the resulting mixture was allowed to stir at 25 °C for 12 h. Satd aq Na\(_2\)S\(_2\)O\(_3\) (5 mL) was added to the mixture, which was further stirred for 2 min. The resulting mixture was then extracted with Et\(_2\)O. The combined organic extracts were washed with water and satd aq NaCl, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under vacuum. The residue was purified by silica gel chromatography using hexane-AcOEt as the eluent to afford 2 as a yellow solid (98%): mp 300 °C, dec; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.18 (s,
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3H), 2.33 (s, 3H), 2.45 (s, 3H), 6.99 (dd, \( J = 8.4, 2.1 \) Hz, 1H), 7.10-7.18 (m, 3H), 7.33 (t, \( J = 7.2 \) Hz, 3H), 7.73 (d, \( J = 8.4 \) Hz, 2H), 7.78 (d, \( J = 8.4 \) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 21.2, 21.4, 21.9, 64.9, 106.1, 117.4, 118.9, 119.4, 120.2, 122.4, 128.8, 130.1, 130.7, 132.2, 132.3, 145.8, 148.1, 149.2, 152.4, 153.3, 153.7, 168.8; IR (neat, cm\(^{-1}\)) 1770; HRMS calcd for C\(_{16}\)H\(_{11}\)O\(_3\) 605.9851, found 605.9846.

4-Ethynyl-3-methoxyphenyl tosylate (8). A mixture of 1-bromo-2-methoxy-4-(tosyloxy)benzene (2.0 g, 5.6 mmol), trimethylsilylacetylene (0.66 g, 6.72 mmol), Cul (10 mg, 0.06 mmol) and PdCl\(_2\)(PPh\(_3\))\(_2\) (85 mg, 0.12 mmol) in a mixture of Et\(_3\)N (5 mL) and DMF (20 mL) was heated at 100 °C for 6 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with Et\(_2\)O and the combined extracts were washed with water and satd aq NaCl. The organic solution was dried over anhydrous Na\(_2\)SO\(_4\) and evaporated. The residue was purified by flash chromatography on silica gel using hexane-AcOEt (5:1) as the eluent to give the TMS-acetylene (2.05 g, 98%) as a colorless solid: mp 104-106 °C (lit.\(^{18d}\) mp 105-107 °C); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 0.24 (s, 9H), 2.44 (s, 3H), 3.75 (s, 3H), 6.45 (dd, \( J = 8.4, 2.2 \) Hz, 1H), 6.54 (d, \( J = 2.2 \) Hz, 1H), 7.30 (d, \( J = 8.5 \) Hz, 3H), 7.69 (d, \( J = 8.4 \) Hz, 2H); IR (neat, cm\(^{-1}\)) 1380, 1280, 1180. The spectral properties were identical to those previously reported.\(^{18d}\)

A solution of the TMS-acetylene (1.12 g, 3.00 mmol) and TBAF (1.0 M solution in THF; 3.0 mL, 3.00 mmol) in THF (60 mL) was vigorously stirred at room temperature for 5 min. Water was added to the mixture, which was extracted with Et\(_2\)O. The organic solution was washed with water and satd aq NaCl, dried over Na\(_2\)SO\(_4\) and evaporated. The residue was purified by chromatography on silica gel using hexane-AcOEt (3:1) as the eluent to afford 8 (0.90 g, 99%) as yellow viscous oil: \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 2.45 (s, 3H), 3.30 (s, 1H),
3.79 (s, 3H), 6.48 (dd, J = 8.4, 2.2 Hz, 1H), 6.59 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5, 1H), 7.72 (d, J = 8.4 Hz, 2H); IR (neat, cm⁻¹) 1380, 1280, 1180; HRMS calcd for C₁₆H₁₄O₄S 302.0615, found 302.0611.

4-Bromo-3-methoxyphenyl tosylate (9). A mixture of 4-bromoresorcinol (10.0 g, 53.0 mmol), K₂CO₃ (22.0 g, 159 mmol) and TsCl (11.1 g, 58.0 mmol) in acetone (150 mL) was refluxed for 21 h. Mel (15.0 g, 106 mmol) was added to the mixture, which was further refluxed for 3 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The combined organic extracts were washed with water and satd aq NaCl, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was further purified by flash chromatography on silica gel using hexane-AcOEt (3:1) as the eluent to give 1-bromo-2-methoxy-4-(tosyloxy)benzene (15.0 g, 79%) as white powder: mp 69-71 °C (lit.¹ mp 69-72 °C); ¹H NMR (CDCl₃) δ 2.46 (s, 3H), 3.79 (s, 3H), 6.41 (dd, J = 8.5, 2.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H); IR (neat, cm⁻¹) 1380, 1280, 1180. The spectral properties were identical to those previously reported.¹⁸d

4-Iodo-3-methoxyphenyl tosylate. A mixture of 4-iodoresorcinol (1.60 g, 6.78 mmol), K₂CO₃ (2.82 g, 20.4 mmol) and TsCl (1.40 g, 7.40 mmol) in acetone (30 mL) was refluxed for 15 h. Mel (2.89 g, 20.4 mmol) was added to the mixture, which was further refluxed for 3 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The combined organic extracts were washed with water and satd aq NaCl, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was further purified by flash
chromatography on silica gel using hexane-AcOEt (4:1) as the eluent to give 4-Iodo-3-
methoxyphenyl tosylate (1.53 g, 56%) as a yellow viscous oil: $^1$H NMR (CDCl$_3$) $\delta$ 2.46 (s, 3H), 3.77 (s, 3H), 6.30 (dd, $J = 8.5$, 2.5 Hz, 1H), 6.52 (d, $J = 2.5$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.63 (d, $J = 8.5$ Hz, 1H), 7.72 (d, $J = 8.5$ Hz, 2H); IR (neat, cm$^{-1}$) 1380, 1280, 1180.

The spectral properties were identical to those previously reported.$^{18d}$

**Synthesis of coumestan.** 2-(2-Acetoxyphenyl)-3-iodobenzo[b]furan (2) was used as the starting material for the synthesis of coumestan.$^{24}$ DMF (1.0 mL), PdCl$_2$(PPh$_3$)$_2$ (0.005 mmol), K$_2$CO$_3$ (0.5 mmol), and 3-iodobenzo[b]furan (2) (0.25 mmol) were stirred under an Ar atmosphere at room temperature for 5 min. The mixture was flushed with CO and fitted with a balloon of CO. The reaction mixture was heated to 60 °C with vigorous stirring for 12 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (15 mL) and washed with water (30 mL) and brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on a silica gel column to afford coumestan in a 100% yield. The compound was obtained as a white solid: mp 180-181 °C (lit.$^{25}$ mp 181-182 °C); $^1$H NMR (CDCl$_3$) $\delta$ 7.39-7.53 (m, 4H), 7.59-7.69 (m, 2H), 8.04 (dd, $J = 7.8$, 1.5 Hz, 1H), 8.13-8.16 (m, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 106.1, 112.0, 112.9, 117.7, 122.1, 123.7, 124.9, 125.4, 127.0, 132.1, 153.9, 155.8, 158.3, 160.2; IR (CH$_2$Cl$_2$) 1737 cm$^{-1}$; HRMS calcd for C$_{15}$H$_8$O$_3$ 236.0476, found 236.0473. The spectral properties were identical to those previously reported.$^{25}$

**Synthesis of coumestrol (11).** 2-(2,4-Diacetoxyphenyl)-3-iodo-6-(tosyloxy)benzo[b]furan (6) was used as the starting material for the synthesis of coumestrol.
DMF (1.0 mL), PdCl$_2$(PPh$_3$)$_2$ (0.005 mmol), K$_2$CO$_3$ (0.5 mmol), and the 3-iodobenzo[b]furan 6 (0.25 mmol) were stirred under an Ar atmosphere at room temperature for 5 min. The mixture was flushed with CO and fitted with a balloon of CO. The reaction mixture was heated to 60 °C with vigorous stirring for 12 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (35 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried over anhydrous Na$_2$SO$_4$, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column to afford coumestrol 11 (20%) and coumestrol tosylate 10 (60%).

Coumestrol tosylate 10. The compound was isolated as white solid: mp >360 °C; $^1$H NMR (CD$_3$OD) δ 2.46 (s, 3H), 6.87-6.88 (m, 1H), 6.91-6.95 (m, 2H), 7.03-7.07 (m, 1H), 7.41-7.44 (m, 3H), 7.72 (d, $J$ = 8.1 Hz, 2H), 7.88 (t, $J$ = 9.0 Hz, 2H).

A mixture of the coumestrol derivative 10 (0.10 mmol) and n-Bu$_4$NF (0.10 mmol) in DMF (5 mL) was stirred at 100 °C for 2 h. The resulting mixture was diluted with water and extracted with diethyl ether (2 x 15 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and evaporated to afford coumestrol as white solid in a 99% yield: mp >360 °C (lit. mp 385 °C); $^1$H NMR (DMSO-$d_6$) δ 6.90-6.96 (m, 3H), 7.16-7.17 (d, $J$ = 1.8 Hz, 1H), 7.68-7.71 (d, $J$ = 8.4 Hz, 1H), 7.84-7.87 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 98.7, 102.1, 103.0, 104.2, 113.7, 114.0, 114.6, 120.6, 122.7, 154.6, 155.9, 157.0, 157.6, 159.5, 161.2; IR (CH$_2$Cl$_2$) 3500-2850, 1703 cm$^{-1}$; HRMS calcd for C$_{15}$H$_8$O$_5$ 268.0375, found 268.0371. The spectral properties were identical to those previously reported.$^{18e}$
Acknowledgements

We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health and the National Science Foundation for partial support of this research and Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for donations of palladium salts.

References


CHAPTER 4. 1,4-PALLADIUM MIGRATION FROM AN ARYL TO AN IMIDOYL POSITION, FOLLOWED BY INTRAMOLECULAR ARYLATION: SYNTHESIS OF FLUOREN-9-ONES

Based on a communication to be submitted to the Journal of the American Chemical Society

Dawei Yue, Marino A. Campo and Richard C. Larock*
Department of Chemistry, Iowa State University, Ames, Iowa 50010
larock@iastate.edu

Abstract

The synthesis of various fluoren-9-ones has been accomplished by the Pd-catalyzed intramolecular C-H activation of imines derived from o-iodoaniline and biarylcarboxaldehydes. This methodology makes use of a 1,4-palladium migration to generate the key imidoylpalladium intermediate, which undergoes intramolecular arylation, producing imines of complex polycyclic compounds containing the fluoren-9-one core structure. This methodology offers an efficient approach to the biologically interesting fluoren-9-one ring system.

Introduction

The ability of palladium to activate C-H bonds has been used extensively in organic synthesis. In recent years, palladium-catalyzed C-H activation has received considerable attention due to the wide variety of reactions this metal can catalyze. For instance,
catalytic amounts of palladium salts have been used to activate the addition of C-H bonds of electron-rich arenes to alkenes and alkynes, as well as to undergo other transformations, such as carbonylation. We have reported that the Pd-catalyzed intramolecular C-H activation in the rearrangement of organopalladium intermediates derived from aryl halides and internal alkynes provides a novel route to 9-benzylidene-9H-fluorenes (Scheme 1).

**Scheme 1**

Similarly, intramolecular C-H activation in organopalladium intermediates derived from o-halobiaryls leads to a 1,4-palladium migration. We have already shown that such intermediates can be trapped by Heck, Suzuki and alkyne annulation reactions (Scheme 2).

**Scheme 2**
We recently reported a novel synthesis of fused polycycles using this Pd aryl-aryl migration process. This methodology involves the use of palladium C-H activation to catalyze a 1,4-palladium migration within biaryls, generating key arylpalladium intermediates, which subsequently undergo C-C bond formation by intramolecular arylation to produce fused polycycles (Scheme 3).

Scheme 3

We have also explored other possible Pd migrations and their synthetic applications. Herein, we wish to report an unusual palladium migration from an aryl to an imidoyl position and its application for the synthesis of fluoren-9-ones.

Fluoren-9-ones are a family of natural products displaying a wide range of biological activity, including antibiotic activity and human telomerase and protein kinase-C inhibitory activity. In recent years, fluorenones have attracted much interest because of groundbreaking discoveries in the biomedical field, which include their use as probes for DNA redox chemistry. Furthermore, fluorenones have been prepared as key synthetic
intermediates for the total synthesis of natural products, such as stealthin and prekinamycin.\(^8\)

The most useful syntheses of fluorenones include Friedel-Crafts ring closures of biarylcarboxylic acids and derivatives,\(^9\) intramolecular \([4 + 2]\) cycloaddition reactions of conjugated enynes,\(^10\) oxidation of fluorenes,\(^11\) and remote metalation of 2-biphenylcarboxamides or 2-biphenyloxazolines.\(^12\) Unfortunately, these methods suffer some drawbacks, mainly the use of strong Lewis acids,\(^8\) heat,\(^8,9\) or strong nucleophilic bases,\(^8\) which do not tolerate many organic functional groups. Alternatively, the palladium-catalyzed cyclization of \(o\)-iodobenzophenones\(^13\) (Scheme 4) and the palladium-catalyzed cyclocarbonylation of \(o\)-haloarylcs\(^14\) (eq 1) provide highly efficient and direct routes to the fluoren-9-one skeleton, as well as other related cyclic aromatic ketones. The drawbacks to these palladium approaches are (1) iodobenzophenones and \(o\)-haloarylcs can be difficult to prepare, (2) the former process is limited by the need for electron-donating groups in the Friedel-Crafts reaction, and (3) the latter process employs toxic CO gas. Thus, new and efficient methods for the preparation of 9-fluorenones are always highly desired.
Results and Discussion

During our studies of other possible palladium migrations, we found that the reaction of imine 1 under our usual palladium migration conditions in the presence of 10 equiv of water produced benzanilide 2 in a 56% yield (eq 2). The formation of this amide suggests that a palladium migration from the aryl to the imidoyl position has taken place to generate intermediate B via a five-membered ring palladacycle A (Scheme 5). This

Scheme 5

would generate a palladium species which upon hydrolysis and subsequent tautomerization
leads to the benzanilide product (path a). There is, however, another pathway to generate the benzanilide. After the oxidative addition of the Pd(0) to the aryl iodide, the arylpalladium intermediate might insert into the imidoyl-H bond to form a five-membered palladacycle A. Without completely migrating to the imidoyl position to form an imidoyl palladium intermediate B, the palladium intermediate A might undergo ligand exchange and subsequent reductive elimination to produce intermediate C (path b). The intermediate C then, by further reductive elimination of Pd and tautomerization, might afford benzanilide 2. The use of a relatively large amount of water and the ease with which imines hydrolyze might account for the fairly low yield of the benzanilide.

To fully understand the mechanism of this unusual palladium migration, we proceeded to investigate a sequential migration/arylation reaction of a more complex imine 3 (Scheme 6). In theory, imine 3 might afford fluoren-9-ylideneaniline if the palladium migrates from an aryl position to an imidoyl position under our Pd migration conditions. Mechanistically, the palladium must first undergo a 1,4-palladium migration from the ortho position of the aniline moiety to the imidoyl position (through path a), followed by arylation at the 2′ position of the biaryl (Scheme 6; Table 1, entry 1) to generate the desired migration/arylation product. On the other hand, if the palladium intermediate does not undergo a complete through-space 1,4-palladium migration, it would have to undergo a rather unfavorable process (path b) to generate a highly strained complex D, which after two reductive eliminations of palladium might afford the final migration product.

Surprisingly, compound 3 readily reacted under our standard reaction conditions at 100 °C and produced a quantitative yield of the desired migration product G within 4 h.
The fairly unstable fluoren-9-ylideneaniline product underwent hydrolysis very easily, affording the corresponding methyl substituted fluoren-9-one 4 in a quantitative yield. The high yield suggests that the palladium intermediate did in fact migrate from the aryl
position to the imidoyl position by a complete through-space 1,4-shift to generate the
imidoyl palladium intermediate E. The imidoyl palladium intermediate E then undergoes
either an insertion into the C-H bond of the neighboring arene (path c) or electrophilic
aromatic substitution (path d). After elimination of HI, both pathways give a six-
membered ring palladacycle F. Subsequent reductive elimination and hydrolysis then
gives the observed arylation product 4.

To further explore the generality of this reaction, several biarylcarboxaldehydes were
synthesized by simple Suzuki couplings using 2-bromobenzaldehyde and various
arylboronic acids. The resulting 2-arylbenzaldehydes were then allowed to react with
commercially available o-iodoaniline to afford almost quantitative yields of the
corresponding imines (Scheme 7). The mild reaction conditions used to prepare these
imines should readily accommodate considerable functionality.

Scheme 7

\[
\begin{align*}
\text{Br} & \quad \text{R} \quad \text{H} \\
\text{Pd(OAc)}_2 & \quad \text{PPh}_3 & \quad \text{DMF} & \quad \text{TsOH} & \quad 80-95 \% & \quad >95 \% \\
\end{align*}
\]

The palladium-catalyzed rearrangement of these imines bearing various functional
groups has been investigated under our standard Pd migration reaction conditions.
Electron-donating groups, such as methyl and methoxy groups on the biaryl substrates
facilitate the arylation step and therefore shorten the reaction time to around 2 to 6 h (Table
1; entries 1, 2, and 6). Although the electron-withdrawing groups, such as a nitro and an
ester group, make the aromatic ring electron deficient, and therefore make the electrophilic aromatic substitution more difficult, they did not affect the overall yields and we were still able to obtain high yields of the desired arylation products (entries 3, 4 and 7). The electron-withdrawing group did, however, affect the reaction time. Substantially longer reaction times were generally required to get complete conversion of these starting materials. In most cases, the yields of the fluoren-9-ones are above 90%.

Biaryl systems bearing two methyl or two fluoro groups were also investigated. The methyl and fluoro group were presumed to introduce steric hindrance in the final arylation step. A longer reaction time was observed and a slightly lower yield was obtained when the dimethyl substrate was employed (entry 6). The compound with two fluoro groups meta to the other aryl group reacted very slowly under our standard reaction conditions and the reaction time was four times as long as that of the dimethyl substrate (entry 7). Both steric and electronic effects appear to account for the difference. Nevertheless, the difluoro product was still obtained in a 95% isolated yield.

Cyclization of the biphenyl 18 with a chloro group ortho to the phenyl was also studied. Theoretically, the interaction of the chloro group in the 2 position and the H in the 2' position favors an arrangement of the two benzene rings perpendicular to each other and therefore disfavors the arylation step, which requires the two benzene rings to lie in the same plane (Figure 1). Statistically, the chloro group also occupies one of the two ortho positions that might normally undergo intramolecular arylation. It was not surprising, therefore, that the reaction was not clean and only a 65% yield of the desired fluoren-9-one product was obtained after 48 h of reaction.
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Table 2. Synthesis of fluorenones via 1,4-palladium migration and consequent arylation.\(^a\)
The reaction was carried out under the previously described standard reaction conditions employing 0.25 mmol of the imine, 5 mol % Pd(OAc)$_2$, 5 mol % (Ph$_2$P)$_2$CH$_2$ and 2 equivs of CsO$_2$CCMe$_3$ in DMF (4 mL) at 100 °C unless otherwise noted. The ratio in parentheses corresponds to the GC yield of products in which the sterically less hindered product was formed predominantly. The reaction temperature was increased to 110 °C. Compound 22 is not stable under our usual hydrolysis conditions; only a 50 % yield of the corresponding ketone product was obtained. In a different run, without the hydrolysis step, the imine intermediate 21 was isolated in an 82% yield.
Biaryl substrates bearing a naphthalene, a furan and an indole moiety have also been studied. When the naphthalene substrate was allowed to react under our usual reaction conditions, arylation took place in both the 3 and 1 positions, with the arylation product in the less hindered 3 position predominant (9:1) (entry 5). This is consistent with Campo's result using the palladium-catalyzed cyclocarbonylation of halobiaryls. A 91% overall yield was obtained.

The furan-containing substrate facilitates electrophilic aromatic substitution and within 2 h the reaction was complete. However, because the resulting 8H-indeno[2,1b]furan-6-one was not stable under our hydrolysis conditions, we were able to isolate only a 50% yield of the 8H-indeno[2,1b]furan-6-one (entry 9). Without hydrolysis, the corresponding 8H-indeno[2,1b]furan-8-ylidene-N-phenylamine was obtained in an 82% yield. An indole-containing substrate was also allowed to react under our standard reaction conditions, but none of the desired product was obtained (entry 10). The strain resulting from the fused ring system bearing two adjoining five-membered rings may account for this unfavorable result.

A mechanistically interesting question is whether the imidoyl palladium intermediate can migrate to a second aryl position. In order to explore this possibility, 2-iodo-5-phenoxy-N-phenylmethyleneariline (25) was prepared and allowed to react under our
standard Pd migration conditions at 100 °C. After 24 h, this substrate failed to react. By simply increasing the reaction temperature to 120 °C, we were able to obtain the desired 1-aminodibenzo[\textit{b,d}]furan (26) in a 35 % yield, although it took 7 d for the reaction to reach completion. The relatively sterically hindered position \textit{ortho} to the phenoxy group apparently hinders Pd migration from the imidoyl position to the more hindered aryl position, thus lengthening the reaction time and lowering the overall yield of this double migration reaction.

**Scheme 8**

Mechanistically, the palladium apparently first inserts into the aryl iodide bond to form intermediate \textbf{G}, which migrates Pd to the imidoyl position by through-space C-H activation. The metal moiety in this first migration intermediate \textbf{H} can return to the
original aromatic ring in either the position where it was first generated or the position ortho to the phenoxy group to produce intermediate I, where it can be trapped by arylation of the other aromatic ring. Simple hydrolysis of the imine affords the corresponding benzaldehyde and the aminodibenzo[b,d]furan (26) (Scheme 8).

Conclusions

In conclusion, we have been able to establish a novel 1,4-palladium shift from an aryl position to an imidoyl position. This migration of palladium has been established by trapping the imidoylpalladium intermediates by intramolecular arylation. This migration process can be very general and synthetically useful. The biologically interesting fluoren-9-one ring system can be readily synthesized in excellent yields utilizing this novel migration process.

Experimental Section

General. All $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 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 a 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. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.
Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of DME, THF, DMF, diethyl ether, ethyl acetate and hexanes were purchased from Fisher Scientific Co. The arylboronic acids were obtained from Frontier Scientific Co. 2-Iodoaniline, 2-bromobenzaldehyde, Cs₂CO₃, pivalic acid and Et₃N were obtained from Aldrich Chemical Co., Inc.

General procedure for synthesis of the biarylcarboxaldehydes. Into 10 mL of a 2:1 DMF/H₂O solution containing 5.0 mmol of 2-bromobenzaldehyde, 5.0 mmol of Na₂CO₃ and 5.0 mmol of arylboronic acid were added and the reaction mixture was stirred for 2 min. Pd(OAc)₂ (5 mol %) was then added and the flask was flushed with Ar, sealed and allowed to stir at 25 °C for 12 h. The reaction mixture was extracted with ethyl ether (2 x 10 mL). The combined ether layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as eluent.

4'-Methylbiphenyl-2-carboxaldehyde. The compound was obtained as a colorless oil: ¹H NMR (CDCl₃) δ 2.42 (s, 3H), 7.24-7.29 (m, 4H), 7.42 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.61 (td, J = 7.6, 1.2 Hz, 1H); 8.01 (dd, J = 8.0, 1.2 Hz, 1H), 9.99 (s, 1H); ¹³C NMR (CDCl₃) δ 21.3, 127.7, 129.3, 130.2, 130.9, 133.7, 133.9, 134.9, 138.2, 146.1, 192.7; HRMS m/z 196.0891 (calcd for C₁₄H₁₂O, 196.0888).

4'-Methoxybiphenyl-2-carboxaldehyde. The compound was obtained as a colorless oil: ¹H NMR (CDCl₃) δ 3.87 (s, 1H), 7.00 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.41-7.48 (m, 2H), 7.61 (td, J = 7.5, 1.2 Hz, 1H); 8.00 (dd, J = 7.5, 1.2 Hz, 1H),
9.99 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 55.6, 114.1, 127.5, 127.8, 130.2, 131.0, 131.5, 133.7, 133.9, 145.8, 159.9, 192.8; HRMS $m/z$ 212.0839 (calcd for C$_{14}$H$_{12}$O$_2$, 212.0837).

**Methyl 2'-formylbiphenyl-4-carboxylate.** The compound was obtained as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 3.97 (s, 3H), 7.43-7.48 (m, 3H), 7.54 (t, $J = 9.0$ Hz, 1H), 7.70 (td, $J = 7.5$, 1.5 Hz, 1H), 8.05 (dd, $J = 7.8$, 1.5 Hz, 1H), 8.13-8.17 (m, 2H), 9.96 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 52.5, 128.1, 128.6, 129.8, 130.1, 130.3, 130.8, 133.8, 133.9, 142.6, 144.8, 166.8, 191.9; HRMS $m/z$ 240.0789 (calcd for C$_{15}$H$_{12}$O$_2$, 240.0786).

**4'-Nitrobiphenyl-2-carboxaldehyde.** The compound was obtained as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.44 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.55-7.63 (m, 3H), 7.71 (td, $J = 7.6$, 1.6 Hz, 1H), 8.06 (dd, $J = 8.0$, 1.2 Hz, 1H), 8.34 (d, $J = 6.8$ Hz, 2H); 9.97 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 123.8, 129.1, 129.3, 130.8, 131.0, 133.8, 134.1, 143.2, 145.0, 147.9, 191.3; HRMS $m/z$ 227.0592 (calcd for C$_{13}$H$_9$NO$_3$, 227.0582).

**3',5'-Dimethylbiphenyl-2-carboxaldehyde.** The compound was obtained as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 2.34 (s, 6H), 6.95 (s, 2H), 7.03 (s, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.99 (d, $J = 7.6$ Hz, 1H), 9.97 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 213.1, 127.3, 127.5, 128.1, 129.7, 130.7, 133.4, 133.8, 137.6, 138.0, 146.3, 192.5; HRMS $m/z$ 210.1047 (calcd for C$_{13}$H$_{14}$O, 210.1045).

**3',5'-Difluorobiphenyl-2-carboxaldehyde.** The compound was obtained as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 6.78-6.81 (m, 3H), 7.29 (d, $J = 7.8$ Hz, 1H), 7.43 (t, $J = 7.5$ Hz, 1H), 7.55 (td, $J = 7.5$, 1.5 Hz, 1H), 7.91 (dd, $J = 7.8$, 1.5 Hz, 1H), 9.87 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 103.7 (t), 113.3 (q), 128.3, 128.9 (t), 130.5, 133.7 (t), 141.3 (m), 143.3 (t), 161.2 (d), 164.5 (d), 191.4; HRMS $m/z$ 218.0547 (calcd for C$_{13}$H$_{8}$F$_2$O, 218.0543).
2'-Chlorobiphenyl-2-carboxaldehyde. The compound was obtained as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.31-7.39 (m, 4H), 7.48-7.54 (m, 2H), 7.66 (td, $J = 7.5$, 1.5 Hz, 1H), 8.04 (dd, $J = 7.5$, 1.5 Hz, 1H), 9.80 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 127.0, 127.6, 128.7, 129.8, 129.9, 131.1, 131.9, 133.7, 133.9, 134.0, 137.0, 142.9, 191.7; HRMS m/z 216.0348 (calcd for C$_{13}$H$_9$ClO, 216.0345).

2-(Furan-3-yl)benzaldehyde. The compound was obtained as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 6.57 (s, 1H), 7.41-7.46 (m, 2H), 7.52-7.62 (m, 3H), 7.97 (dd, $J = 7.8$, 1.2 Hz, 1H), 10.21 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 112.3, 112.6, 122.6, 127.8, 127.9, 130.6, 133.9, 134.0, 136.4, 141.4, 143.6, 192.2; HRMS m/z 172.0528 (calcd for C$_{11}$H$_8$O$_2$, 172.0524).

N-tert-Butoxycarbonyl-2-(2'-formylphenyl)indole. The compound was obtained as a colorless oil: $^1$H NMR (CDCl$_3$) $\delta$ 1.23 (s, 9H), 6.58 (s, 1H), 7.27 (t, $J = 7.0$ Hz, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.44 (d, $J = 7.0$ Hz, 1H), 7.52-7.61 (m, 3H), 7.80 (dd, $J = 7.6$, 1.2 Hz, 1H), 8.30 (dd, $J = 8.4$, 0.8 Hz, 1H), 10.00 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 52.5, 128.1, 128.6, 129.8, 130.1, 130.3, 130.8, 133.8, 133.9, 142.6, 144.8, 166.8, 191.9; HRMS m/z 321.1369 (calcd for C$_{20}$H$_{19}$NO$_3$, 321.1365).

General procedure for the synthesis of biaryl-2-ylmethyleneanilines. To a solution of biarylcaboxaldehyde (0.25 mmol) and 2-iodoaniline (0.25 mmol) in toluene (3 mL) under N$_2$ was added anhydrous MgSO$_4$ (0.50 mmol). The reaction mixture was stirred at 100 °C until TLC analysis indicates the disappearance of the starting material. The reaction mixture was then filtered and the resulting solvent was evaporated under
reduced pressure to afford the crude product, which was used without further characterization.

**2-Iodo-N-(4'-methoxybiphenyl-2-ylmethylene)aniline.** The compound was obtained as a yellow oil: \(^1\text{H NMR} (\text{CDCl}_3) \delta 3.74 (s, 3H), 6.78 (d, J = 6.8 \text{ Hz}, 2H), 6.92 (d, J = 8.4 \text{ Hz}, 2H), 7.17-7.33 (m, 4H), 7.42 (t, J = 7.2 \text{ Hz}, 2H), 7.79 (d, J = 8.0 \text{ Hz}, 1H), 8.28 (s, 1H), 8.42 (d, J = 7.6 \text{ Hz}, 1H); \(^{13}\text{C NMR} (\text{CDCl}_3) \delta 55.3, 95.0, 113.8, 118.4, 126.9, 127.5, 128.0, 129.3, 130.3, 131.1, 131.2, 131.4, 133.2, 138.9, 143.7, 153.2, 159.3, 160.5; HRMS \text{m/z} 413.0281 (\text{calcd for C}_{20}\text{H}_{16}\text{INO, 413.0277}).

**General procedure for the palladium-catalyzed migration reaction.** The appropriate imine (0.25 mmol), Pd(OAc)\(_2\) (2.8 mg, 0.0125 mmol), 1,1-
bis(diphenylphosphino)methane (dppm) (4.8 mg, 0.0125 mmol), and CsO\(_2\)CCMe\(_3\) (CsPiv) (0.117 g, 0.5 mmol) in DMF (4 mL) under Ar at 100 °C were stirred for the specified length of time. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (35 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried over MgSO\(_4\), filtered, and the solvent removed under reduced pressure to afford the crude imine product, which was used for the hydrolysis without further characterization.

**General procedure for hydrolysis of the fluoren-9-one imines.** To an acetone (5 mL) solution of the crude imine product, 1.0 N HCl (2 mL) was added. The resulting reaction mixture was stirred until disappearance of the starting material. The mixture was
then diluted with H$_2$O and extracted with diethyl ether (2 x 15 mL). The organic layers were combined, dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure to afford the crude fluoren-9-ones, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-Methylfluoren-9-one (4). The reaction mixture was chromatographed using 7:1 hexanes/ethyl acetate to afford 47.1 mg (97 %) of the indicated compound as a yellow solid: mp 90-91 °C (lit.$^{18}$ mp 92 °C); $^1$H NMR (CDCl$_3$) δ 2.33 (s, 3H), 7.19-7.24 (m, 2H), 7.33 (d, $J=7.6$ Hz, 1H), 7.04-7.41 (m, 3H), 7.58 (d, $J=7.2$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 21.4, 120.0, 120.2, 124.2, 125.0, 128.6, 134.3, 134.4, 134.7, 135.1, 139.3, 141.8, 144.7, 194.2. The spectral properties were identical to those previously reported.$^1$

2-Methoxyfluoren-9-one (6). The reaction mixture was chromatographed using 6:1 hexanes/ethyl acetate to afford 52.6 mg (100 %) of the indicated compound as a yellow solid: mp 78-79 °C (lit.$^1$ mp 78 °C); $^1$H NMR (CDCl$_3$) δ 3.82 (s, 3H), 6.94 (dd, $J=8.4$, 2.8 Hz, 1H), 7.14-7.18 (m, 2H), 7.34-7.41 (m, 3H), 7.56 (d, $J=7.6$ Hz, 1H); IR (CH$_2$Cl$_2$) 1717 cm$^{-1}$. The spectral properties were identical to those previously reported.$^{19}$

Methyl fluorenone-2-carboxylate (8).$^{20}$ The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) δ 3.95 (s, 3H), 7.37 (t, $J=7.2$ Hz, 1H), 7.54 (t, $J=7.6$ Hz, 1H), 7.60 (d, $J=8.0$ Hz, 2H), 7.71 (d, $J=7.6$ Hz, 1H), 8.21 (dd, $J=8.0$, 1.6 Hz, 1H), 8.30 (s, 1H); $^{13}$C NMR (CDCl$_3$) δ 52.6, 120.4, 121.4, 124.8, 125.6, 130.4, 131.3, 134.4, 135.0, 135.2, 136.5, 143.5, 148.6, 166.3, 192.9; HRMS m/z 238.0634 (calcd for C$_{15}$H$_{10}$O$_3$, 238.0630).
2-Nitrofluoren-9-one (10). The compound was obtained as a yellow solid: mp 221-223 °C, lit mp 222-224 °C; $^1$H NMR (CDCl$_3$) $\delta$ 7.46 (td, $J = 7.6, 1.2$ Hz, 1H), 7.61 (td, $J = 7.6, 1.2$ Hz, 1H), 7.67-7.71 (m, 2H), 7.77 (d, $J = 7.2$ Hz, 1H), 8.42 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.47 (d, $J = 1.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 119.8, 120.9, 122.0, 125.3, 130.1, 131.2, 135.2, 135.3, 135.7, 142.5, 149.0, 149.9, 191.1; HRMS $m/z$ 225.0429 (calcd for C$_{13}$H$_7$NO$_3$, 225.0426).

Benzo[b]fluoren-11-one (12). The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) 7.35 (dt, $J = 7.4, 0.9$ Hz, 1H), 7.47 (td, $J = 8.1, 1.2$ Hz, 1H), 7.55 (td, $J = 8.1, 1.3$ Hz, 1H), 7.56 (td, $J = 7.4, 1.1$ Hz, 1H), 7.72 (dt, $J = 7.5, 0.8$ Hz, 1H), 7.75 (dt, $J = 8.2, 0.7$ Hz, 1H), 7.83 (dd, $J = 8.1, 0.6$ Hz, 1H), 7.87 (s, 1H), 7.89 (dt, $J = 8.1, 0.6$ Hz, 1H), 8.17 (s, 1H); $^{13}$C NMR (CDCl$_3$) 119.5, 121.4, 124.9, 126.1, 127.4, 129.2, 129.4, 129.6, 131.2, 133.2, 134.1, 135.4, 136.6, 137.4, 138.8, 145.3, 193.5; HRMS $m/z$ 230.0734 (calcd for C$_{17}$H$_{10}$O, 230.0732).

Benzo[a]fluoren-11-one (13). The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) 7.24-7.27 (m, 1H), 7.40-7.44 (m, 3H), 7.56-7.60 (m, 3H), 7.75 (d, $J = 8.1$ Hz, 1H), 7.94 (d, $J = 8.1$ Hz, 1H), 8.93 (dd, $J = 8.4, 0.9$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) 118.2, 120.1, 124.0, 124.5, 126.6, 127.0, 128.7, 129.4, 129.6, 130.3, 134.3, 134.6, 134.8, 136.0, 144.0, 146.3, 195.5; HRMS $m/z$ 230.0736 (calcd for C$_{17}$H$_{10}$O, 230.0732).

1,3-Dimethylfluoren-9-one (15). The compound was obtained as a yellow oil. The spectral properties were identical to those previously reported.

N-(1,3-Dimethyl-9H-fluoren-9-ylidene)aniline. The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 2.40 (s, 3H), 2.69 (s, 3H), 6.46 (d, $J = 7.6$ Hz, 1H), 6.86
(td, $J = 7.6, 1.2$ Hz, 1H), 6.93-6.95 (m, 3H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.23-7.28 (m, 2H), 7.38 (t, $J = 7.6$ Hz, 2H), 7.53 (d, $J = 7.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 19.8, 21.9, 118.1, 118.3, 119.9, 123.6, 127.1, 127.5, 129.4, 131.3, 131.4, 131.9, 132.5, 138.3, 141.5, 142.8, 143.5, 152.5, 164.2; HRMS $m/z$ 283.1365 (calcd for C$_{21}$H$_{17}$N, 283.1361).

1,3-Difluorofluoren-9-one (17).$^{23}$ The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 6.66 (td, $J = 9.2, 1.6$ Hz, 1H), 7.05 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.38 (td, $J = 7.6, 1.6$ Hz, 1H), 7.50-7.55 (m, 2H), 7.68 (d, $J = 7.2$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 104.9, 105.2 (q), 116.7 (d), 121.0, 124.7, 130.6, 134.6, 134.9, 142.1, 148.5 (q), 158.8 (d), 161.3, 166.8 (d), 169.4 (d), 188.8; IR (CH$_2$Cl$_2$) 3054, 2930, 1711 cm$^{-1}$; HRMS $m/z$ 216.0390 (calcd for C$_{13}$H$_{8}$F$_2$O, 216.0387).

$N$-(1,3-Difluoro-9H-fluoren-9-ylidene)aniline. The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 6.51 (d, $J = 8.0$ Hz, 1H), 6.77 (dd, $J = 7.6, 2.0$ Hz, 1H), 6.97-7.05 (m, 3H), 7.13 (dd, $J = 7.6, 2.0$ Hz, 1H), 7.20 (t, $J = 7.2$ Hz, 1H), 7.33 (td, $J = 7.6, 0.8$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 2H), 7.56 (d, $J = 7.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 103.9 (d), 104.7 (t), 118.2, 119.5 (m), 120.9, 124.4, 127.5, 128.5, 129.2, 129.5, 131.7, 131.9, 141.8, 146.1 (m), 151.7, 158.8 (d), 160.5 (d), 161.4 (d), 164.6 (d), 167.1 (d); HRMS $m/z$ 291.0864 (calcd for C$_{19}$H$_{11}$F$_2$N, 291.0860).

4-Chlorofluoren-9-one (19).$^{24}$ The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.24 (t, $J = 7.2$ Hz, 1H), 7.34 (t, $J = 7.2$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.59 (d, $J = 7.2$ Hz, 1H), 7.71 (d, $J = 7.2$ Hz, 1H), 8.18 (d, $J = 7.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 122.8, 124.3, 124.7, 129.7, 129.8, 130.2, 134.3, 135.2, 136.4,
136.6, 140.9, 143.4, 192.8; IR (CH$_2$Cl$_2$) 1718 cm$^{-1}$; HRMS m/z 214.0192 (calcd for C$_{13}$H$_7$ClO, 214.0189).

$N$-(Indeno[1,2-d]furan-6-ylidene)aniline (21). The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 6.51 (d, $J$ = 2.0 Hz, 1H), 7.15-7.25 (m, 5H), 7.29 (t, $J$ = 7.6 Hz, 1H), 7.33 (d, $J$ = 2.0 Hz, 1H), 7.41 (t, $J$ = 7.2 Hz, 2H), 7.73 (d, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 106.2, 119.8, 121.5, 123.4, 125.6, 127.3, 128.9, 131.1, 134.8, 138.9, 141.0, 150.1, 150.5, 150.8, 152.4; HRMS m/z 245.0843 (calcd for C$_{17}$H$_{11}$NO, 245.0841).

5-Phenoxy-2-iodoaniline. 3-Phenoxyaniline (7.8 mmol) was added to a mixture of I$_2$ (7.9 mmol) and AgOAc (7.9 mmol) in ethanol (50 mL) at room temperature. The mixture was stirred for 14 h after which the solid was removed by filtration and the filtrate was evaporated under vacuum to afford a black residue, which was dissolved in ethyl ether and washed with satd aq Na$_2$S$_2$O$_3$ and water. The organic layer was dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent. The compound was obtained as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 4.07 (s, 2H), 6.17 (dd, $J$ = 8.7, 3.0 Hz, 1H), 6.37 (d, $J$ = 3.0 Hz, 1H), 6.98-7.01 (m, 2H), 7.10 (tt, $J$ = 7.5, 1.2 Hz, 1H), 7.29-7.34 (m, 2H), 7.51 (d, $J$ = 8.7 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 76.4, 104.9, 110.9, 119.4, 123.8, 129.9, 139.7, 148.1, 156.8, 159.1; HRMS m/z 310.9811 (calcd for C$_{12}$H$_{10}$INO, 310.9808).

2-Iodo-5-phenoxy-$N$-phenylmethyleneaniline (25). This compound was prepared following the procedure for the preparation of biaryl-2-ylmethyleneanilines. The resulting imine was used for the next step without further characterization.
**1-Aminodibenzo[b,d]furanamine (26).** The compound was obtained as a yellow oil. The spectral properties were identical to those previously reported.\textsuperscript{25}

**Acknowledgements**

We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for partial support of this research. Thanks are also extended to Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., for donating the Pd(OAc)\textsubscript{2} and PPh\textsubscript{3} and Frontier Scientific, Inc. for donating the arylboronic acids.

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GENERAL CONCLUSIONS

In this dissertation the scope and limitations of several electrophilic cyclization processes have been presented. In particular, electrophilic cyclization has been used for the synthesis of a variety of heterocycles, including benzo[b]furans, isochromenes, dihydroisoquinolines, isobenzofurans and coumestans. An unusual palladium migration has also been explored and applied to the synthesis of fluoren-9-ones.

Chapter 1 describes the synthesis of 2,3-disubstituted benzo[b]furans by the palladium-catalyzed coupling and electrophilic cyclization of terminal alkynes. A highly chemoselective electrophilic cyclization has been achieved by carefully choosing the protecting group on the oxygen functionality. Various electrophiles, such as I₂, Br₂, PhSeCl and p-O₂NC₆H₄SCl, can be used to introduce different functionalities into the desired cyclization products. The success of this process is dependent upon the substituents on the arenes and the carbon-carbon triple bond. While vinylic- and aryl-substituted acetylenes undergo electrophilic cyclization smoothly, alkyl and trimethylsilyl acetylenes don't react under our standard electrophilic cyclization conditions. Furopyridines can also be synthesized in good yields by our electrophilic cyclization using o-methoxyalkynylpyridines.

Chapter 2 presents the synthesis of heterocycles by electrophilic cyclization reactions of acetylenic aldehydes, ketones and imines. The overall synthetic process involves the coupling of a terminal acetylene with o-iodoarenecarboxaldehydes or ketones by a palladium-catalyzed coupling reaction, followed by electrophilic cyclization with various electrophiles in the presence of proper nucleophiles. Oxygen- and nitrogen-containing
heterocycles can be quickly assembled by this three component process in good to excellent yields. The resulting heterocyclic compounds, however, are generally unstable and hard to purify.

Chapter 3 describes the synthesis of coumestan and coumestrol by selective electrophilic cyclization, followed by palladium-catalyzed intramolecular carbonylation and lactonization. The biologically interesting coumestan system can be quickly constructed by this very efficient approach from common starting materials. The palladium-catalyzed reaction effects as both carbonylation and lactonization in one step. The success of this overall approach relies on the selectivity of our electrophilic cyclization approach to the corresponding benzo[b]furans.

Chapter 4 examines the scope and synthetic utility of a 1,4-Pd through space migration. The synthesis of various fluoren-9-ones has been accomplished by the Pd-catalyzed intramolecular C-H activation of imines derived from 2-iodoaniline and biarylcarboxaldehydes. This methodology makes use of a novel 1,4-palladium migration from an aryl position to an imidoyl position to generate the key imidoyl palladium intermediate, which undergoes intramolecular arylation to produce imines of complex polycyclic compounds containing the fluoren-9-one core structure. Both electronic effects and steric effects have been investigated. While steric effects play an important role and longer reaction times and lower yields are observed in more hindered systems, the electronic effects do not lower the overall yields. The imine products can be easily converted to the corresponding fluoren-9-ones upon hydrolysis under very mild reaction conditions.
APPENDIX A. CHAPTER 1 $^1$H AND $^{13}$C NMR SPECTRA
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APPENDIX B. CHAPTER 2 $^1$H AND $^{13}$C NMR SPECTRA
APPENDIX C. CHAPTER 3 $^1$H AND $^{13}$C NMR SPECTRA
APPENDIX D. CHAPTER 4 $^1$H AND $^{13}$C NMR SPECTRA
ACKNOWLEDGMENTS

I would like to express my sincere gratitude and appreciation to Professor Richard C. Larock. I am indebted to him for his patience, understanding, and financial support.

I would like to thank the past and present members of the Larock group that I have worked with. In particular, I would like to thank Haiming Zhang for taking the time and teaching me how to do palladium chemistry in the early days.

I would like to thank my parents, Zhengguo Yue and Xiaowan Xu, for their encouragement and support.

Finally, I would like to thank my wife Pangao Liao, whose support and incredible sacrifices made all of this possible. WE DID IT!