Organopalladium approaches to interphenylene prostaglandin analogs, heterocycles and carbocycles

Srinivasan Babu
Iowa State University

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ORGANOPALLADIUM APPROACHES TO INTERPHENYLENE PROSTAGLANDIN ANALOGS, HETEROCYCLES AND CARBOCYCLES

Iowa State University

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Organopalladium approaches to interphenylene prostaglandin analogs, heterocycles and carbocycles

by

Srinivasan Babu

A Dissertation Submitted to the Graduate Faculty in Partial Fulfillment of the Requirements for the Degree of DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.
In Charge of Major Work

Signature was redacted for privacy.
For the Major Department

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Iowa State University
Ames, Iowa

1987
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INTRODUCTION

Biologically important compounds such as interphenylene prostaglandin analogs, indoles, quinolines, isoquinolines and carbocycles have been synthesized using a catalytic palladium approach. Our methodology to the prostaglandin analogs involves a novel one pot addition of the two side chains to a symmetrical bridged, bicyclic olefin, such as norbornene, in the presence of catalytic amounts of a palladium(0) complex. The strategy to the synthesis of heterocycles and carbocycles involves the intramolecular addition of arylpalladium compounds to olefinic bonds in the presence of a phase transfer reagent. This methodology offers high yields of products and requires mild temperature conditions.
PART I. ORGANOPALLADIUM APPROACHES TO INTERPHENYLENE PROSTAGLANDIN ENDOPEROXIDE ANALOGS
The prostaglandins are one of the most important classes of natural products. They have been the subject of investigation for well over 50 years. Since their independent discovery in the 1930s by Von Euler and Goldblatt, many biological properties such as vasodepression and smooth muscle contraction have been attributed to these compounds. Prostaglandins are 20 carbon hydroxyacids with a wide variety of biological functions. Some inhibit blood platelet aggregation while some induce blood platelet aggregation. In addition, they possess many other biological properties which include inhibition of gastric and intestinal secretion and stimulation of insulin release. Thus, as viewed from the standpoint of biological activity, the pharmacological potential of prostaglandins is immense.

Biological pathway to prostaglandins

Technical difficulties hampered the progress of prostaglandin research for almost 30 years. In 1960, the structures of prostaglandin E₁ (PGE₁) and prostaglandin F₂α were determined by Bergstrom and Sjovall. At that time, interest focused on the biogenesis of prostaglandins. It was discovered that these primary prostaglandins originated from an unsaturated fatty acid, arachidonic acid. By a series of enzyme catalyzed reactions, this acid is converted into the
primary prostaglandins, prostacyclin and the thromboxanes. This is usually termed the arachidonic acid cascade (Scheme 1). The biogenesis of prostaglandins from arachidonic acid was discovered independently by two different groups.\textsuperscript{4,5}

By the late 1960s, the total synthesis of prostaglandins was already in progress. To date numerous syntheses of these once rare compounds have been recorded. This topic has been the subject of many books and reviews. Among them, the most recent review by Noyori and Suzuki\textsuperscript{6} describes in great detail the many synthetic approaches taken by different chemists.

It is important to note the significant properties of some of the primary prostaglandins and the manner by which they differ from the other cascade products. PGE\textsubscript{1} and PGE\textsubscript{2} are powerful inhibitors of blood platelet aggregation, whereas thromboxane A\textsubscript{2} (TXA\textsubscript{2}) is an aggregator of blood platelets. These two substances arise from the same endoperoxide precursor PGH\textsubscript{2}, yet they exhibit biologically opposite properties. Thus, attention was diverted from the primary prostaglandins to the unstable bicyclic endoperoxide precursor PGH\textsubscript{2} (Fig. 1).

\begin{figure}
\centering
\includegraphics{PGH2_diagram}
\caption{PGH\textsubscript{2}}
\end{figure}
Scheme 1. Arachidonic Acid Cascade

- Arachidonic Acid

  \[ \text{Arachidonic Acid} \]

  \[ \text{OOH} \] (PGG₂)

  \[ \text{OH} \] (PGH₂)

  \[ \text{CO₂H} \] (PGF₂)

  \[ \text{OH} \] (TXA₂)

  \[ \text{OH} \] (PGE₂)

  \[ \text{OH} \] (PGI₂)

  \[ \text{OH} \] (TXB₂)
It was found that PGH₂ has a very short half life in biological (aqueous) systems and yet possesses many fascinating properties. PGH₂ induces rapid irreversible blood platelet aggregation and is 200 times more active than PGE₂ in stimulating contraction of rabbit aorta strip, a standard assay of prostaglandin activity. However, the half life of this interesting compound, as stated earlier, is only five minutes in aqueous systems. Even the primary prostaglandins which are important biologically have very short half lives under biological conditions.

**Need for novel prostaglandin analogs**

In view of the unstable nature of prostaglandins and their bicyclic precursor PGH₂, the synthesis of stable analogs of both PGH₂ and the primary prostaglandins possessing similar activity became highly desirable. Before discussing the strategy behind the synthesis of these analogs, it is important to understand how PGH₂ and the other prostaglandins are biochemically degraded into biologically inactive compounds. It was found that there are three modes of enzymatic attack on PGF₂α. One mode of attack occurs at the 13,14 double bond to give the 13,14 dihydro-15-oxo product. Also occurring simultaneously is the oxidation of the carboxylic acid chain which involves sequential removal of C₁ to C₄ of the carboxylic acid side chain. Finally, the
oxidation of C-20 to the carboxylic acid side chain takes place (Scheme 2).  

Scheme 2. Degradation of PGF$_2\alpha$  

The synthetic design of many prostaglandin analogs has been based on the knowledge of the metabolic degradation described above (Scheme 2). Various modifications have been made in the 15-hydroxyl group in efforts to retard dehydrogenation at carbon-15. Notably effective have been 15-methyl or 15,15-difluoro compounds. In order to prevent oxidation at the carboxylic acid side chain, various modifications have been made. These have involved introduction of alkyl groups at various carbons or substitution of a heteroatom for a
carbon. Also, in the carboxylic acid side chain, substitution of a meta-substituted aromatic ring for carbons 4 through 6 has been effective in blocking oxidation. Blockage of oxidation of carbon-20 has been effected by the introduction of bulky aromatic groups.

Synthesis and biological properties of PGH₂ analogs

The synthesis of PGH₂ endoperoxide analogs has involved substitution of the unstable peroxy bridge by more stable two atom bridges. Thus prepared are \( \text{N}=\text{N}, \text{NH}-\text{O}, \text{S}-\text{S}, \text{CH}=\text{CH}, \text{CH}_2-\text{CH}_2, \text{CH}_2-\text{O} \) and \( \text{CH}_2-\text{NH} \) bridged bicyclic prostaglandin endoperoxide analogs. The strategy and the synthesis of some PGH₂ analogs is discussed by Nicolau.⁸ To date many analogs have been synthesized. Though it is not possible to record every PGH₂ analog that has been synthesized, the following list of analogs will give the reader an idea of the interesting structural modifications that have been made on the unstable PGH₂ molecule.
The above are examples of PGH₂. As can be seen from the structures, a variety of skeletons have been employed. In addition, variations in the stereochemistry of the substituents on the bicyclo[2.2.1]heptane ring have also resulted in biologically active compounds.

While discussion of the synthesis of each of the PGH analogs is not possible, most syntheses have followed either of the following two routes: (a) Diels-Alder route, in which the bicyclic ring is constructed by a [4+2] cyclization followed by a series of Michael additions and Wittig olefination reactions (Scheme 3); (b) prostaglandin route, in which the starting material is a naturally occurring prostaglandin. An example of the synthesis of one such analog is shown below (Scheme 4).
Scheme 3. General Synthesis of a PGH$_2$ Analog by the Diels-Alder Route

Scheme 4. General Synthesis of a PGH$_2$ Analog by the Prostaglandin Route
The Diels-Alder reaction has the disadvantage of giving rise to unwanted exo-endo substituted products. In many cases the unwanted products predominate. The prostaglandin route requires very expensive starting materials, naturally occurring prostaglandins, which by themselves are hard to synthesize. Therefore, one can see the major drawbacks inherent in both routes.

The table below (Table 1) lists the biological activities of all the \( \text{PGH}_2 \) analogs listed above.

**Interphenylene prostaglandin analogs**

Among the many steps taken to prevent rapid degradation of the primary prostaglandins, it was found that substitution of the carboxylic acid side chain by a meta-substituted phenyl group proved quite effective in retaining the stability of the molecule under biological conditions. A number of interphenylene prostaglandin analogs have been synthesized and some of them have been found to possess substantial biological activity. A list of such analogs is seen below.

The general synthetic approaches to all of these prostacyclin and prostaglandin interphenylene analogs have been similar to those used in the synthesis of the prostaglandins. Most of these compounds possess important biological properties and, in addition, greater stability. The labile enol ether portion of the prostacyclin has been replaced by rigid aromatic groups. As anticipated, these newly made
Table 1. Biological activity of known PGH₂ analogs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Eight times as active as PGG₂ in stimulating blood platelet aggregation; 6 times as potent as PGG₂ in inducing serotonin release; 6.9 times as active as PGH₂ and 1450 times as active as PGE₂ in stimulating contraction of rabbit aorta strip.</td>
</tr>
<tr>
<td>3</td>
<td>Potent inhibitor of PGH₂ induced blood platelet aggregation. Thromboxane A₁ synthetase inhibitor.</td>
</tr>
<tr>
<td>4</td>
<td>Potent inhibitor of thromboxane A₂ synthetase.</td>
</tr>
<tr>
<td>5</td>
<td>Potent inhibitor of thromboxane A₂ synthetase.</td>
</tr>
<tr>
<td>6</td>
<td>Potent broncho constrictor. Inhibits artificially induced blood platelet aggregation.</td>
</tr>
<tr>
<td>7</td>
<td>Potent broncho constrictor. Antagonizes PGE₁ induced C-AMP formation.</td>
</tr>
<tr>
<td>8</td>
<td>Twenty-four times as active as PGH₂ and 5000 times as active as PGE₂ in stimulating contraction of rabbit aorta strip. Induces rapid irreversible blood platelet aggregation.</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Not reported.</td>
</tr>
<tr>
<td>10</td>
<td>Induces rapid platelet aggregation. Functions as an antagonist of thromboxane A&lt;sub&gt;2&lt;/sub&gt; receptors.</td>
</tr>
<tr>
<td>11</td>
<td>Selective and potent thromboxane A&lt;sub&gt;2&lt;/sub&gt; receptor antagonist. Inhibits platelet aggregation induced by compound 9.</td>
</tr>
<tr>
<td>12</td>
<td>Inhibits arachidonic acid induced blood platelet aggregation.</td>
</tr>
<tr>
<td>13</td>
<td>Not reported.</td>
</tr>
<tr>
<td>14</td>
<td>Inhibits arachidonic acid induced blood platelet aggregation. Inhibits thromboxane A&lt;sub&gt;2&lt;/sub&gt; synthetase.</td>
</tr>
<tr>
<td>15</td>
<td>Inhibits platelet aggregation. Inhibits thromboxane A&lt;sub&gt;2&lt;/sub&gt; synthetase.</td>
</tr>
<tr>
<td>16</td>
<td>Inhibits platelet aggregation. Inhibits thromboxane A&lt;sub&gt;2&lt;/sub&gt; synthetase.</td>
</tr>
<tr>
<td>17</td>
<td>Not reported.</td>
</tr>
<tr>
<td>18</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
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<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Not reported.</td>
</tr>
<tr>
<td>20a</td>
<td>Specific inhibitor of $\text{PGE}_1$ synthetase.</td>
</tr>
<tr>
<td>20b</td>
<td>Inhibits synthesis of $\text{PGE}_1$.</td>
</tr>
<tr>
<td>21</td>
<td>Weak inhibitor of ADP-induced platelet aggregation and thromboxane $\text{A}_2$ synthetase.</td>
</tr>
<tr>
<td>22</td>
<td>Not reported.</td>
</tr>
<tr>
<td>23</td>
<td>Inhibits blood platelet aggregation.</td>
</tr>
<tr>
<td>24</td>
<td>$1/40$ as active as $\text{PGG}_2$ in inducing blood platelet aggregation. Potent veno constrictor.</td>
</tr>
<tr>
<td>25</td>
<td>Inhibits blood platelet aggregation.</td>
</tr>
<tr>
<td>26</td>
<td>Not reported.</td>
</tr>
<tr>
<td>27</td>
<td>Not reported.</td>
</tr>
<tr>
<td>28a</td>
<td>Mild inhibitor of blood platelet aggregation.</td>
</tr>
<tr>
<td>28b</td>
<td>Potent inhibitor of blood platelet aggregation.</td>
</tr>
</tbody>
</table>
Figure 2. Interphenylene prostaglandin analogs
R = H, Me; R' = lower alkyl or R' is cyclic; R^2 is H only if R' is lower alkyl; R^3 = H, (R)-OH or (S)-OH; A = trans-vinylene (30 compounds)

Figure 2. Continued
R - R³ = groups associated with prostaglandins

Figure 2. Continued
Figure 2. Continued
analogs possess biological properties similar to PGI₂. The newly introduced aromatic groups offer stability to these molecules in biological systems. Table 2 below lists the biological properties of these interphenylene prostaglandin analogs.

The biological properties of both PGH₂ and interphenylene prostaglandin analogs stimulated our own interest in that area. It was conceived that "interphenylene PGH analogs" would not only be an interesting addition to the list of known prostaglandin analogs, but also important biologically. The following chapter will discuss in detail the compounds envisioned for our synthetic and biological study.

As stated earlier in this chapter, present approaches to the synthesis of PGH₂ analogs have certain disadvantages. In order to circumvent the problems pertaining to stereochemistry, Larock and co-workers have used novel organometallic approaches to develop rapid, stereospecific routes to some of the PGH₂ analogs seen above. The objective of this research has been to apply various aspects of organometallic chemistry towards the synthesis of interphenylene prostaglandin analogs. It was envisioned that an organopalladium species would stereospecifically add to strained bicyclic olefins such as norbornene, norbornadiene and 7-oxanorbornene, to yield intermediate σ-alkyl palladium compounds which would then be trapped by a terminal alkyne. This would result in the
Table 2. Biological properties of interphenylene prostaglandin analogs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>Not reported.</td>
</tr>
<tr>
<td>30</td>
<td>Potent inhibitor of blood platelet aggregation.</td>
</tr>
<tr>
<td>31</td>
<td>Potent inhibitor of blood platelet aggregation.</td>
</tr>
<tr>
<td>32</td>
<td>No PG12 activity.</td>
</tr>
<tr>
<td>33</td>
<td>Potent inhibitor of ADP-induced blood platelet aggregation.</td>
</tr>
<tr>
<td>34a</td>
<td>Thirty times more potent than PG1 as an inhibitor of ADP-induced human platelet aggregation.</td>
</tr>
<tr>
<td>34b</td>
<td>Not reported.</td>
</tr>
<tr>
<td>35a</td>
<td>Potent inhibitor of ADP-induced human platelet aggregation.</td>
</tr>
<tr>
<td>35b</td>
<td>Potent inhibitor of human platelet aggregation.</td>
</tr>
<tr>
<td>35c</td>
<td>Not reported.</td>
</tr>
<tr>
<td>35d</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>
Table 2. Continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>35e</td>
<td>Not reported.</td>
</tr>
<tr>
<td>36</td>
<td>Potent inhibitor of human blood platelet aggregation and dilator of perfused cat artery.</td>
</tr>
<tr>
<td>37</td>
<td>Showed more potency than PGE₁, but less than PGI₂, in inhibiting platelet aggregation and dilating isolated perfused cat coronary artery.</td>
</tr>
<tr>
<td>38</td>
<td>Not reported.</td>
</tr>
<tr>
<td>39</td>
<td>Potent inhibitor of blood platelet aggregation.</td>
</tr>
<tr>
<td>40a</td>
<td>Not reported.</td>
</tr>
<tr>
<td>40b</td>
<td>Not reported.</td>
</tr>
<tr>
<td>41</td>
<td>Not reported.</td>
</tr>
<tr>
<td>42</td>
<td>Not reported.</td>
</tr>
<tr>
<td>43</td>
<td>Almost twice as potent as PGE₁ in platelet aggregation.</td>
</tr>
<tr>
<td>44</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>
Table 2. Continued

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>Not reported.</td>
</tr>
<tr>
<td>46a</td>
<td>As active as PGI₂ (PGI₂ mimic) in inhibiting platelet aggregation and lowering blood pressure.</td>
</tr>
<tr>
<td>46b</td>
<td>As active as PGI₂ (PGI₂ mimic) in inhibiting platelet aggregation and lowering blood pressure.</td>
</tr>
<tr>
<td>47a</td>
<td>Not reported.</td>
</tr>
<tr>
<td>47b</td>
<td>Not reported.</td>
</tr>
<tr>
<td>48</td>
<td>Not reported.</td>
</tr>
<tr>
<td>49a</td>
<td>Potent as PGI₂, but possesses considerably enhanced stability towards chemical and metabolic degradation.</td>
</tr>
<tr>
<td>49b</td>
<td>Potent as PGI₂, but possesses considerably enhanced stability towards chemical and metabolic degradation.</td>
</tr>
<tr>
<td>50a</td>
<td>Not reported.</td>
</tr>
<tr>
<td>50b</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>
Table 2. Continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>Potent inhibitor of blood platelet aggregation.</td>
</tr>
<tr>
<td>52</td>
<td>Inhibits exvivo platelet aggregation. Also has gastric antisecretory and antiulcer activities.</td>
</tr>
<tr>
<td>53</td>
<td>Useful as cardiovascular agents, platelet aggregation inhibitors, antithrombotions and bronchodilators (no data).</td>
</tr>
<tr>
<td>54</td>
<td>Not reported.</td>
</tr>
<tr>
<td>55</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>

addition of the two carbon chains to a symmetric double bond in one step, stereospecifically. Also, this would be the shortest route to interphenylene prostaglandin analogs. Hopefully, the compounds obtained would not only possess structural diversity, but also important biological activity. The next chapter will discuss, in detail, the synthetic strategy and the experimental results of our research.
ORGANOPALLADIUM APPROACHES TO INTERPHENYLENE PROSTAGLANDIN ENDOPEROXIDE ANALOGS

**Historical**

As noted in the previous chapter, some of the interphenylene analogs of the primary prostaglandins not only possess structural simplicity, but also potent biological activity. These observations stimulated our interest in the synthesis of novel interphenylene prostaglandin endoperoxide analogs.

Earlier work by Larock and co-workers on the synthesis of prostaglandin endoperoxides has involved organopalladium additions to bicyclic olefins with subsequent acetylide displacement (eq. 1). Using this approach, a number of prostaglandin endoperoxide (PGH₂) analogs have been synthesized. Most of these are quite active in the inhibition of blood platelet aggregation, but are not as potent as previously synthesized analogs and several natural prostaglandins. The general scheme for the synthesis of one such analog is shown below (Scheme 5).
Organomercurials are relatively inert compounds. However, transmetallation occurs easily with Pd(II) salts, giving rise to an intermediate organopalladium species which rapidly inserts the olefin to form a $\sigma$-alkyl palladium complex 56. Lack of a cis-$\beta$ hydrogen prevents this palladium intermediate from undergoing palladium hydride, "$\text{HPdX}$", elimination. Further, the sulfur atom can coordinate to the palladium stabilizing intermediate 56. Acetylide displacement of the palladium moiety in the presence of two equivalents of triphenylphosphine then affords intermediate 57 which can be easily converted to analog 58 by known synthetic transformations. This approach introduces the two side chains in two
separate steps, circumventing problems that might arise employing a Diels-Alder approach.

Catellani and Chiusoli\textsuperscript{60,61} have developed a novel and elegant approach to effect the same transformation (see eq. 1). This involves the one step addition of a vinyl or aromatic group and a terminal acetylene to the strained double bond of a bicyclic olefin, such as norbornene. The reaction involves treatment of a vinyl or an aryl bromide with a terminal acetylene and norbornene in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0) \([\text{Pd(PPh}_3\text{)}_4]\) and one equivalent of sodium acetate (eq. 2).

\[
\begin{align*}
\text{norbornene} + \text{RBr} + \text{R'C=CH} & \xrightarrow{3\% \text{ Pd(PPh}_3\text{)}_4, \text{NaOAc, } \Delta} \text{product} \\
\text{R} & = \text{vinyl or aryl}
\end{align*}
\]

No further efforts were made by Chiusoli to extend this synthetic route to prostaglandin endoperoxide analogs. We thought that this approach might prove effective for such syntheses. The interphenylene prostaglandin analogs shown below (Fig. 3) were considered as suitable target molecules. If this one pot approach were successful, the two side chains would be introduced in just one step. The scheme envisioned is shown below (Scheme 6).
The analogs 59, 60 and 61 differ from the natural prostaglandins and other prostaglandin analogs with respect to the stereochemistry of the two side chains (cis, compared to the trans stereochemistry found in prostaglandins and most
other analogs). The presence of an acetylenic, instead of a vinyl, moiety was of interest since it has imparted greater biological potency in other prostaglandin analogs. Thus, it was thought that this modification might introduce greater biological activity into our target molecules (Fig. 3).

Additionally, it was thought that this proposed synthetic method when applied to substituted aryl halides, would give rise to a new set of analogs shown in Figure 4. In these

![Figure 4](image)

Figure 4. Interphenylene prostaglandin analogs it was hoped that the 1,4-substituted phenyl ring would mimic the cis double bond found in natural prostaglandins, at the same time blocking oxidation during biochemical processes. The lower side chain, however, is the same as in the benzyl analogs. The current interest in oxygen derivatives of PGH encouraged us to examine the synthesis and properties of PGH analogs bearing an oxygen in the one atom bridge. Hopefully, these compounds (Figs. 3 and 4) would possess interesting biological activity. Prior to our work, interphenylene PGH analogs of the type indicated in Figs. 3 and 4 were unknown.
Results and discussion

As a model study, it was decided to apply Chiusoli's conditions to the following reaction (eq. 3). When

\[
\begin{align*}
\text{norbornene} + \text{XCH}_2\text{Ph} + \text{HC} &= \text{CCH}_5\text{H}_11 & \text{Pd(PPh}_3\text{)}_4 \\
\text{OH} & & \text{NaOAc} \\
\text{anisole} & & \Delta
\end{align*}
\]

\(X = \text{Br, Cl}\)

norbornene, benzyl bromide and racemic 1-octyn-3-ol were heated at 80°C in the presence of 3% Pd(PPh\(_3\))\(_4\) in degassed anisole, an intractable product mixture was obtained. However, when benzyl chloride was subjected to similar conditions, excellent yields of the anticipated product were obtained. In order to optimize the yield, we examined several different reaction conditions (Table 3).

In each of these reactions, the concentrations of benzyl chloride, racemic 1-octyn-3-ol and sodium acetate were kept constant (one equivalent with respect to the olefin).

The exclusive formation of the cis-exo product may be explained by the following mechanism (Scheme 7). The first step involves the oxidative addition of benzyl chloride to the Pd(PPh\(_3\))\(_4\) catalyst giving rise to the intermediate benzyl-palladium chloride complex. Rapid insertion of norbornene
Table 3. Reaction conditions examined in the synthesis of compound 65

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of olefin</th>
<th>% Pd catalyst</th>
<th>Reaction time (days)</th>
<th>Reaction temperature (°C)</th>
<th>Isolated yield of 65 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>65</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>8</td>
<td>1</td>
<td>70</td>
<td>81</td>
</tr>
</tbody>
</table>
Scheme 7

\[
\begin{align*}
\text{Scheme 7} & \\
\text{CH}_2\text{Cl} + \text{PdL}_4 & \rightarrow \text{CH}_2\text{Pd-ClL} + 2 \text{L} \\
\end{align*}
\]

- 33

into the carbon-palladium bond of this complex results in the formation of a \( \sigma \)-alkyl palladium intermediate 66. This intermediate in turn complexes with the acetylene giving rise to a positively charged palladium species. Removal of the acetylenic hydrogen by base generates an organopalladium intermediate, which upon reductive elimination results in the formation of the final adduct. It should be noted that the absence of a cis \( \beta \)-hydrogen in the complex 66 prevents "HPdX"
elimination. Since benzylpalladium chloride addition to norbornene is cis and reductive elimination in the final step proceeds with retention of configuration, the product obtained is exclusively cis-exo.

This one pot addition reaction was then extended to norbornadiene, bicyclo[2.2.2]octene and 5,6-diaza-5,6-dicarboethoxynorbornene. The reaction with norbornadiene proceeded smoothly although accompanied by formation of a minor impurity (~5% by $^1$H NMR spectral analysis) inseparable by chromatography. In this case eight equivalents of diene were used in order to prevent diaddition to the diene. The final product 67 was obtained in 53% yield. Increasing the amount of diene to 20 equivalents made no significant change in the yield or in the relative amount of impurity formed. In the case of bicyclo[2.2.2]octene and 5,6-diaza-5,6-dicarboethoxynorbornene, the reaction did not give the desired addition.
product. Varying the reaction conditions did not change the results, as many products were obtained in each case.

**Synthesis of methyl(3-chloromethylphenoxy)acetate**

Having obtained the optimal reaction conditions for the model systems, it was decided to prepare the desired ester analogs, using optically pure (S)-1-octyn-3-ol and methyl(3-chloromethylphenoxy)acetate (68). The synthesis of compound 68 was accomplished in a straightforward manner starting with m-hydroxybenzaldehyde (Scheme 8). Treatment of m-hydroxybenzaldehyde with methyl bromoacetate in the presence of potassium carbonate in refluxing acetone for 16 hours gave the formyl ester 69 in an 88% distilled yield. Selective reduction of the aldehyde in the presence of the ester at 0°C
with sodium borohydride gave the alcohol \( \text{70} \) in 95% yield. Conversion of the benzylic alcohol to the chloride via the mesylate was achieved in 82% yield using Meyers' procedure. 62

**Resolution of optically pure \((S)\)-1-octyn-3-ol**

Optically pure \((S)\)-1-octyn-3-ol was resolved using a modification of Fried's procedure. 63 The general scheme that was adopted for the resolution is shown below (Scheme 9). Racemic 1-octyn-3-ol was heated with phthalic anhydride at 160-165°C for 21 hours under nitrogen. The half phthalate ester \( \text{71} \) was obtained in 55% yield. Recrystallization of the half
phthalate ester from benzene (twice) and subsequent treatment with (S)-(-)-phenethylamine in refluxing dichloromethane for 30 minutes yielded the amine salt. The mother liquor was cooled to room temperature and then kept in a freezer overnight. The S,S diastereomer of the amine salt crystallizes out. After four successive recrystallizations from dichloromethane, the amine salt was obtained optically pure. It should be noted that to affect recrystallization of the desired diastereomer of the amine salt (S,S), it was critical to recrystallize the half phthalate ester twice before treatment with the amine. The optical purity of the amine salt was determined by $^1$H NMR spectral analysis, monitoring the ethanol hydrogens of the two diastereomers, which appeared as two doublets at $\delta$ 2.48 and $\delta$ 2.52 ($J = 1.5$ Hz). The doublet at $\delta$ 2.48 corresponds to the S,S diastereomer. Saponification with 10% sodium hydroxide yielded the optically pure alcohol 72 in an 88% distilled yield. The optical rotation was measured in chloroform; $\left[\alpha\right]_{D}^{20}$$_{\text{CHCl}_3} = -6.79$ [literature value, $^6$$_3$ $\left[\alpha\right]_{D}^{20}$$_{\text{CHCl}_3} = -5.5$]. The optical purity of the alcohol itself was established by $^1$H NMR spectral analysis using an optically active shift reagent tris-[3-heptafluoropropylhydroxymethylene]-d-camphorato]-europium(III). The optical purity of the alcohol 72 was $\sim$100%.
Interphenylene PGH ester analogs

Having obtained the requisite starting materials, we decided to synthesize the interphenylene PGH ester analogs via the one pot synthetic route employed in the model studies. When norbornene (four equivalents), optically pure (S)-1-octyn-3-ol (72) and the substituted benzyl chloride 68 were heated at -70°C for a day in anisole in the presence of 8% Pd(PPh₃)₄ and one equivalent of anhydrous sodium acetate, the expected product 73 was obtained in 58% isolated yield as an inseparable mixture of the two possible diastereomers (eq. 5).

\[
\begin{array}{c}
\text{4 norbornene} + \text{Cl} \quad \text{O} \quad \text{CO₂CH₃} + \text{HCSCH₃} \quad \text{OH} \quad \text{8% Pd(PPh₃)₄} \\
\quad \text{NaOAc} \quad \text{70-72°C} \quad \text{one day} \quad \text{anisole} \quad 58% \\
\end{array}
\]

The reaction was then extended to norbornadiene (eight equivalents of the diene were used), and the desired product
74 was obtained as a mixture of diastereomers in 37% isolated yield (eq. 6).

When 7-oxa-norbornene was subjected to similar conditions, the expected product 75 as a mixture of diastereomers was obtained in 34% isolated yield along with the diadduct 76 (eq. 7). The formation of the diadduct 76
could be explained by the following scheme (Scheme 10).

It is envisioned that the initial \( \sigma \)-alkyl palladium

Scheme 10
intermediate 76A could add to another 7-oxanorbornene molecule giving rise to a second σ-alkylpalladium species, which then reacts with the terminal alkyne to yield compound 76.

Decreasing the amount of olefin used to two equivalents had no effect on the yield of the product or in eliminating diadduct formation (compound 76). Under these conditions, the yield of compound 75 dropped to 26%. Raising the temperature to 80°C, while maintaining the usual conditions of four equivalents of olefin, increased the yield of the desired compound 75 to 45%.

The NMR spectral data for compounds 73, 74 and 75 deserve special mention. Proton NMR spectral and decoupling studies provided proof of the relative stereochemistry of the two side chains. For the sake of discussion, compounds 73, 74 and 75 will be numbered in the following manner around the bicyclic system (Fig. 5).

![Figure 5. X = O, CH₂](image)

In the case of compound 73 (X = CH₂), the 13C NMR spectrum showed the presence of 26 resonances, all occurring in the expected absorption region. Since there are only 25 different
carbons in compound 73, the extra peak could arise from the
diastereomer of compound 73, wherein one of the carbons
absorbs in a slightly different region. The $^{13}$C NMR spectrum
thus revealed the existence of the two diastereomers of
compound 73.

The $^1$H NMR spectrum of compound 73 also revealed some
interesting features. The HC(2) hydrogen exhibits a doublet
at $\delta$ 2.62 with $J = 8.7$ Hz. The coupling constants for cis-
endo hydrogens of similar systems have coupling constants
varying from 8-10 Hz. Since HC(2) and HC(1) are nearly
perpendicular to one another, coupling between these two
hydrogens is greatly reduced. The two diastereotopic benzylic
hydrogens have different chemical shift values. One hydrogen
absorbs at $\delta$ 2.86 and the other around $\delta$ 2.42. At this stage,
decoupling experiments proved to be very helpful in confirming
the proton assignment. Irradiation of the resonance at $\delta$ 2.86
causd the peak at $\delta$ 2.42 to collapse to a doublet ($J = 8.3$
Hz). Thus, the peaks at $\delta$ 2.86 and $\delta$ 2.42 can be assigned to
the diastereotopic benzylic hydrogens. Also, during the same
decoupling experiment the peak due to HC(3) was observed as a
triplet at $\delta$ 1.86 with $J = 6$ Hz. In conclusion, irradiation
of one of the benzylic hydrogens resulted in changes in the
absorption patterns of the other benzylic hydrogen and HC(3).
No other changes were observed elsewhere in the spectrum.
Irradiation of the peak at $\delta$ 2.42 caused the absorption at $\delta$
2.86 to collapse to a singlet and the peak at $\delta$ 1.86 to collapse to a very broad triplet, but the peak at $\delta$ 2.35 remained unchanged. This confirms the previous assignment. Irradiation of the peak at $\delta$ 1.86 caused the peak at $\delta$ 2.62 to collapse to a singlet. Thus, the absorption at $\delta$ 2.62 can be assigned to HC(2), while the peaks at $\delta$ 2.86 and $\delta$ 2.42 collapse to doublets with $J = 14.0$ Hz. The decoupling experiments have, therefore, removed any ambiguities that were originally present in the proton NMR spectral assignments. Exact mass and infrared spectral data offer further evidence for the overall structure of the compound as assigned.

The spectral properties of compound 74 were quite similar to that of compound 73. The $^{13}$C NMR spectrum exhibited the presence of 25 resonances; exactly the number expected for the proposed structure. The presence of the other diastereomer was inferred from the absorption of one of the carbons at $\delta$ 38.24. This carbon absorption had a broadened shoulder relative to the other carbon absorptions, possibly indicating the carbon center belonging to the other diastereomer. The $^1H$ NMR spectrum of compound 74 revealed nothing notably different from compound 73. The vinyl region appeared as a broad singlet. Decoupling experiments similar to those performed on compound 73 were useful in assigning HC(2), HC(3) and the benzylic hydrogens. Excluding very minor changes in chemical shifts, the $^{13}$C and $^1H$ NMR spectra of compound 74 were nearly
identical to those of compound 73. Infrared and mass spectral data confirmed the structure as assigned.

The $^1H$ NMR spectrum of compound 75 turned out to be interesting as well as straightforward to interpret. The hydrogens of the bridgehead carbons, HC(1) and HC(4), have considerable differences in their chemical shifts, $\delta$ 4.55 and $\delta$ 4.26 respectively. As expected, these turned out to be broadened doublets with $J = 4.2$ Hz and $J = 5.6$ Hz respectively. One of the benzylic hydrogens ($\delta$ 2.83-2.89) was buried under the doublet due to HC(2) ($\delta$ 2.86). These assignments were confirmed by decoupling studies. The peak due to HC(3) appeared as a multiplet in the range of $\delta$ 2.06-2.19. Upon irradiating the hydrogens giving rise to the peak at $\delta$ 2.86, the multiplet at $\delta$ 2.06-2.19 collapsed to a doublet with $J = 9.9$ Hz. Thus, HC(3) couples with only one of the benzylic hydrogens now, the coupling with HC(4) being too small to observe. Upon irradiation of the peaks at $\delta$ 2.57 and $\delta$ 2.62, the multiplet centered at $\delta$ 2.83-2.89 collapses to a less complicated multiplet, reinforcing the belief that the vicinal coupling between the two benzylic hydrogens does exist. Simultaneously, a change in multiplicity is observed in the region $\delta$ 2.06-2.19 due to the endo proton on C-3. This can only be attributed to the other benzylic hydrogen at $\delta$ 2.62. Hence the multiplet in the region $\delta$ 2.06-2.19 is assigned to HC(3). Irradiation of the peak at $\delta$ 2.15 causes
changes in multiplicity in the region $\delta$ 2.57-2.62, further confirming this assignment. Infrared and exact mass measurements further confirmed the structure of the compound.

The interpretation of spectra of the diadduct 76 was more difficult than that of compound 75. The $^1$H NMR spectrum did not offer sufficient evidence as to its structure. However, the $^{13}$C NMR spectrum showed the presence of 31 resonances; 30 different absorptions are expected for the proposed structure. The extra carbon absorption could be attributed to the other diastereomer of compound 76. Evidence from IR studies and exact mass measurements, finally confirmed its structure. The stereochemistry assigned to this compound is based only on mechanistic arguments.

The esters 73 and 74 were then converted to the acids 60 and 61 by saponification with 2N KOH in refluxing methanol. Ester 75 was converted to the acid 59 by stirring with 2N KOH at room temperature for two days. The yields of acids 59, 60 and 61 were 98%, 95% and 88% respectively (eqs. 8 and 9).
Compounds 59, 60 and 61, when tested by E. R. Squibb and Sons, Inc. for inhibition of blood platelet aggregation induced by arachidonic acid, proved to be virtually inactive.

Arylpalladation approaches to interphenylene PGH ester analogs Replacing the substituted benzyl halide with a para substituted bromo- or iodoarene, in theory, should lead to esters of the interphenylene analogs shown earlier (see Fig. 4). Simple hydrolysis of the resulting esters would then yield the corresponding acids. The strategy involved in the synthesis of these compounds is straightforward (Scheme 11).

Synthesis of p-iodo-and p-bromophenoxy-acetic-acid methyl esters The requisite esters were made in two steps starting from the corresponding halophenols using the general procedure shown below (Scheme 12). Treatment of the p-bromo or p-iodo phenols with chloroacetic acid in the presence of two equivalents of sodium hydroxide in refluxing water gave the corresponding phenoxyacetic acid derivatives in >90% yield. Esterification of the acids with methanol in the
Scheme 11

\[
\text{Product} + X - \text{Phenyl} \text{CO}_2R + \text{HC} = \text{C} \quad \text{MeOH} \quad \Delta \quad \text{KOH}
\]

\[
X = \text{Br, I}
\]

Scheme 12

\[
X - \text{Phenyl} \text{CO}_2R + \text{ClCH}_2\text{CO}_2H \quad \text{NaOH} \quad \text{H}_2\text{O} \quad 4 \text{ hours} \quad \text{MeOH} \quad \text{H}_2\text{SO}_4
\]

\[
X = \text{Br, 65}\% \quad X = \text{I, 90}\%
\]
presence of catalytic amounts of concentrated sulfuric acid afforded the corresponding esters in high yields.

**Arylpalladation reactions** When norbornene, methyl p-bromophenoxyacetate and optically pure (S)-1-octyn-3-ol were treated with 8% Pd(PPh₃)₄ and anhydrous sodium acetate in anisole for two days at 80°C, the expected product 77 was obtained in a poor yield with a large amount of unreacted starting halide. Surprisingly, the alcohol could not be recovered (eq. 10). Changing the reaction conditions or switching to the more reactive iodoarene gave no improvement in the yield of the product (Table 4). In fact, the previously derived optimal conditions for the bromoarene failed to yield any of the desired product with the iodoarene (entry 1, Table 4).

It was thought that a protected alcohol might improve the reaction in case the alcohol was the source of the problem.
<table>
<thead>
<tr>
<th>$p$-X$_2$C$_6$H$_4$OCH$_2$CO$_2$CH$_3$</th>
<th>Reaction temperature ($^\circ$C)</th>
<th>Reaction time (days)</th>
<th>Isolated yield of product (%)</th>
<th>Yield of recovered aryl halide (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>80</td>
<td>2</td>
<td>11</td>
<td>76</td>
</tr>
<tr>
<td>Br</td>
<td>80</td>
<td>2</td>
<td>-</td>
<td>93</td>
</tr>
<tr>
<td>Br</td>
<td>90</td>
<td>4.5</td>
<td>many products</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>isolated</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>80</td>
<td>2</td>
<td>&lt;5</td>
<td>30</td>
</tr>
</tbody>
</table>

In each of the reactions, the olefin was taken in a fourfold excess with respect to the aryl halide and the alcohol. The amount of Pd(PPh$_3$)$_4$ catalyst remained the same (8%).
However, when the best conditions from Table 4 (entry 1) were applied to the arylpalladation reaction with a tetrahydro-pyranyl ether protected alcohol, absolutely none of the desired compound could be isolated. Only the starting materials were recovered. Changing the reaction conditions only led to the destruction of starting materials (eq. 11).

\[
\begin{align*}
&\text{Cyclohexene} + \text{Br-Ph-O-CH}_2\text{CO}_2\text{CH}_3 + \text{OTHP} + 8\% \text{Pd(PPh}_3)_4 \text{NaOAc} \\
\text{H} &\text{H} + \text{HC}\equiv\text{C}\text{C}_5\text{H}_11 \\
\text{Cyclic Product} + \text{starting materials} &\text{0%}
\end{align*}
\]

It was thought that an electron-donating group like an ether group might be inhibiting the oxidative addition of the aryl halide to the electron-rich palladium(0) complex (eq. 12).

\[
\begin{align*}
\text{RO-Ph-X} + \text{PdL}_4 &\rightarrow \text{RO-Ph-Pd-X} + 2\text{L}
\end{align*}
\]

It is reasonable that an electron-rich palladium complex would rather attack an electron-poor carbon-halide bond. In order to ascertain whether electron donation by resonance is
actually impeding the progress of the first step, it was envisioned that the ether group meta to the halogen might change the trend. Hence, it was decided to attempt aryl-palladation reactions using methyl m-bromophenoxyacetate. The synthesis of this ester was accomplished using a literature procedure (eq. 13). 65,66

\[
\begin{align*}
\text{Br} & \quad \text{ClCH}_2\text{CO}_2\text{H} \\
\text{NaOH} & \quad \text{H}_2\text{O} \\
\text{reflux} & \quad 12 \text{ hours}
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{CO}_2\text{H} & \quad 88\%
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{CO}_2\text{CH}_3 & \quad 78 \quad 89\%
\end{align*}
\]

(13)

Upon treating norbornene, (S)-l-octyn-3-ol and the aryl halide 78 with Pd(PPh₃)₄ catalyst and one equivalent of sodium acetate in anisole at 80°C for a period of 40 hours, it was observed that the expected product 79 was obtained in a very poor yield (6%) (eq. 14). Since both the aryl halide and the starting alcohol had the same R_f on TLC, they could not be separated from one another. Moreover, impurities prevented clean isolation of starting materials. Varying the reaction conditions had no effect on the yield of the reaction. Higher
temperatures gave no product at all. Switching to the more reactive iodoarene worsened the reaction. In those reactions, absolutely no product could be isolated. The reaction time made no difference either. Lengthening the reaction time led to no product at all.

Changing the substituent para to the halogen in the arene seemed to be the only reasonable way to solve the problem. This time the role of an acetate group was examined. The readily available p-bromo and p-iodophenylacetates were then subjected to the arylpalladation reaction. When norbornene, (four equivalents), p-iodophenylacetate and racemic 1-octyn-3-ol were reacted with Pd(PPh₃)₄ (8%) and one equivalent of sodium acetate in anisole at 80°C, very little of the expected product 80 was obtained (8%) (eq. 15). In the case of p-bromophenylacetate, no product could be seen. Only starting
material was isolated. In both cases the reaction was stopped after 24 hours as it started to turn to tar. When the same reactions were repeated using the tetrahydropyranly (THP) ether protected alcohol, absolutely no products were isolated. Only starting materials were recovered. Extended reaction times also led to formation of tar.

As the amounts of compounds 77, 79 and 80 obtained from the arylpalladation reactions were very small, their structures were determined based entirely on proton NMR, IR and mass spectral data. Also, the spectra obtained were compared with those of known compounds possessing similar structures. The three compounds are numbered in the following manner for spectral assignment (Fig. 6).

The $^1$H NMR spectra of all three compounds showed patterns characteristic of cis-di-exo substituted products. The two
Figure 6. Numbering system

Endo hydrogens HC(2) and HC(3) revealed the splitting of an AB system. The two doublets for HC(2) and HC(3) were seen at δ 2.92 (J = 8.7 Hz) and δ 2.82 (J = 8.7 Hz) respectively for compound 77. In the case of compound 79, the two overlapping AB doublets were seen at δ 2.61 with J = 9 Hz for HC(2) and HC(3). The two AB doublets for compound 80, however, were seen at δ 2.98 [HC(3), J = 9 Hz] and δ 2.85 [HC(2), J = 9 Hz] respectively. The coupling constants for cis-endo hydrogens in these systems usually range from 8-11 Hz. The HC(1) proton was seen as a closely spaced doublet (J = 1.5 Hz at δ 2.51) and HC(4) was a broad singlet at δ 2.41 for compound 77. In the case of compound 79, HC(1) and HC(4) were singlets at δ 2.55 and δ 2.41 respectively. The HC(1) and HC(4) absorptions for compound 80 were singlets at δ 2.57 and δ 2.41. Exact
mass data for compound 77 and IR data (hydroxyl and ester absorptions) added further confirmation to the structure of the compound. Similarly, exact mass and IR data confirmed the structural assignments for compounds 79 and 80. The $^{13}$C NMR spectra of these compounds could not be obtained as only very small amounts of material were in hand.

Some of the salient features in the synthetic approach to interphenylene PGH analogs can be summarized as follows. The two side chains (aryl or benzyl) and the terminal alkyne are introduced to a symmetric bridged bicyclic olefin in one step stereoselectively. These reactions make use of readily available starting materials and catalytic amounts of a palladium(0) complex. Though the arylpalladation reactions were not successful, the benzylpalladation reactions afforded an entry into the interphenylene PGH analog systems. This approach not only tolerates different functional groups (alcohols and esters), but introduces both the side chains in their entirety in one step, stereoselectively. Judging from the complexity of the molecules that have been synthesized, it can be inferred that employing other routes to these systems would mean more reaction steps and less elegance. Moreover, the stereochemistry of the two side chains (cis-exo) could be very difficult to introduce using normal synthetic routes such as the Diels-Alder reaction.
Other attempted approaches to PGH₂ analogs

The benzylpalladation approach which was successful in the synthesis of interphenylene PGH analogs, in theory, should be applicable to the synthesis of PGH₂ analogs (such as compound 82) provided the benzyl halide is substituted by an alkyl or a vinyl halide. The scheme involving the use of allyl halides is outlined below (Scheme 11). It was envisioned that the bicyclic adduct 81 could be obtained by treating norbornene, with an allyl halide and (S)-1-octyn-3-ol in the presence of catalytic amounts of Pd(PPh₃)₄ and one equivalent of sodium acetate in anisole at 80°C. Selective ozonolysis of the olefinic bond in 81 to the corresponding aldehyde, followed by a Wittig olefination would yield the PGH₂ analog 82. This straightforward strategy, however, was not successful in the laboratory.
Thus, treatment of allyl chloride and racemic 1-octyn-3-ol with norbornene (four equivalents) in the presence of Pd(PPh₃)₄ (8%) and sodium acetate in anisole at 80°C did not provide the anticipated product; only starting material (alcohol) was recovered. Switching to the more reactive halides, such as allyl bromide and allyl iodide, gave no improvement, as these reactions yielded many products. Allyl acetate was then substituted for the allyl halides in the above reaction. Even then, the reaction yielded many products. Protecting the alcoholic moiety in the starting alkyne also resulted in no success. Lowering the temperature in all of the above reactions yielded only unreacted starting materials.

At this stage, it was conceived that a vinyl ether group would be a better precursor to the aldehyde 83. The synthesis of compound 82 using a haloenol ether is depicted in the following scheme (Scheme 12). The bicyclic vinyl ether adduct which could be obtained from the palladium addition reaction could then be subjected to acid hydrolysis to yield the intermediate aldehyde 83, which upon Wittig olefination would yield the desired analog 82. Unfortunately, when cis-2-bromoethoxyethylene, racemic 1-octyn-3-ol and norbornene (four equivalents) were heated to 80°C in the presence of catalytic amounts of Pd(PPh₃)₄ and sodium acetate in anisole at 80°C, many products were obtained. When the same reaction was
carried out at room temperature, the vinyl-alkyne coupled product was isolated in a very high yield; no trace of the desired bicyclic adduct could be observed (eq. 16).

\[
\begin{align*}
4 \text{ norbornene} & + \text{Br-alkyne} + \text{HC=CCHC}_{5}\text{H}_{11} \text{OH} \\
\xrightarrow{8\% \text{ Pd(PPh}_{3}\text{)}_{4}, \text{NaOAc, anisole, room temperature}} & \text{BtO} \text{-alkyne} \text{-HC=CCHC}_{5}\text{H}_{11} \text{OH} \\
& 91\%
\end{align*}
\]

Increasing the amount of norbornene (20 equivalents) did not change the course of the reaction. When vinyl bromide was
used instead of the bromovinyl ether, only the starting alcohol was isolated both at room temperature and at 80°C.

Another approach to the aldehyde 83 is via the following scheme (Scheme 13).

Scheme 13

\[
\begin{align*}
4 \text{Norbornene} + XCH_2CO_2R + \text{HC} = \text{C} - \text{CH}_2CH\text{CH}_2\text{C}_5\text{H}_11 \xrightarrow{8\% \text{Pd(PPh}_3)_4} \text{CHO} \\
X = \text{Br, I} & \quad \text{NaOAc} \\
\Delta & \quad \text{DIBAL}
\end{align*}
\]

When ethyl iodoacetate, racemic 1-octyn-3-ol, norbornene (four equivalents), sodium acetate and catalytic amounts of Pd(PPh_3)_4 were heated at 80°C in anisole, none of the desired product was isolated. Instead, many products were observed upon analysis by TLC. Conducting the same reaction at a lower temperature, or using ethyl bromoacetate instead of the corresponding iodo compound, had no impact on the nature of the reaction.
Thus, the catalytic palladium approaches outlined above were not successful in the synthesis of $\text{PGH}_2$ analogs. The reason for the lack of success in the desired addition reaction is not apparent.
EXPERIMENTAL SECTION

Equipment

Proton NMR spectra were recorded on either an EM-360 or a Nicolet NT-300 spectrometer. $^{13}$C NMR spectra were recorded on either a JEOL-FX900 or Nicolet NT-300 (operating at 75 MHz for carbon nuclei) spectrometer. Infrared spectra were recorded on a Beckman-42050 spectrophotometer. Mass spectral data were obtained on an MS-50 high resolution mass spectrometer.

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. Anisole was distilled over sodium under reduced pressure. Acetone was distilled over potassium carbonate and used immediately. N,N-Dimethylformamide (DMF) was distilled over calcium hydride. Methanol was distilled over magnesium methoxide. 7-Oxabicyclo[2.2.1]heptene was prepared using a literature procedure. Tetrakis(triphenylphosphine)palladium(0) $[\text{Pd(PPh}_3\text{)}_4]$ was prepared by the method of Coulson. Compound 78, $\text{p}$-iodo and $\text{p}$-bromophenoxyacetic-acid methyl esters were made by methods reported in the literature.

Preparation of methyl 3-(chloromethyl)phenoxyacetate 68

Compound 68 was prepared in three steps starting from $\text{m}$-hydroxybenzaldehyde (Aldrich). To a stirred solution of $\text{m}$-hydroxybenzaldehyde (1.32 g, 10 mmol) and potassium
carbonate (1.40 g, 10 mmol) in acetone was added methyl bromoacetate (1.52 g, 10 mmol) under nitrogen. The mixture was refluxed for 12 h, by which time the reaction mixture turned lighter and potassium bromide was observed to precipitate. After having cooled, the mixture was poured into water and extracted with ether. The extracts were then dried over sodium sulfate and concentrated on a rotary evaporator to yield the crude product. Vacuum distillation (0.2 mm Hg at 125°C) yielded the pure product 69 (1.7 g, 88% yield) as a colorless oil which turns yellow on exposure to air: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.70 (3 H, s, OCH\(_3\)), 4.60 (2 H, s, OCH\(_2\)CO\(_2\)), 7.20-7.70 (4 H, m, aryl), 9.90 (1 H, s, CHO); IR (neat) 2700 (HC=O), 1760 (MeOc=O) cm\(^{-1}\); MS, m/z 194.05739; calcd for C\(_{10}\)H\(_{10}\)O\(_4\), 194.05791.

To a flame dried, round bottom flask was added sodium borohydride (0.52 g, 13.6 mmol) and methanol (20 mL). The mixture was stirred at room temperature for a few min and then cooled to 0°C. The formyl ester 3 (2.4 g, 12.4 mmol) dissolved in methanol (20 mL) was added to the sodium borohydride solution with stirring, while backflushing with nitrogen. After 30 min, another portion of sodium borohydride (0.24 g, 6.2 mmol) was added. The reaction, as indicated by TLC, was complete within five min. The reaction mixture was then quenched at 0°C with dilute HCl and extracted with ether. The aqueous washings were extracted with ether and the
combined extracts were dried over sodium sulfate. Removal of the solvent under vacuum yielded the colorless, oily hydroxy ester 70 in almost quantitative yield (2.42 g). The virtually pure alcohol was used without further purification. $^1$H NMR (CDCl$_3$) $\delta$ 2.70 (1 H, br s, OH), 3.75 (3 H, s, OCH$_3$), 4.6 (4 H, s, ArCH$_2$ and OCH$_2$CO$_2$), 6.7-7.6 (4 H, m, aryl); IR (thin film) 3700 (OH), 1750 (C=O) cm$^{-1}$; MS, m/z 196.07306; calcd for C$_{10}$H$_{12}$O$_4$, 196.07356.

To a stirred mixture of this alcohol 70 (2.4 g, 12.3 mmol) and s-collidine (1.64 g, 13.5 mmol) under nitrogen was added lithium chloride (0.57 g, 13.5 mmol) dissolved in a minimum amount of dry DMF. On cooling to 0°C, a suspension was formed which was treated with methanesulfonyl chloride (1.54 g, 13.5 mmol). Stirring was continued for 2 h and the reaction mixture was then poured into ice. The aqueous layer was extracted with cold 1:1 ether/pentane and the combined extracts were washed with saturated copper nitrate solution until no further intensification of the blue copper solution occurred, indicating complete removal of s-collidine. The organic extracts were dried over sodium sulfate and concentrated to yield the crude halide 68. Further purification by column chromatography using 2:1 hexanes/ethyl acetate as eluent yielded 2.15 g (82%) of pure 68: $R_f$ 0.51, 2:1 hexanes/ethyl acetate; $^1$H NMR (CDCl$_3$) $\delta$ 3.82 (3 H, s, OCH$_3$), 4.62 (2 H, s, ClCH$_2$), 4.70 (2 H, s, OCH$_2$CO$_2$), 6.80-7.42 (4 H,
Resolution of 1-octyn-3-ol

1-Octyn-3-ol was resolved via crystallization of the ammonium salt of its half phthalate ester prepared as follows. Phthalic anhydride (74 g, 0.5 mole) was added to 1-octyn-3-ol (63.1 g, 0.5 mole) (Aldrich) and was heated with stirring at 165-170°C for 21 h under nitrogen. After cooling to 60°C, benzene (100 ml) was added. After the addition of 200 ml of hexanes, the mixture was stirred at 0°C for 4 h. Filtration yielded a white solid which was washed with hexanes. The solid was dried under reduced pressure. The half phthalate ester 71 (75 g, 0.275 mole) with a melting point of 70-71°C was obtained in 55% yield.

After dissolving the solid (75 g) in benzene (100 mL) at 60°C, hexanes (200 mL) was added to the solution. The solution was then stirred at 0°C for 3 h. After filtration, the white solid was dried under reduced pressure at 50°C for 3 h. The half phthalate ester was obtained as a white solid in 92% yield (69.2 g), mp 71-73°C.

This solid was again crystallized from benzene (110 mL) and hexanes (180 mL) to afford the half phthalate ester in 63% yield (44 g), mp 76-77°C (lit. mp 76-77°C).

The half phthalate ester was then converted to its amine salt as follows. (S)-(−)-α-Phenethyl amine (19.4 g, 0.16
mole) (Aldrich) was added dropwise via a syringe to a suspension of the half phthalate ester 71 (44 g, 0.16 mole) in CH₂Cl₂ (36 mL) under reflux and stirred for 30 min. A small amount of amine salt as a seed was added to the solution, after cooling. The reaction mixture was then allowed to stand in a freezer overnight and the crystals formed were collected, washed with acetone, and dried under reduced pressure at room temperature. The first crop (20 g, 31% yield) was then added to CH₂Cl₂ (45 mL) and the mixture was refluxed with stirring for 30 min. After complete dissolution of the solid, the clear solution was allowed to cool to room temperature. A few seed crystals were added and the solution was kept in a freezer overnight. The crystals were filtered, washed with CH₂Cl₂ (10 mL), and dried under vacuum at room temperature (12.42 g, 62% yield; mp 133-136°C). Two further recrystallizations furnished material with a melting point of 135-136°C (lit. 63 mp 133.5-135°C).

The optical purity of the amine salt could be monitored by ¹H NMR spectral analysis. The acetylenic hydrogen doublets for the two diastereomers appear at δ 2.48 (S-S) and δ 2.52 (R-S). Only the former peak was present in the ¹H NMR spectrum of the above thrice recrystallized salt.

(S)-1-Octyn-3-ol (72) was isolated as follows. The (S-S)-amine salt (9.58 g, mp 135-136°C) was added to 10% NaOH (55 mL) and the solution stirred at 60°C for 1 h. After
cooling to room temperature, the solution was extracted three
times with CH$_2$Cl$_2$ (100 mL). The combined extracts were
successively washed with 1N HCl, concentrated HCl (7 mL in 20
mL of water), brine, saturated sodium bicarbonate, and brine,
and dried over sodium sulfate. After removal of the solvent,
the residue was distilled to give pure (S)-1-octyn-3-ol (2.69
\( g \)) as a colorless oil in 88% yield: bp 88-89°C, -20 mm Hg;
\([\alpha]_D^{20} \text{CHCl}_3 = -6.79^\circ \) (literature\(^\ddagger\) \([\alpha]_D^{20} = -5.5^\circ\) and \([\alpha]_D^{20} = 6.5^\circ\).

The \( ^1H \) NMR spectrum of (S)-1-octyn-3-ol (8 mg) with
Eu(hfbc)$_3$ (14 mg) in 0.3 mL of CDCl$_3$ indicated a broadened
singlet at \( \delta 7.81 \) corresponding to the hydrogen alpha to the
hydroxy group. A singlet corresponding to the R-isomer
(usually about 0.3 ppm downfield relative to the S-isomer) was
not observed. Hence, the alcohol obtained is "100% optically
pure.

Synthesis of compounds 65, 67, 73, 74, 77, 79 and 80
The procedure for the synthesis of compound 65 is
representative of that used to prepare all of the above
compounds. To a round bottom flask with a sidearm equipped
with a reflux condenser was introduced, under nitrogen,
Pd(PPh$_3$)$_4$ (45 mg, 0.039 mmol) and anhydrous sodium acetate (41
mg, 0.5 mmol). A solution of distilled benzyl chloride (64
mg, 0.5 mmol), racemic 1-octyn-3-ol (63 mg, 0.5 mmol), and
norbornene (188 mg, 2 mmol) (Aldrich) in degassed anisole (1
ml) was added to the flask. The mixture was heated at 70°C for approximately 24 h. After cooling, dilute sulfuric acid was added and the solution was extracted with diethyl ether. After drying the ether extracts over anhydrous sodium sulfate, the solvents were removed under vacuum and the residue chromatographed on a silica gel column using hexanes/ethyl acetate mixtures as the eluent. The expected product 65 was isolated in 81% yield (126 mg): $R_f$ 0.48, 5:1 hexanes/ethyl acetate; $^1$H NMR (CDCl$_3$) $\delta$ 0.88-2.20 (19 H, m, aliphatic and OH), 2.85 (1 H, d, $J = 13$ Hz, HC(2)), 3.12 (2 H, m, ArCH$_2$), 4.45 (1 H, m, CHOH), 7.30 (5 H, m, aryl); $^{13}$C NMR (CDCl$_3$) $\delta$ 142.35, 128.95, 128.24, 125.64 (all aryl), 86.80 and 83.75 (C=O), 62.68 (CHOH), 46.63, 45.00, 39.80, 39.08, 38.24, 33.8, 31.54, 29.91, 28.48, 24.97, 22.63, 14.05 (all aliphatic); IR (neat) 3360 (OH) cm$^{-1}$; MS, m/z 310.2287; calcd for C$_{22}$H$_{30}$O, 310.2282.

Compound 67: 53% yield; $R_f$ 0.48, 5:1 hexanes/ethyl acetate; $^1$H NMR (CDCl$_3$) $\delta$ 1.05-2.21 (17 H, m, aliphatic and OH), 2.88 (1 H, d, $J = 14$ Hz, HC(2)), 3.35 (2 H, m, ArCH$_2$), 4.68 (1 H, m, CHOH), 6.38 (2 H, br s, vinylic), 7.55 (5 H, m, aryl). In addition, the following signals were seen (possibly from the accompanying impurity): $\delta$ 2.5 (m), 2.76 (m), 5.2 (br m), 5.6 (s); $^{13}$C NMR (CDCl$_3$) $\delta$ 141.64, 138.53, 135.10, 128.89, 128.21, 125.72 (all aryl), 87.02 and 83.66 (C=O), 62.82 (CHOH), 49.95, 48.50, 47.20, 45.22, 43.61, 42.61, 39.43,
38.24, 34.45, 32.50, 31.50, 24.94, 22.54, 13.61 (aliphatic) (the extraneous carbon absorptions are from the accompanying impurity); IR (neat) 3350 (OH) cm\(^{-1}\); MS, m/z 290.2040; calcd for C\(_{22}\)H\(_{26}\)O (M-18), 290.2039.

**Compound 73**: 58% yield; \(R_f\) 0.33, 3:1 hexanes/ethyl acetate; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.85-1.75 (18 H, m, aliphatic and OH), 1.86 (1 H, br t, \(J\) = 9.6 Hz, endo HC(3)), 1.97 (1 H, m, HC(4)), 2.29-2.35 (1 H, m, HC(1)), 2.42 (1 H, dd, \(J\) = 10.6 Hz, \(J\) = 10.5 Hz, diastereotopic ArCH), 2.62 (1 H, d, \(J\) = 10.7 Hz, endo HC(2)), 2.86 (1 H, br dd, \(J\) = 14.4 Hz, \(J\) = 5.1 Hz, diastereotopic ArCH), 3.85 (3 H, s, OCH\(_3\)), 4.29-4.41 (1 H, m, CHOH), 4.70 (2 H, s, OCH\(_2\)CO\(_2\)), 6.72 and 6.73 (1 H, d, \(J\) = 7.8 Hz, aryl, diastereomers), 6.79 (1 H, s, aryl), 6.85 (1 H, d, \(J\) = 7.5 Hz, aryl), 7.20 (1 H, t, \(J\) = 7.7 Hz, aryl). Irradiation of the proton giving rise to the peak at \(\delta\) 2.86 causes the peak at \(\delta\) 1.86 to collapse to a broad triplet (\(J\) = 6 Hz) and the peak at \(\delta\) 2.42 collapses to a doublet (\(J\) = 8.3 Hz).

Irradiation of the proton giving rise to the peak at \(\delta\) 2.62 causes the peak at \(\delta\) 1.86 to collapse to a simplified multiplet. Irradiation of the proton giving rise to the peak at \(\delta\) 2.42 causes the peak at \(\delta\) 2.86 to collapse to a singlet and the peak at \(\delta\) 1.86 remains the same. Irradiation of the proton giving rise to the multiplet at \(\delta\) 2.29-2.35 causes no change except for a sharpening of the peak at \(\delta\) 1.86.

Irradiation of the proton giving rise to the multiplet at \(\delta\)
1.97 causes the peak at δ 2.62 to collapse to a singlet; the peaks at δ 2.86 and 2.42 are now doublets with J = 13.7 Hz and 14.5 Hz respectively, and the multiplet at δ 1.97 is a sharp singlet. $^{13}$C NMR (CDCl$_3$) δ 169.49 (C=O), 157.72, 144.19, 129.15, 122.52, 115.66, 111.39 (all aryl), 86.57 and 83.79 (C C), 65.32 (OCH$_2$), 62.79 (CHOH), 52.22 (OCH$_3$), 46.42, 44.93, 39.85, 39.04, 38.95, 38.17, 33.77, 31.47, 29.82, 28.40, 24.97, 22.58, 14.00 (aliphatic); IR (neat) 3500 (OH), 1760 (C=O) cm$^{-1}$; MS, m/z 398.2457; calcd for C$_{25}$H$_{35}$O$_4$, 398.24644.

Compound 74: 37% yield; $R_f$ 0.33, 3:1 hexanes/ethyl acetate; $^1$H NMR (CDCl$_3$) 0.85-1.86 (13 H, m, aliphatic and OH), 2.43-2.48 (2 H, m, HC(4) and diastereotopic ArCH), 2.53 (1 H, d, J = 9.0 Hz, HC(2)), 2.91 (1 H, br s, HC(1)), 3.10 (1 H, dd, J = 13 Hz, J = 5.1 Hz, diastereotopic ArCH), 3.83 (3 H, s, OCH$_3$), 4.38 (1 H, m, CHOHOH), 4.66 (2 H, s, OCH$_2$CO$_2$), 6.07 (2 H, br s, vinylic), 6.73 (1 H, dd, J = 5.3 Hz, J = 2 Hz, aryl), 6.79 (1 H, s, aryl), 7.24 (1 H, d, J = 6 Hz, aryl), 7.24 (1 H, dd, J = 7.0 Hz, aryl); $^{13}$C (NMR) δ 169.50 (C=O), 157.77, 145.97, 138.50, 135.65, 129.25, 122.52 (all aryl), 115.68, 111.52 (C=C), 87.19 and 83.69 (C C), 65.33 (OCH$_2$CO$_2$), 62.76 (CHOH), 52.21 (OCH$_3$), 50.24, 45.26, 43.61, 42.53, 39.40, 38.24 and 38.17 (diastereomeric), 34.35, 31.47, 24.96, 22.60, 14.00 (all aliphatic); IR (neat) 3420 (OH), 1750 (C=O) cm$^{-1}$; MS m/z 396.2296; calcd for C$_{25}$H$_{35}$O$_4$, 396.2301.
Compound 75: 45% yield; Rf 0.55, 1:1 hexanes/ethyl acetate; \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 0.86-1.80 (16 H, m, aliphatic and OH), 2.06-2.19 (1 H, m, endo HC(3)), 2.57 and 2.62 (1 H, dd, \( \overline{J} = 10.8 \text{ Hz}, \overline{J} = 3 \text{ Hz}, \) diastereotopic ArCH), 2.86 (1 H, d, \( \overline{J} = 8.4 \text{ Hz}, \) endo HC(2)), 2.83-2.89 (1 H, m, diastereotopic ArCH, buried under doublet of HC(2)), 3.81 (3 H, s, OCH\(_3\)), 4.26 (1 H, d, \( \overline{J} = 5.6 \text{ Hz}, \) HC(4)), 4.36-4.38 (1 H, m, CHOH), 4.55 (1 H, d, \( \overline{J} = 4.2 \text{ Hz}, \) HC(1)), 4.64 (2 H, s, OCH\(_2\)CO\(_2\)), 6.70 and 6.72 (1 H, d, \( \overline{J} = 8.1 \text{ Hz}, \) aryl, diastereomers), 6.79 (1 H, s, aryl), 7.22 (1 H, t, \( \overline{J} = 8.0 \text{ Hz}, \) aryl). Irradiation of the proton giving rise to the peak at \( \delta \) 2.86 causes the multiplet at \( \delta \) 2.06-2.19 to collapse to a doublet (\( \overline{J} = 9.9 \text{ Hz} \)). Irradiation of the proton giving rise to the peaks at \( \delta \) 2.57 and \( \delta \) 2.62 causes the multiplet at \( \delta \) 2.83-2.89 to collapse to a simplified multiplet; the multiplet at \( \delta \) 2.06-2.19 also collapses to a simplified multiplet. Irradiation of the proton giving rise to the peak at \( \delta \) 2.06-2.19 causes changes in multiplicity at \( \delta \) 2.57-2.62; \(^{13}C \) NMR (CDCl\(_3\)) \( \delta \) 169.47 (C=O), 157.94, 143.29, 129.51, 122.61, 115.70, 111.87 (all aryl), 84.65 and 84.34 (C C), 82.95 and 79.06 (C\(_1\) and C\(_4\)), 79.00 (C\(_1\) or C\(_4\), diastereomeric), 65.37 (OCH\(_2\)), 62.72 (CHOH), 52.24 (OCH\(_3\)), 48.24, 40.30, 38.08, 37.69, 31.48, 29.31, 29.18, 24.94, 22.58, 14.00 (all aliphatic); IR (neat) 3420 (OH), 1760 (C=O) cm\(^{-1}\); MS, m/z 400.22409; calcd for C\(_{24}\)H\(_{32}\)O\(_5\), 400.22408.
Compound 76 and its diastereomer were also isolated from the above reaction (for numbering see Fig. 5): \( R_f \) 0.33, 1:1 hexanes/ethyl acetate; \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 0.83-1.78 (20 H, m, aliphatic and OH), 2.00 (1 H, br t, \( J = 8.8 \) Hz, endo HC(3)), 2.14 (1 H, br t, \( J = 9.1 \) Hz, endo HC(2')), 2.15-2.28 (1 H, m, endo HC(3'), buried under the triplet at \( \delta \) 2.14), 2.39 (1 H, br t, \( J = 12.5 \) Hz, ArCH), 2.68 (1 H, br d, \( J = 12.8 \) Hz, ArCH), 2.80 (1 H, d, \( J = 8.3 \) Hz, endo HC(2)), 3.79 (3 H, s, OCH\(_3\)), 4.18 (1 H, m, HC(1)), 4.41 (1 H, m, CHO\(_2\)), 4.49-4.56 (3 H, m, HC(1', 4' and 4)), 4.63 (2 H, s, OCH\(_2\)CO\(_2\)), 6.70-6.75 (1 H, m, aryl), 6.80-6.88 (2 H, m, aryl), 7.19 (1 H, t, \( J = 7.6 \) Hz, aryl); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 169.66 (C=O), 158.04, 143.77, 129.50, 122.72, 115.63, 112.17 (all aryl), 85.68 and 83.95 (C=C), 82.82, 80.59, 80.16, 79.32, 65.48, 62.86, 52.31, 49.72, 49.17, 48.91, 41.93, 38.27, 35.74, 31.63, 31.57, 30.82, 30.05, 29.73, 25.16, 25.07, 22.67 and 14.10 (all aliphatic); IR (neat) 3480 (OH), 1760 (C=O) cm\(^{-1}\); MS, m/z 496.28382; calcd for C\(_{30}\)H\(_{40}\)O\(_6\), 496.28250.

Synthesis of compounds 59, 60 and 61

The procedure for the hydrolysis of compound 73 to compound 60 is representative. Hydroxy ester 73 (55.7 mg, 0.14 mmol) was refluxed for 2 h in 5 mL of methanol and 1 mL of 2M KOH. After cooling, the reaction was diluted with ether, acidified with 25 mL of 2N sulfuric acid, washed with 50 mL of brine, and dried over sodium sulfate. Removal of the
solvent under vacuum and purification of the residue by chromatography using 20:20:1 hexanes/ethyl acetate/glacial acetic acid yielded the pure acid 60 as a colorless oil; 95% yield; $R_f$ 0.31, 20:20:1 hexanes/ethyl acetate/glacial acetic acid; $^1$H NMR (CDCl$_3$) $\delta$ 0.86-1.93 (18 H, m, alky1), 1.98 (1 H, m, endo HC(3)), 2.1 (1 H, s, OH), 2.34 (1 H, m, HC(1)), 2.46 (1 H, dd, $J = 10.2$ Hz, diastereotopic ArCH), 2.62 (1 H, d, $J = 8.0$ Hz, endo HC(2)), 2.88 (1 H, br d, $J = 9.3$ Hz, diastereotopic ArCH), 4.36 (1 H, m, CHOH), 4.66 (2 H, s, OCH$_2$CO$_2$), 4.95 (1 H, s, CO$_2$H), 6.73 (1 H, d, $J = 7.6$ Hz, aryl), 6.79 (1 H, s, aryl), 6.85 (1 H, d, $J = 7.5$ Hz, aryl), 7.21 (1 H, t, $J = 7.8$ Hz, aryl); $^{13}$C NMR (CDCl$_3$) $\delta$ 157.53, 144.30, 129.28, 122.68, 115.66 and 115.59 (diastereomeric), 111.60 (all aryl), 86.93 and 83.50 (C C), 62.98 (CHOH), 46.42, 46.36, 45.02, 40.16, 39.13 and 39.06 (broadened, diastereomeric), 38.98, 33.90, 31.50, 29.92, 28.42, 24.98, 22.64, 14.04; IR (neat) 3600-2700 (OH, CO$_2$H), 1740 (C=O) cm$^{-1}$; MS, m/z 384.23007; calcd for C$_{24}$H$_{32}$O$_4$: 384.23000. Anal. Calcd. for C$_{24}$H$_{32}$O$_4$: C, 75.02; H, 8.39. Found: C, 75.03; H, 8.30.

Compound 61: 88% yield; $R_f$ 0.30, 20:20:1 hexanes/ethyl acetate/acetic acid; $^1$H NMR (CDCl$_3$) $\delta$ 0.83-1.89 (15 H, m, aliphatic and OH), 2.49-2.55 (3 H, m, diastereotopic ArCH and norbornyl HC(2) and HC(4)), 2.91 (1 H, s, HC(1)), 3.10 (1 H, br d, $J = 15$ Hz, ArCH), 4.38 (1 H, m, CHOH), 4.66 (2 H, s, OCH$_2$CO$_2$), 5.36 (1 H, br s, CO$_2$H), 6.06 (2 H, br s, vinylic),
6.75 (1 H, br d, _J = 8.7 Hz, aryl), 6.79 (1 H, s, aryl), 6.85 (1 H, d, _J = 7.6 Hz, aryl), 7.21 (1 H, t, _J = 7.8 Hz, aryl); 
\textsuperscript{13}C NMR (CDCl\textsubscript{3}) \delta 157.57, 144.05, 138.56, 135.66, 129.32, 122.62, 115.64 (all aryl), 115.56 and 111.76 (C=C), 87.53 and 83.38 (C,C), 65.42 (OCH\textsubscript{2}), 63.00 (CHOH), 50.30, 45.67 and 45.62 (diastereomeric), 43.70, 42.53, 42.44, 39.40, 38.13 and 38.08 (diastereomeric), 34.41, 31.47, 24.96, 22.61, 14.01 (all aliphatic); IR (neat) 3500-2700 (OH, CO\textsubscript{2}H), 1735 (C=O) cm\textsuperscript{-1}; MS, m/z 382.21479, calcd for C\textsubscript{24}H\textsubscript{30}O\textsubscript{4}, 382.21442. Anal. Calcd for C\textsubscript{24}H\textsubscript{30}O\textsubscript{4}: C, 75.40; H, 7.90. Found: C, 75.19; H, 7.85. 

Compound \textit{59} was prepared by the same basic procedure described above except that the reaction was run at room temperature for two days: 98% yield; \textit{R}_f 0.31, 20:20:1 hexanes/ethyl acetate/glacial acetic acid; \textit{H} NMR (CDCl\textsubscript{3}) \delta 0.86-1.80 (16 H, m, aliphatic and OH), 2.06-2.20 (1 H, m, endo HC(3)), 2.62 (1 H, t, _J = 13.8 Hz, diastereotopic ArCH), 2.84-2.90 (2 H, m, diastereotopic ArCH, buried under the doublet of HC(2)), 4.28 (2 H, d, _J = 4.2 Hz, HC(4)), 4.36 (1 H, br t, _J = 6.3 Hz, CHOH), 4.57 (1 H, d, _J = 3.9 Hz, HC(1)), 4.66 (3 H, s, broadened at the base, OCH\textsubscript{2}CO\textsubscript{2} and CO\textsubscript{2}H), 6.76 (1 H, d, _J = 7.8 Hz, aryl), 6.80 (1 H, s, aryl), 6.86 (1 H, d, _J = 7.8 Hz, aryl), 7.22 (1 H, t, _J = 8.1 Hz, aryl); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \delta 157.75, 143.38, 129.63, 122.80, 115.78 and 115.72 (diastereomeric), 112.26 (all aryl), 84.69 and 84.50 (C,C), 83.10 and 79.39 (C\textsubscript{1} and C\textsubscript{4}), 65.17 (OCH\textsubscript{2}), 62.90 (CHOH),
48.23, 40.43, 38.10, 37.72, 31.54, 29.34, 29.28, 14.00 (all aliphatic); IR (neat) 3600-2700 (HO, CO₂H), 1740 (C=O) cm⁻¹; MS, m/z 386.2093, calcd for C₂₃H₃₀O₅, 386.2099. Anal. Calcd for C₂₃H₃₀O₅: C, 71.46; H, 7.76. Found: C, 69.43; H, 7.84.

Compound 2Z*: 11% yield; Rᵢ 0.33, 4:1 hexanes/ethyl acetate; ¹H NMR (CDCl₃) δ 0.85-1.67 (16 H, m, aliphatic), 2.00 (1 H, br d, J = 11.1 Hz, HC(7), syn to the two side chains), 2.41 (1 H, br s, HC(4)), 2.51 (1 H, d, J = 1.5 Hz, HC(1)), 2.82 (1 H, d, J = 8.7 Hz, HC(3) endo), 2.92 (1 H, d, J = 8.7 Hz, HC(2) endo), 3.79 (3 H, s, OCH₃), 3.81 (1 H, s, OH), 3.97 (1 H, m, CHOH), 4.61 (2 H, s, OCH₂CO₂), 6.82 (2 H, ABd, J = 8.5 Hz, OR', 7.14 (2 H, ABd, J = 8.5 Hz); IR (neat) 3450 (OH), 1750 (C=O) cm⁻¹; MS, m/z calcd for C₂₄H₃₂O₄, 384.2285, found 384.2293.

Compound 79: 6% yield; Rᵢ 0.35, 3:1 hexanes/ethyl acetate; ¹H NMR (CDCl₃) δ 0.84-1.63 (17 H, m, aliphatic and OH), 1.97-2.02 (1 H, m, HC(7), syn to the two side chains), 2.41 (1 H, br s, HC(4)), 2.55 (1 H, br s, HC(1)), 2.61 (2 H, AB system, J = 9 Hz, HC(2) and HC(3) endo), 3.81 (3 H, s, OCH₃), 3.95 (1 H, m, CHOH), 4.61 (2 H, s, OCH₂CO₂), 6.70 (1 H, d, J = 1 Hz, OR'), 6.77 (1 H, s, OR'), 6.84 (1 H, d, J = 1 Hz, OR').


\[ \text{Compound 80: 8\% yield; } R_f 0.34, \text{ 5:1 hexanes/ethyl acetate; } \]  
\[ ^1H \text{ NMR (CDCl}_3) \delta 0.85-1.62 (17 H, m, aliphatic and OH), 2.01 (1 H, d, } J = 10.5 \text{ Hz, aliphatic), 2.28 (3 H, s, OCOCH}_3), 2.41 (1 H, br s, HC(4)), 2.57 (1 H, br s, HC(1)), 2.85 (1 H, ABd, } J = 9 \text{ Hz, HC(2) endo), 2.98 (1 H, ABd, } J = 9 \text{ Hz, HC(3) endo), 3.96 (1 H, m, CHOCH), 6.96 (2 H, d, } J = 8.4 \text{ Hz, } \]  
\[ \text{7.20 (2 H, d, } J = 8.4 \text{ Hz); IR (neat) 3420 (OH), 1758 (C=O) cm}^{-1}; \text{ MS, m/z calcd for } C_{23}H_{30}O_3, 354.2195, \text{ found 354.2195.} \]
REFERENCES


31. Larock, R. C.; Leach, D. R. Unpublished results, Department of Chemistry, Iowa State University.


PART II. ORGANOPALLADIUM APPROACHES TO HETEROCYCLES
Because of the very potent and diverse biological activity exhibited by indole (1) and its various derivatives, this heterocyclic system has been the target of considerable attention in chemistry, biology and medicine.¹ Indole derivatives are essential to both plants and animals. Skatole [3-methylindole (2)], which can be isolated from various sources, is reported to have antidiuretic² and tuberculostatic activity.³ Tryptophan (3), a naturally occurring amino acid is known to inhibit the growth of tuberculosis.⁴,⁵ Indole acetic acid (4) is a major plant growth hormone⁶ and indomethacin (5) has been reported to have antiinflammatory, antipyretic and analgesic activity.⁷

There have been many reported synthetic approaches to indoles. The most versatile among these are the Fischer, Bischler, Madelung, Reissert, Nenitzescu and Gassman procedures and their various modifications.¹ᵃ,ᵇ,⁸ It is beyond the scope of this discussion to explain in detail the aforementioned synthetic approaches. However, a discussion of pertinent organometallic approaches to the indole ring system will be covered in detail.

One of the most recent approaches to indoles which involved an organometallic reagent was reported by Wender and White.⁹ This was based on the work of Gilman et al.¹⁰ It involves the successive treatment of 2-bromoaniline (6) with
methyllithium (two equivalents), pivaloyl chloride (one equivalent), and t-butyllithium (two equivalents) to provide an organodimetallic intermediate which is subsequently reacted with 2-chlorocyclohexanone, followed by base treatment, to provide the indole 7 in good yield (Scheme 1). The advantage of this methodology is that all the operations can be performed in one pot using commercially available 2-bromoaniline.

Studies on free radical mediated carbon-carbon bond forming reactions have intensified enormously in recent years. Perhaps nowhere has the use of free radical intermediates been better exploited than in the synthesis of ring compounds.11 The toleration of many functional groups in this reaction
makes it very versatile in organic synthesis. A typical reaction leading to a dihydroindole system is shown below (eq. 1). In this reaction an aryl radical, generated from the
corresponding bromide by tri-n-butyltinhydride, cyclizes and the resulting \( \beta \)-phenylethio radical fragments, yielding the dihydroindole 8 and the phenylthiyl radical.\(^{12}\)

The versatility of radical reactions would be enhanced still further if practical procedures could be made available to introduce functionality during the cyclization by use of appropriate radical trapping reagents. This general problem has been addressed recently\(^{13}\) and the use of cobalt(1) reagents (from cobaloximes and vitamin B\(_{12}\)) in the synthesis of ring fused heterocycles by intramolecular cyclization from the corresponding aryl halides has been illustrated. It was found that \( N\)-allyl,\( N\)-methyl iodoaniline (9) gave 1,3-dimethylindole (10) in one step (32\% yield) on treatment with cobalt complex 11 and sodium amalgam (eq. 2).

![Chemical structure](image1)

(eq. 2)

![Chemical structure](image2)

(eq. 2)
The use of organotransition metal complexes in the synthesis of heterocyclic compounds has become prevalent in recent years. Zerovalent nickel complexes have been used to cyclize 2-chloro-N-methyl-N-allylaniline (12) to 1,3-dimethylindole (10) (eq. 3). The suggested reaction mechanism is demonstrated in Scheme 2. Thus, oxidative addition of the aryl halide 12 to the Ni(0) complex gives rise to the

Scheme 2
aryl nickel complex 13, which upon addition to the double bond generates a σ-alkynickel complex. Hydridonickel elimination, followed by double bond migration, yields the heterocycle 10. Oxindole derivatives were also synthesized using a similar procedure (eq. 4).\textsuperscript{16,17}

![Chemical structure](image)

Rodriguez and Canoira\textsuperscript{18} similarly demonstrated the application of zerovalent nickel complexes in the synthesis of indoles. However, the poor yields of the desired heterocycles and the formation of side products (mainly uncyclized, reduced starting material) make this approach unattractive.

Castro and co-workers\textsuperscript{19} have reported that the addition of a cuprous acetylide to 2-iodoaniline produces indoles if the reaction is performed in N,N-dimethylformamide, but if pyridine is used as the solvent, a mixture of the acetylene substitution product and the indole are obtained (eq. 5).

Heterocyclic synthesis via organopalladium intermediates has been explored by several workers. Two types of palladium reagents have been used for this purpose, palladium(II) and palladium(0). Pd(II) salts involving transmetallation reactions will be discussed first. Thus, thallation and
subsequent palladium-promoted olefination of acetanilide provides a novel route to nitrogen heterocycles (Scheme 3).\textsuperscript{20}

Hegedus et al.\textsuperscript{21} have cyclized 2-allylanilines using a palladium(II) salt to prepare indoles (eq. 6). This is a
Scheme 3

A typical example of a palladium-mediated intramolecular amination of an olefin. A general synthetic approach to the pyrrolo-indoloquinone ring system, common to the mitomycin antibiotics, was recently developed by Weider et al. (eq. 7).²²

Similar reactions have been reported to produce polycyclic products cleanly.²³,²⁴ Thus, σ-alkylpalladium(II) complexes,
arising from intramolecular amine attack and lacking a 
\( \beta \)-hydrogen, insert an olefin and provide a facile 
difunctionalization of olefins in a one-pot procedure that is 
potentially catalytic in palladium (eq. 8).

Palladium(0)-catalyzed cyclizations leading to indoles 
have been very widely studied. Thus, the intramolecular
"Heck" arylation\textsuperscript{25} of 2-halo-N-allylanilines to 3-methylindole was examined by Odle et al.\textsuperscript{26}; Hegedus et al.\textsuperscript{27} (eq. 9). This procedure works well for systems in which the side chain olefin is conjugated to a carbonyl group. Thus, 2-halo-N-acryloyl or cinnamoylanilines are converted to oxindoles using both Pd(O)\textsuperscript{28-30} and Ni(O)\textsuperscript{15} catalysts (eqs. 10, 11).
Intramolecular cyclizations of enaminones involving aryl palladium complexes was studied by Iida et al. The cyclization proceeded smoothly to afford carbazoles using both catalytic and stoichiometric palladium(0) complexes. A typical reaction is shown below (eq. 12).

\[
\begin{align*}
\text{Br} & \quad \text{Pd(OAc)}_2(\text{PPh}_3)_2 \\ \text{N} & \quad \text{NaHCO}_3 \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]

Though the intramolecular addition of aryl palladium compounds to olefinic bonds leading to heterocycles looks attractive, it has a few drawbacks. The product yields in most cases are only fair and the temperatures used to induce such additions are rather high, often 110 to 130°C. Furthermore, a number of substrates fail to cyclize under those reaction conditions. It should be noted, however, that aryl-palladium intermediates fare better than their arylcobalt or arylnickel counterparts.

The focus of our research was to reexamine the intramolecular Heck reaction and to develop feasible reaction conditions which would make it more versatile in organic synthesis, particularly in the synthesis of heterocycles and carbocycles. It was thought that a minor variation of the
same methodology utilizing milder temperatures would be highly desirable. The heterocycles we set out to prepare using this approach were indoles (including oxindoles), quinolines and isoquinolines.

Recently, Jeffrey$^{32,33}$ reported palladium-catalyzed addition reactions done under solid-liquid phase transfer conditions. The reaction consists of treating a vinyl or an aryl iodide and an olefin in the presence of catalytic amounts of palladium acetate (1 or 2 mole %), a base (potassium carbonate or sodium bicarbonate) and tetra-$n$-butylammonium chloride (phase transfer reagent) in $N,N$-dimethylformamide (DMF) at or near room temperature. A typical reaction done under these conditions is represented below (eq. 13). The high yields of products obtained in these reactions, in addition to the mild temperature employed, make this procedure very attractive for synthetic purposes. Employing the same solid-liquid phase transfer conditions for intramolecular cyclizations, in theory, should yield cyclized products under very mild conditions. Also, this procedure might prove

$$\text{PhI} + 2 \text{H}_2\text{C}=\text{CHCO}_2\text{CH}_3 \xrightarrow{2\% \text{Pd(OAc)}_2, \text{NaHCO}_3, \text{n-Bu}_4\text{NCl, DMF, RT}} \text{Ph} \begin{array}{c} \text{C}=	ext{C} \\ \text{CO}_2\text{CH}_3 \end{array} \quad 97\%$$

(eq. 13)
effective in cases where cyclizations were not achieved previously. 26

Results and discussion

The following compounds 9, 14a-b, 15-21 were considered for cyclization. Compounds 14a-b, 16, 18 and 22 were prepared
by methods reported in the literature. This involves the treatment of the ortho-haloaniline with lithium diisopropylamide (LDA) and quenching with the appropriate alkenyl halide (eq. 14). Compounds 9 and 20 were made from 14a and 16 in the presence of LDA and methyl iodide (eq. 15). Compound 15 was obtained by treating compound 14a with excess acetic anhydride at room temperature for two days (eq. 16). Compounds 19 and 20 were obtained by treating ortho-iodoaniline with the corresponding acid halide in the presence of triethylamine in THF (eq. 17). Compound 21 was made by treating ortho-
iodoacetanilide with methyl-4-bromocrotonate in the presence of sodium hydride (1.4 equivalents) in THF at 0°C (eq. 18).

In order to obtain the best conditions for the intramolecular version of the Heck reaction leading to heterocycles, compounds 14a and 14b were chosen for model studies. Compound 14a, in particular, was subjected to a variety of reaction conditions. In a typical reaction, compound 14a was treated with palladium acetate (2 mole %), tetra-n-butylammonium chloride (one equivalent) and a base (2.5 equivalents) in DMF at room temperature. The reaction, which was monitored by TLC analysis, was usually complete within 1-3 days (see Table 1). The cyclized product, 3-methylindole (2, skatole) was usually obtained in good yields. A typical reaction is represented below (eq. 19). Table 1 below lists the variety of conditions that were employed for the cyclization reactions.
Table 1. Pd-Catalyzed Cyclizations of Compounds 14a and 14b Leading to 2 in DMF

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Number of days at room temperature</th>
<th>Number of days at 80°C</th>
<th>Base (2.5 equiv.)</th>
<th>Added salt (1 equiv.)</th>
<th>Pd-catalyst (2 mole)</th>
<th>Yield of 2 (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>14a</td>
<td>1</td>
<td>-</td>
<td>Na₂CO₃</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>14a</td>
<td>3</td>
<td>-</td>
<td>K₂CO₃</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>14a</td>
<td>3</td>
<td>-</td>
<td>NaHCO₃</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>14a</td>
<td>3</td>
<td>-</td>
<td>Li₂CO₃</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>14a</td>
<td>1</td>
<td>-</td>
<td>Et₃N</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>14a</td>
<td>2</td>
<td>-</td>
<td>Na₂CO₃</td>
<td>-</td>
<td>Pd(OAc)₂</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
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<td>-</td>
<td>Na₂CO₃</td>
<td>LiCl</td>
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<td>44</td>
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<tr>
<td>8</td>
<td>14a</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>14a</td>
<td>2</td>
<td>-</td>
<td>Et₃N</td>
<td>-</td>
<td>Pd(OAc)₂</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>14a</td>
<td>1</td>
<td>-</td>
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<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
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<td>-</td>
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<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>34</td>
</tr>
<tr>
<td>12</td>
<td>14a</td>
<td>2</td>
<td>-</td>
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<td>n-Bu₄NCl</td>
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<td>93</td>
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<tr>
<td>13</td>
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<tr>
<td>14</td>
<td>14a</td>
<td>2</td>
<td>-</td>
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<td>n-Bu₄NCl</td>
<td>PdCl₂</td>
<td>78</td>
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<tr>
<td>15</td>
<td>14a</td>
<td>1</td>
<td>-</td>
<td>Na₂CO₃</td>
<td>n-Bu₄NCl</td>
<td>Pd(DBA)₂</td>
<td>95</td>
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Table 1. Continued

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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Number of days at room temperature</th>
<th>Number of days at 80°C</th>
<th>Base (2.5 equiv.)</th>
<th>Added salt (1 equiv.)</th>
<th>Pd-catalyst (2 mole)</th>
<th>Yield of 2 (%)</th>
</tr>
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<tr>
<td>16</td>
<td>14b</td>
<td>1</td>
<td>2</td>
<td>Na₂CO₃</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>38</td>
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<tr>
<td>17</td>
<td>14b</td>
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<td>1</td>
<td>Et₃N</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>14b</td>
<td>2</td>
<td>1</td>
<td>NaOAc</td>
<td>n-Bu₄NCl</td>
<td>Pd(OAc)₂</td>
<td>6</td>
</tr>
</tbody>
</table>

*Reaction run in DMSO.*
The results can be summarized as follows. The cyclization is affected by the type of base employed. The best results (in terms of shorter reaction time and higher product yields) were obtained with sodium carbonate, sodium acetate and triethylamine (entries 1, 5 and 12) as bases. Changing the palladium catalyst has quite an effect on both the yield of the product and the rate of the reaction. Pd(OAc)$_2$ and Pd(DBA)$_2$ (DBA = dibenzylideneacetone) proved to be better than PdCl$_2$. As far as the substrate reactivity is concerned, the ortho-iodo compound 14a proved to be far superior to the ortho-bromo compound 14b. This was anticipated and there is literature precedent for this observation. The presence of the phase transfer reagent, n-Bu$_4$NCl, is essential as evidenced by entries 6, 7 and 9 (reactions done both in the absence of n-Bu$_4$NCl and in the presence of LiCl). In the absence of n-Bu$_4$NCl the reaction shows little progress after one day and the yield of the product is low. Other phase transfer reagents such as tetra-n-butylammonium hydrogen
sulfate, tri-n-octylmethylammonium chloride or tetra-n-butylammonium bromide were not tried as it was reported by Jeffrey that tetra-n-butylammonium chloride proved to be much more efficient.\textsuperscript{32} Other workers have used palladium(0) mediated oxidation of primary and secondary alcohols in the presence of the phase transfer reagent n-Bu\textsubscript{4}NCl.\textsuperscript{34} Of the many conditions listed above (see Table 1), it is obvious that sodium carbonate, sodium acetate or triethylamine should be employed as bases, Pd(OAc)\textsubscript{2} as the catalyst, n-Bu\textsubscript{4}NCl as the phase transfer reagent and N,N-dimethylformamide as the solvent in subsequent cyclization reactions. Cyclizations of substrates 14a and 14b, mediated by catalytic amounts of Pd(PPh\textsubscript{3})\textsubscript{4}, leading to compound 2 have been reported by Hegedus et al. (see eq. 9).\textsuperscript{26} The product yields are 87\% and 60\%, respectively.

The results of subsequent cyclization reactions performed on compounds 9, and 15-21 are summarized in Table 2. The results reported in Table 2 can be explained as follows. Compound 9 undergoes cyclization smoothly to 1,3-dimethylindole in good yields at room temperature, although the rate of the reaction is significantly slower than the reaction of compound 14a which took only one day to reach completion (see entry 1, Table 1). A substituent on the nitrogen thus slows down the cyclization. The analogous cyclization induced via an organocobalt intermediate gave the product in only 32\%
Table 2. Pd-Catalyzed Cyclization of Compounds 9, and 15-21 in DMF in the Presence of Tetra-n-butylammonium Chloride

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Base</th>
<th>Number of days at room temperature</th>
<th>Number of days at 80°C</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Na₂CO₃</td>
<td>3</td>
<td>-</td>
<td>![Product Image]</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>Et₃N</td>
<td>2</td>
<td>-</td>
<td>![Product Image]</td>
<td>81</td>
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<tr>
<td></td>
<td>NaOAc</td>
<td>3</td>
<td>-</td>
<td>![Product Image]</td>
<td>78</td>
</tr>
<tr>
<td>15</td>
<td>Et₃N</td>
<td>2</td>
<td>-</td>
<td>![Product Image]</td>
<td>46</td>
</tr>
<tr>
<td>23</td>
<td>Et₃N</td>
<td>-</td>
<td>1</td>
<td>![Product Image]</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Na₂CO₃</td>
<td>-</td>
<td>3</td>
<td>![Product Image]</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>NaOAc</td>
<td>-</td>
<td>1</td>
<td>![Product Image]</td>
<td>90</td>
</tr>
<tr>
<td>Substrate</td>
<td>Base (2.5 equiv.)</td>
<td>Number of days at room temperature</td>
<td>Number of days at 80°C</td>
<td>Product</td>
<td>Isolated yield (%)</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------</td>
<td>-----------------------------------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------------------</td>
</tr>
<tr>
<td>16</td>
<td>$\text{Na}_2\text{CO}_3$</td>
<td>-</td>
<td>2</td>
<td>16 (starting material)</td>
<td>76</td>
</tr>
<tr>
<td>16</td>
<td>$\text{NaOAc}$</td>
<td>-</td>
<td>1</td>
<td>24a or 24b (not pure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{Et}_3\text{N}$</td>
<td>-</td>
<td>2</td>
<td>24a or 24b (not pure)</td>
<td>22</td>
</tr>
<tr>
<td>17</td>
<td>$\text{Et}_3\text{N}$</td>
<td>-</td>
<td>1</td>
<td>17 (starting material)</td>
<td>69</td>
</tr>
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Table 2. Continued

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Base (2.5 equiv.)</th>
<th>Number of days at room temperature</th>
<th>Number of days at 80°C</th>
<th>Product</th>
<th>Isolated yield (%)</th>
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<tbody>
<tr>
<td>NaOAc</td>
<td>-</td>
<td>1</td>
<td>many products</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Na₂CO₃</td>
<td>-</td>
<td>1</td>
<td>many products</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Na₂CO₃</td>
<td>-</td>
<td>1</td>
<td><img src="image" alt="" /></td>
<td>36</td>
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<tr>
<td>NaOAc</td>
<td>-</td>
<td>1</td>
<td>26</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Et₃N</td>
<td>-</td>
<td>1</td>
<td>26</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Et₃N&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>1</td>
<td>26</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Na₂CO₃</td>
<td>1</td>
<td>-</td>
<td>none isolated</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions run in the presence of HCO₂Na (one equivalent).

<sup>b</sup>Two equivalents of HCO₂Na were used.
Table 2. Continued

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Base (2.5 equiv.)</th>
<th>Number of days at room temperature</th>
<th>Number of days at 80°C</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaOAc</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>none</td>
<td>isolated</td>
</tr>
<tr>
<td>Et₃N</td>
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<td>-</td>
<td>-</td>
<td>none</td>
<td>isolated</td>
</tr>
<tr>
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<td>1</td>
<td>-</td>
<td>none</td>
<td>isolated</td>
</tr>
<tr>
<td>NaOAc</td>
<td>-</td>
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<td>-</td>
<td>none</td>
<td>isolated</td>
</tr>
<tr>
<td>Et₃N</td>
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<td>-</td>
<td>none</td>
<td>isolated</td>
</tr>
<tr>
<td>20</td>
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<td>-</td>
<td>1</td>
<td>20 (starting material)</td>
<td>55</td>
</tr>
<tr>
<td>NaOAc</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>97 (84)</td>
<td></td>
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<tr>
<td>Et₃N</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>54</td>
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</table>

^Recrystallized yield.
Table 2. Continued

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Base (2.5 equiv.)</th>
<th>Number of days at room temperature</th>
<th>Number of days at 80°C</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
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<tr>
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<td></td>
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<td>-</td>
<td>1</td>
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<tr>
<td></td>
<td>Na$_2$CO$_3$</td>
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<td><img src="image" alt="Chemical Structure 3" /></td>
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<tr>
<td>22</td>
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<td>-</td>
<td>2</td>
<td><img src="image" alt="Chemical Structure 4" /></td>
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<td><img src="image" alt="Chemical Structure 5" /></td>
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<td>1</td>
<td><img src="image" alt="Chemical Structure 6" /></td>
<td>73</td>
</tr>
</tbody>
</table>
from the corresponding chloro-substituted substrate in the presence of a Ni(O) complex in 46% yield.\textsuperscript{14,15}

In the case of the N-acetyl substrate 15, the cyclization does not go to completion at room temperature. The yield of the desired product was only moderate (46%) at room temperature. Heating the reaction to 80°C, however, drives the reaction to completion. Perhaps, the lone pair of electrons on the oxygen of the carbonyl group is coordinating to the palladium and thus inhibiting addition to the double bond (Scheme 4). The 6-membered chelate shown in Scheme 4 can tie up the palladium and this explains the lack of reactivity of substrate 15 at room temperature. The same compound 23 was obtained from ortho-thallated acetaniline in a fair yield.
using Pd(II) and allyl chloride, although one equivalent of the palladium(II) salt had to be used.\textsuperscript{20}

Cyclization of substrate 16 should yield the corresponding tetrahydrocarbazole. However, a dihydrocarbazole was obtained instead, albeit in only a low yield and contaminated by an impurity. Surprisingly, further dehydrogenation to the aromatic carbazole did not occur (eq. 20). Proton NMR spectral analysis indicated that there were two possible positions for the olefinic bond. A triplet at $\delta$ 2.88 corresponding to the methylene group adjacent to the B ring provided clear evidence for one of the two assigned structures.
(24a or 24b). The compound 24 (a or b) isolated from the sodium acetate run was relatively pure, in comparison with the one isolated from the Et_3N run. Gas chromatographic (GC) analysis showed the presence of an impurity in minor amounts. However, the structure of the impurity could not be determined from GC/MS studies. The reason for the lack of reactivity in the presence of Na_2CO_3 is not apparent.

It was thought that a methyl substituent on the nitrogen might clean up the reaction. However, when compound 17 was subjected to the usual cyclization conditions (heated to 80°C for a day as the reaction fails to proceed at room temperature) many products were obtained in both the sodium acetate and the sodium carbonate runs. GC analysis revealed the presence of many products of which two of them were present in relatively larger amounts. From GC/MS studies the two major products appear to be compounds 25a and 25b or olefinic isomers of these compounds (eq. 21). The reaction

\[
\begin{align*}
\text{CH}_3 & \quad \text{Pd(0)} \\
\text{base} & \quad \text{80°C} \\
25a & + 25b \\
\text{other compounds}
\end{align*}
\]

was quite dirty and isolation of any single product by column chromatography proved too difficult. Thus, compound 16 fared
better than compound 17 in yielding only one product. It should be noted that our cyclization of compound 16 to the dihydrocarbazole product progressed much better than that reported by Hegedus et al. for the same compound. In his reaction with Pd(PPh₃)₄ as the catalyst, only unreacted starting material (compound 16) was recovered. However, activated double bonds (conjugated to a carbonyl group) have been shown to assist in intramolecular addition reactions leading to carbazoles (see eq. 12).^^

The cyclization of compound 18 has some interesting features, since there are no β-hydrogens available for palladium hydride elimination to occur once the aryl palladium complex adds to the olefinic bond to form a 5-membered ring. However, if the aryl group is added to the terminal end of the double bond, the resulting σ-palladium species has a β-hydrogen that would facilitate palladium hydride elimination (Scheme 5). As anticipated, no product was obtained upon submitting compound 18 to cyclization both at room temperature and at 80°C. However, in the presence of one equivalent of sodium formate [which can reduce the σ-alkylpalladium(II) species to Pd(0)], the initially formed cyclic intermediate should split out Pd(0) as shown in Scheme 6. The σ-palladium complex A, formed by initial addition of the aryl palladium species to the olefin, undergoes ligand exchange wherein the formate group displaces the anionic ligand in A. Expulsion of
Scheme 5

\[
\text{Scheme 6}
\]

\[
\text{Scheme 6}
\]

\[
\text{Scheme 6}
\]

\[
\text{Scheme 6}
\]
CO$_2$ results in the formation of an $\sigma$-alkylpalladium hydride species $B$ which undergoes reductive elimination to give the final product 26. Since Pd(0) is regenerated the reaction becomes catalytic in palladium. Reduction of vinyl and aryl halides by Pd(PPh$_3$)$_4$ and sodium formate has been reported in the literature (eq. 22).$^{35}$

$$
\begin{align*}
\text{C}_6\text{H}_5\text{CH}=&\text{CHBr} & 
\xrightarrow{5\% \text{ Pd}(\text{PPh}_3)_4} & 
\text{C}_6\text{H}_5\text{CH}=&\text{CH}_2 \\
(\text{PhCH}_2)_3\text{N} & & \text{HCO}_2\text{Na} & & 110^\circ\text{C}
\end{align*}
$$

Our reaction proceeds best with Et$_3$N as the base and worst with NaOAc as the base. Increasing the sodium formate concentration to two equivalents, under our best (Et$_3$N) conditions, decreased the yield to 12%. In all of the above reactions, an unidentifiable aliphatic product was also isolated. Since the $^1$H NMR spectrum of this compound had no aromatic protons, the formation of the reduced starting material was ruled out. However, the structure of this by-product could not be determined by spectral analysis. The cyclization reaction proceeds only at 80°C; at room temperature only unreacted starting materials could be isolated. While six-membered ring closure did not occur, such a ring closure has been observed in the cyclization of 2-bromo-N-(2-carboethoxyallyl)aniline to 3-carboethoxyquinoline (eq. 23).$^{26}$
There are only a few methods reported for the synthesis of the indolinone (oxindole) nucleus even though this heterocyclic system has been the focus of increasing attention because of its varied physiological properties. The synthesis of oxindole involving Pd(0) catalyzed hydrogenation of an aryl nitrolactone is shown below (eq. 24).

Organotransition metal approaches to the oxindole nucleus have been investigated by Mori and Ban and Terpko and Heck. Both organopalladium ([Pd(OAc)₂/PR₃ catalyst] and organonicelk [Ni(PPh₃)₄] approaches yielded the oxindole product, but in only moderate yields (see eqs. 10 and 11). Our synthesis of oxindoles from the corresponding halide is basically a modification of the Ban and Heck methods. Thus, when compound 19 was subjected to cyclization, no organic products could be isolated. This was the case with all three
bases at 80°C. At room temperature only starting materials were obtained with Na₂CO₃ and NaOAc as bases. With Et₃N, even at room temperature, no organic product was obtained. The reaction mixture which looks very messy may in fact contain a polymer of the starting material 19.

However, phenyl-substituted oxindole 27 was formed very cleanly upon submitting the starting halide 20 to the usual cyclization conditions. The reaction proceeded very smoothly with NaOAc at 80°C in one day to form the oxindole 27 in nearly quantitative yield. The crude product which was very pure was recrystallized from a hexanes/chloroform mixture in 84% yield. The same reaction in the presence of Et₃N yielded the product in 54% recrystallized yield. The reaction does not proceed with sodium carbonate as the base. At room temperature, the reaction shows no progress with any of the three bases. Terpko and Heck 28 obtained the same oxindole 27 using 5% Pd(OAc)₂/PPh₃ in 58% yield, after heating the reaction at 110°C for 18 hours. Ban, who synthesized an analogous system, was able to achieve cyclization in 47% (his best) yield.

Compound 27 that was isolated could be a mixture of E and Z isomers. Differentiating the two isomers by ¹H NMR spectral studies was not possible. The existence of the two isomers was revealed only by ¹³C NMR spectral studies (19 carbon resonances were seen). Terpko and Heck 28 reported the
formation of only one isomer. However, no analytical data on the compound were provided by him.

Pd-catalyzed cyclization of compound 21 to compound 28 proceeded in rather low yield (20%) with Et$_3$N as the base at 80°C for one day. As expected for disubstituted olefins the reaction does not occur at room temperature. Perhaps, steric hindrance is responsible for the slower reaction rates in these cases. In the presence of sodium carbonate and sodium acetate, the yields of the desired product were only 7% and 9% respectively. In addition to the desired product, a few other products were seen by TLC analysis. Separation of these compounds by column chromatography was not possible. Ban et al. reported a yield of 43% of the same product 28 using catalytic amounts of Pd(OAc)$_2$ and PPh$_3$ in the presence of excess tetramethylethylenediamine (TMEDA) at 125°C.

Substrate 22 cyclizes smoothly at 80°C to yield compound 29 under the usual conditions. The best yield (73%) was obtained with Et$_3$N as base. The yields of the cyclized product 29 were 46% and 43% with NaOAc and Na$_2$CO$_3$ as bases, respectively. The reaction was complete within a day under Et$_3$N and NaOAc conditions. With Na$_2$CO$_3$, even after two days some of the starting material remained unreacted (33% isolated). At room temperature, cyclization was not observed even under the best (Et$_3$N) condition.
The Pd(0)-catalyzed intramolecular addition of aryl halides to olefins leading to indole and oxindole derivatives, in the presence of a phase transfer reagent, is clearly superior to the existing methods. In some cases (compounds with monosubstituted olefins) our reaction proceeds very well at room temperature, whereas other workers cited above had to induce cyclization at very high temperatures. Compounds with disubstituted olefinic bonds had to be heated in order to effect cyclization. Still, in most cases the yields of the desired products were significantly higher when compared to those reported in the literature. Throughout the course of this work, only the cyclization of substrate 21 fell short of the yield reported in the literature. Overall, our modification of the existing methodology was very successful in the synthesis of indoles and their derivatives. Further studies in the synthesis of other heterocycles using our palladium-catalyzed methodology were carried out and will be discussed in the following section.
A number of quinoline alkaloids have been isolated from rutaceous plants. Among them are edulitine (30), folimine (31) and folifidene (32). These alkaloids and many others bearing the quinoline ring system possess important biological properties and have been the target of synthesis for many years. Though many synthetic approaches have been described, the current discussion will concentrate only on organometallic approaches to the quinoline system.

In 1978, Cortese et al. extended the Pd-catalyzed vinylic substitution reaction to the synthesis of 2-quinolones. Reactions of 2-iodoaniline or its derivatives with dimethyl maleate would be expected to yield intermediate amino esters which would cyclize to quinolones. Indeed, this does occur in the three examples reported (eq. 25). Similarly, 4-phenyl-2-quinoline was obtained in 66% yield by reacting o-iodoaniline with (Z)-N-phenylcinnamamide (eq. 26). The stereochemistry is correct for direct cyclization, but as in the above case the
use of (E)-N-phenylcinnamamide instead of the Z-isomer also gives the quinoline, but only in 15% yield.

In an attempt to favor ring closure to six-membered ring quinoline products, the palladium-promoted cyclization of α-substituted N-acryloyl-α-bromoanilines was studied (eq. 27). It was reasoned that the aryl group would prefer to
add to the terminal methylene carbon rather than the tertiary carbon, as addition to the internal carbon would result in a \(\sigma\)-alkylpalladium complex with no \(\beta\)-hydrogen. 2-Quinolone derivatives were formed in this reaction but, surprisingly, their structures were not the expected ones. Two compounds were tested, one with an \(\alpha\)-methyl group and the other with an \(\alpha\)-phenyl group. The product in both cases was the 4-substituted 2-quinolones rather than the expected 3-substituted derivative (eq. 27). This rearrangement has been explained by the following mechanism (Scheme 7). The initial closure of the organopalladium intermediate leads to a five-membered ring product containing a 3-palladiomethyl group. In these complexes there is no \(\beta\)-hydrogen to be eliminated with palladium, as there is when the \(\alpha\)-carbon is unsubstituted. Since the usual palladium hydride elimination is not possible, elimination of the aminocarbonyl group with the palladium appears to occur and this is followed by readdition of the aminocarbonylpalladium group to the resulting double bond in the opposite direction. The last adduct can now undergo palladium hydride elimination irreversibly to give the observed, rearranged 4-substituted 2-quinolone.
Hegedus et al. observed another unusual mode of cyclization when an amine-substituted allylbenzoquinone was subjected to stoichiometric palladium(II) treatment. They
observed exclusive formation of the quinoline product instead of the expected indole product (eq. 28). The reaction was remarkably insensitive to the nature of the palladium catalyst. Upon repeating the same reaction, in the presence of benzoquinone (an oxidant) and in the absence of the palladium catalyst, the same quinoline product was observed. It was reasoned that this cyclization was an oxidative process effected by the benzoquinone, since benzoquinone alone was effective in the cyclization. Mori et al.\textsuperscript{15} utilized a catalytic Ni(0) complex to induce intramolecular cyclization to dihydroquinoline derivatives (eq. 29).

Though this cyclization proceeds in high yield, subsequent rearrangement of the double bond and spontaneous aromatization to the desired quinoline has not been observed. Perhaps, a
secondary aniline would have been a better substrate for cyclization and ultimate dehydrogenation to quinolines.

For our study, we chose the following substrates for cyclization. Compound 33 was made by methods reported in the literature. This involves the treatment of ortho-iodo-aniline with lithium diisopropylamide (LDA) and quenching with 3-butenyl bromide (eq. 30).

\[
\text{IL} \quad \text{LDA} \quad \text{I} \\
\text{THF} \quad -78^\circ C \to \text{RT} \\
\text{33} \quad 37\%
\]

In order to prepare compound 34, first \textit{cis}-5-(methanesulfonyloxy)pent-2-ene had to be made from the readily available \textit{pent}-3-yn-1-ol. Thus, \textit{cis} hydrogenation with 5\% Pd/C [poisoned with Pb(OAc)\textsubscript{2}] in the presence of one atmosphere of hydrogen yielded the \textit{cis}-alkene in an almost quantitative yield. Mesylation of this alcohol was effected by treatment with triethylamine and methanesulfonyl chloride in dichloromethane (eq. 31). The overall yield for the two reactions was
81%. 2-Iodoaniline was treated with LDA and quenched with compound 36 to yield compound 34 in 43% yield.

Compound 35 was prepared by the condensation of 2-iodoaniline and vinylacetyl chloride (made by the treatment of vinylacetic acid with oxalyl chloride in ether) (eq. 32).43

The best cyclization conditions used previously (Et\textsubscript{3}N, Na\textsubscript{2}CO\textsubscript{3} and NaOAc as bases) were then applied to these substrates. Table 3 shows the different conditions that were examined in attempting to induce cyclization to quinoline products.

Thus, when compound 33 was subjected to the usual cyclization treatment [2% Pd(OAc)\textsubscript{2}, n-Bu\textsubscript{4}NCl, base in DMF] the
Table 3. Pd-Catalyzed Cyclization of Compounds 31-33 Leading to Quinolines

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Base (2.5 equiv.)</th>
<th>Number of days at room temperature</th>
<th>Number of days at 80°C</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
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<td>33</td>
<td>Na₂CO₃</td>
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<td><img src="image" alt="Chemical Structure" /></td>
<td>92-97</td>
</tr>
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<td>NaOAc</td>
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<td>-</td>
<td>37</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Et₃N</td>
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<td>-</td>
<td>33 (starting material)</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>pyridine</td>
<td>1</td>
<td>-</td>
<td>33 (starting material)</td>
<td>~100</td>
</tr>
<tr>
<td>34</td>
<td>Na₂CO₃</td>
<td>1</td>
<td>-</td>
<td>34 (starting material)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Et₃N</td>
<td>1</td>
<td>-</td>
<td>34 (starting material)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>NaOAc</td>
<td>1</td>
<td>-</td>
<td>34 (starting material)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Na₂CO₃</td>
<td>-</td>
<td>1</td>
<td>many products</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>---</td>
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<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>-</td>
<td>1</td>
<td></td>
<td>35 (starting material)</td>
<td>49</td>
</tr>
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<td>-</td>
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<td></td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td>Na$_2$CO$_3$</td>
<td>1</td>
<td>-</td>
<td></td>
<td>35 (starting material)</td>
<td>-</td>
</tr>
<tr>
<td>NaOAc</td>
<td>1</td>
<td>-</td>
<td></td>
<td>35 (starting material)</td>
<td>-</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>-</td>
<td>1</td>
<td></td>
<td>unknown products</td>
<td>-</td>
</tr>
<tr>
<td>Na$_2$CO$_3$</td>
<td>-</td>
<td>1</td>
<td></td>
<td>unknown products</td>
<td>-</td>
</tr>
<tr>
<td>NaOAc</td>
<td>-</td>
<td>1</td>
<td></td>
<td>unknown products</td>
<td>-</td>
</tr>
</tbody>
</table>
expected product 4-methyl quinoline (product of further dehydrogenation) was obtained in excellent yields with Na₂CO₃ and NaOAc as bases. In these reactions, Pd(0) metal was seen falling out of the reaction mixture after a few hours. However, under completely homogeneous conditions (pyridine and Et₃N as bases), no reaction seemed to occur. In these cases only starting materials were isolated. Raising the reaction temperature was considered unnecessary.

As anticipated, the disubstituted olefin 34 was less reactive when compared to compound 33. The room temperature cyclization of compound 34 yielded only starting materials with all three bases. However, upon raising the reaction temperature to 80°C, the expected product 4-ethylquinoline 38 was obtained in moderate yields using either triethylamine or sodium acetate as the base. The same reaction in the presence of Na₂CO₃ gave many products.

Surprisingly, compound 35 did not undergo cyclization to the desired 2-hydroxy-4-methylquinoline as expected. At room temperature, no reaction occurs, but upon heating to 80°C, many unidentifiable products were obtained.

The yields of quinoline products obtained in our first two examples were much better than Ban's [both Ni(0) and Pd(OAc)₂/PR₃ catalysts were used]. The reaction shows
much promise in that it could be used in the synthesis of more complex quinoline alkaloids and other natural products bearing this heterocyclic system.
ISOQUINOLINES

Despite their simple structure, much interest in the isoquinoline alkaloids has developed over the years and several new naturally occurring compounds have been found. Plants belonging to the family Cactaceae are known to contain simple tetrahydroisoquinolines. Naturally occurring doryanine (39) and doryfomine (40) were isolated from sassafras tree.44

\[
\text{39 doryanine} \quad \text{40 doryfomine}
\]

A number of isoquinoline alkaloids possessing important biological properties exist in nature and many of them have been synthesized in the laboratory.45

Among the organometallic approaches to isoquinolines, the ones by Korte et al.46 and Ban et al.40 are noteworthy. The Hegedus method was based upon π-allylnickel halides and π-olefin palladium complexes. Thus, 2-(2-propenyl)-N-methylbenzamide (41) was prepared from 2-bromo-N-methylbenzamide and π-allylnickel bromide (eq. 33). Compound 41 was then subjected to intramolecular cyclization under stoichiometric Pd(II) conditions. The resultant cyclized isoquinolone was obtained in high yield. The major drawbacks to this approach are the use of air sensitive π-allylnickel complexes and stoichiometric amounts of a palladium(II) salt.
Ban and co-workers\textsuperscript{40} obtained 4-benzylisoquinoline, along with the 4-benzylidene derivative, when the corresponding aryl halide was subjected to Pd-promoted cyclization (eq. 34).

The high temperature, the long reaction time and the low yield of the desired product (27\%) make this procedure undesirable for synthetic purposes. The reason for the low reactivity of these halides may be due to the stable nature of the initially formed ortho-palladated dialkylaminobenzylpalladium complex.
This may, to a certain extent, prevent intramolecular addition to the olefinic bond. However, intermolecular additions of orthopalladated compounds have been reported. Recently, O'Sullivan and Parkins reported the synthesis of isoindolinimines by the insertion of isocyanides into the metal-carbon bond of an ortho-palladated primary benzylamine complex (eq. 35). Cyclopalladated complexes have also been (1) used to give insertion products with alkynes, (2) acylated in the presence of acetyl
chloride to yield the ortho-substituted acylbenzylamine, and (3) carbonylated in the presence of CO to produce ortho-palladated complexes. In 1983, Barr et al. reported a synthetic approach to the isoquinoline ring system via a cyclopalladated palladium complex (Scheme 8). Cyclopalladation of compound 43 occurs readily to yield complex 44 in the presence of Pd(II). Upon treatment with methyl vinyl ketone, the expected substitution product 45 was obtained in 73% yield. Compound 45 was then carried on to tetrahydroisoquinoline 46 using known standard chemistry. As in the case of Hegedus' method, the above scheme requires stoichiometric amounts of palladium.
Our method consists of essentially modifying the work done by Ban (see eq. 34). We decided to try to synthesize isoquinolines using catalytic amounts of Pd(OAc)$_2$ and tetra-n-butylammonium chloride as the phase transfer reagent. Hopefully, our methodology would provide better yields of the desired products.

For our study we chose the following substrates 47-52 for cyclization. Compound 47 was prepared from 2-iodobenzyl-alcohol by initial mesylation with methanesulfonyl chloride in the presence of Et$_3$N, followed by treatment with excess allylamine. The overall yield for the two reactions was 91% (eq. 36). Compound 48 was prepared by treating 2-iodobenzylamine with LDA (1.5 equivalents) and quenching with allylbromide (two equivalents) (eq. 37). Compound 49 was prepared by the condensation of 2-iodobenzylamine with cinnamoyl chloride (eq. 38). Compounds 50 and 51 were made
starting from 2-iodobenzoic acid. Upon treating the acid with excess oxalyl chloride in ether at 0°C, 2-iodobenzoyl chloride was obtained in almost quantitative yield. Allylamine was added to the acid chloride at 0°C in THF to yield amide 50, and cinnamyl amine along with excess (10 equivalents) triethylamine were added to the acid chloride to yield compound 51 (eq. 39). Compound 52 was obtained by treating the mesylate of 2-iodobenzylalcohol with cinnamyl amine (four
equivalents) and potassium carbonate (one equivalent) (eq. 40).

\[
\text{I} \quad \text{CO}_2\text{H} \quad \text{(COCl)}_2 \
\text{ether} \quad 0^\circ\text{C}, \quad 15 \text{ hrs} \
\rightarrow 
\text{I} \quad \text{COCl} 
\rightarrow \text{THF} \quad 0^\circ\text{C} 
\rightarrow \text{NH}_2 
\rightarrow \text{HO} 
\rightarrow \text{N} 
\rightarrow 63\% 
\rightarrow \text{50 recrystallized yield} 
\]

\[
\text{I} \quad \text{C}=\text{C} 
\rightarrow \text{THF} \quad 0^\circ\text{C} 
\rightarrow \text{N} 
\rightarrow 52\% 
\rightarrow \text{51 recrystallized yield} 
\]

\[
\text{OMs} 
\rightarrow \text{K}_2\text{CO}_3 
\rightarrow \text{THF} \quad 0^\circ\text{C} \rightarrow \text{RT} 
\rightarrow \text{overnight} 
\rightarrow \text{52} 
\rightarrow 55\% 
\]

The results of the palladium-catalyzed cyclization of compounds 47-52 leading to isoquinolines are summarized in Table 4.

Compound 47 undergoes smooth cyclization in the presence of 2% \(\text{Pd(OAc)}_2\), \(\text{n-Bu}_4\text{NCl}\) and DMF, to the desired 4-methyl-isoquinoline 53 at 80°C with all three bases. However, the
Table 4. Pd-Catalyzed Cyclizations of Compounds 47-52

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Pd catalyst (2%)</th>
<th>Base (2.5 equiv.)</th>
<th>Reaction temperature (°C)</th>
<th>Reaction time (days)</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
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*Reaction run in the absence of phase transfer reagent.*
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<tr>
<td>Pd(OAc)₂</td>
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![Chemical Structure Image]
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50

| Pd(OAc)$_2$ | NaOAc           | 80                | 1                         | starting material   | 95      |
| Pd(OAc)$_2$ | Et$_3$N         | 80                | 1                         | starting material   | 29      |
| Pd(OAc)$_2$ | Na$_2$CO$_3$    | 80                | 1                         | starting material   | 50      |
| Pd(OAc)$_2$ | NaOAc           | 100               | 1                         | many products       | -       |
| Pd(OAc)$_2$ | Na$_2$CO$_3$    | 100               | 2                         | starting material + tar | -       |
Table 4. Continued

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$^b$Ratio of 55/56 = 1.
Table 4. Continued

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<td>Isolated Yield (%)</td>
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</table>
room temperature may be explained by the inability of the chelated ortho-palladation complex to undergo olefin insertion. Our best yield (39%) for this system is still much better, however, than the yield reported by Ban et al.\textsuperscript{40} (27%) for a similar system. The reaction in the presence of 2\% Pd(PPh\textsubscript{3})\textsubscript{4} yields only starting material, both in the presence and absence of the phase transfer reagent.

The diallyl compound 48 fails to undergo cyclization to the desired isoquinoline either at room temperature or at 80\°C. At room temperature only starting materials were isolated. At 80\°C, many products were formed with sodium carbonate and sodium acetate. With Et\textsubscript{3}N almost 50\% of the starting material could be recovered.

Compound 49 does not cyclize at 80\°C with Na\textsubscript{2}CO\textsubscript{3} or Et\textsubscript{3}N. However, with NaOAc trace amounts of the desired product 54 were obtained. However, the reaction goes to completion in one day and the cyclic adduct 54 was obtained in 21\% yield when the reaction was run with NaOAc as the base at 100\°C. The reaction mixture turns tarry after prolonged heating (two days). In order to optimize the yield, the cyclization was carried out in the presence of 2\% Pd(PPh\textsubscript{3})\textsubscript{4} as the catalyst. This time the desired product was obtained in 39\% yield; the other conditions remained the same. When the same reaction with Pd(PPh\textsubscript{3})\textsubscript{4} was carried out in the absence of the phase transfer reagent, none of the desired product could be
isolated. Thus, the phase transfer reagent is necessary to induce cyclization, but the role of the reagent is still open for discussion. The product obtained is not a mixture of stereoisomers, but purely one isomer as indicated by $^{13}$C NMR spectral studies. However, the stereochemistry could not be established from such limited data.

Finally, compound was subjected to the cyclization conditions. As suspected, only starting materials were obtained at 80°C. At 100°C, however, the desired product was obtained in 42% yield with Et$_3$N as the base. The reaction gives many products with NaOAc, and with Na$_2$CO$_3$ only starting material was recovered. As in the previous case, switching to the Pd(PPh$_3$)$_4$ catalyst plus Et$_3$N improved the yield to 58%. Surprisingly, the reaction seems to progress well even in the absence of the phase transfer reagent. In the absence of the phase transfer reagent, an almost 1:1 mixture of the completely aromatized product and the initially formed cycloadduct were obtained. The separation of these two products was not possible by column chromatography. The ratio was determined by $^1$H NMR spectral analysis and the $^{13}$C NMR spectrum also revealed the presence of the two isomers.

Compound cyclizes at 110°C under the usual conditions only in the presence of Na$_2$CO$_3$ as base. However, the initially cyclized product did not undergo double bond migration to yield the desired isoquinoline product. In the
presence of NaOAc, compound 51 yields only the reduced product. With Et$_3$N no organic product could be recovered.

Compound 52 fails to undergo cyclization to the desired isoquinoline under all three conditions (NaOAc, Na$_2$CO$_3$, Et$_3$N) at 110°C. With Et$_3$N, only starting material (~9%) was recovered. In the presence of Na$_2$CO$_3$ or NaOAc unidentifiable products were obtained.

The presumed ability of our organopalladium approach to heterocycles to tolerate many functional groups during intramolecular cyclization should offer major advantages over the other methods presently available. Our methodology offers a solution to a lot of problems that were faced by chemists attempting similar cyclization reactions. The yields of the products obtained by our methodology are significantly higher than those reported in the literature for analogous systems. In addition, many of the cyclizations are achieved under milder reaction conditions. Also, some of the substrates, which were unreactive using other organopalladium methods, underwent cyclization to yield the desired products.

Applications of this methodology to the synthesis of natural products, containing the heterocyclic systems studied, can be expected in the future.
OXYGEN HETEROCYCLES

Intramolecular aryl palladium addition to olefins leading to oxygen heterocycles, such as benzopyrans, was also examined. As a model study, we decided to apply our previous best cyclization conditions to substrate 58. The synthesis of substrate 58 was achieved in a straightforward manner (eq. 41). Thus, o-iodophenol was treated with 4-bromobutene in refluxing acetone, in the presence of K$_2$CO$_3$, to yield compound 58. The yield of compound 58 was 55%.

Compound 58 was then subjected to the usual cyclization conditions, which involves treatment with 2% Pd(OAc)$_2$, n-Bu$_4$NCl (one equivalent) and 2.5 equivalents of base (either Na$_2$CO$_3$, NaOAc or Et$_3$N) in DMF. Cyclization was observed at 80°C only under Na$_2$CO$_3$ conditions (eq. 42). However, the two isomers, compounds 59 and 60, were obtained in a ratio of 1.1:1. The combined yield of the two isomers was 68%. The
identity and the relative ratio of the two isomers were determined by $^1$H NMR spectral analysis. Integration of the resonances due to one of the terminal vinylic protons and the only vinylic proton in isomer 60 in the NMR spectrum is the basis of our inference. Furthermore, GC/MS results added proof to our conclusion. The cyclization does not proceed at room temperature under the best (Na$_2$CO$_3$) condition.

Application of this reaction in the synthesis of other oxygenated heterocycles can be expected in the future.
EXPERIMENTAL SECTION

Equipment

Proton NMR spectra were recorded on a Nicolet NT-300 spectrometer. $^{13}$C NMR spectra were recorded on a Nicolet NT-300 (operating at 75 MHz for carbon nuclei) spectrometer. Infrared spectra were recorded on a Beckman-42050 spectrophotometer. Mass spectral data were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with an SE-30 capillary column or an OV-101 packed column. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected.

Reagents

All chemicals were used directly as obtained unless otherwise noted. N,N-Dimethylformamide (DMF) was distilled over calcium hydride under reduced pressure. Tetrahydrofuran (THF) was distilled over a sodium-benzophenone mixture. Tetra-n-butylammonium chloride (96%, Aldrich) was used directly as obtained and stored in a desiccator. Compounds 14a-b, 16, and 18 were prepared using a literature procedure. Compounds 9, 17, 22, 33, 34, and 48 were prepared basically by the same procedure. The following procedure for the preparation of compound 9 is representative of that used for the other compounds.
N-Allyl-2-iodoaniline (14a) (0.518 g, 2 mmol) was dissolved in 10 ml of dry THF in a 50 ml round bottom flask. The solution was flushed with nitrogen and cooled to -78°C (dry ice-acetone bath). LDA (2.1 mmol) (from 2.15 mmol of diisopropylamine and 2.15 mmol of n-butyl lithium) in dry THF (3 ml) was slowly added, and the resulting mixture was allowed to warm to 0°C over 10 minutes. After the resulting solution was recooled to -78°C, methyl iodide (0.290 g, 2.2 mmol) was slowly added and the solution stirred for 10 minutes, allowed to warm to room temperature and stirred for two hours at that temperature. The reaction mixture was partitioned between ether and saturated sodium chloride solution and the ether layer separated. The ether extracts were dried over magnesium sulfate and concentrated. The crude oil was purified by medium pressure liquid chromatography using 2:1 hexanes/ethyl acetate as eluent. Compound 9 was obtained in 85% (0.449 g) yield: Rf 0.65 (2:1 hexanes/ethyl acetate); 1H NMR (CDCl3) δ 2.69 (3 H, s, NCH3), 3.55 (2 H, d, J = 6.3 Hz, allylic), 5.17 (1 H, d, J = 10.2 Hz, terminal vinyl, cis to the internal vinylic hydrogen), 5.25 (1 H, d, J = 17.4 Hz, terminal vinyl, trans to the internal vinylic hydrogen), 5.95 (1 H, m, internal vinyl), 6.76 (1 H, m, aryl), 7.06 (1 H, d, J = 8.1 Hz, aryl), 7.29 (1 H, m, aryl), 7.85 (1 H, d, J = 7.8 Hz, aryl); IR (neat) 3030 (C-H) cm⁻¹; m/z calcd for C10H12NI, 273.0014; found, 273.0015.
Compound 17
Yield, 88%; R_f 0.77 (30:1 hexanes/ethyl acetate); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 1.26-2.03 (6 H, m, alkyl), 2.66 (3 H, s, NCH\(_3\)), 3.91 (1 H, m, vinyl), 5.79 (2 H, m, vinyl), 6.74 (1 H, t, \(J = 7.5\) Hz, aryl), 7.09 (1 H, d, \(J = 8.1\) Hz, aryl), 7.28 (1 H, t, \(J = 7.5\) Hz, aryl), 7.85 (1 H, d, \(J = 7.8\) Hz, aryl); IR (neat) 3050, 3010 (C-H) cm\(^{-1}\); m/z calcd for C\(_{13}\)H\(_{16}\)NI 313.03206; found, 313.03275.

Compound 22
Yield, 98%; R_f 0.70 (10:1 hexanes/ethyl acetate); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 1.72 (3 H, m, CH\(_3\)), 3.72 (2 H, t, \(J = 5.4\) Hz, allylic), 4.21 (1 H, s, NH), 5.55-5.76 (2 H, vinyl, trans), 6.43 (1 H, br t, \(J = 9\) Hz, aryl), 6.56 (1 H, dd, \(J_1 = 8.4\) Hz, \(J_2 = 1.2\) Hz, aryl), 7.19 (1 H, br t, \(J = 8.8\) Hz, aryl), 7.65 (1 H, dd, \(J_1 = 7.5\) Hz, \(J_2 = 1.5\) Hz, aryl); IR (neat) 3395 (NH), 3060 (C-H) cm\(^{-1}\); m/z calcd for C\(_{10}\)H\(_{12}\)NI 273.00145; found 273.0010.

Compound 33
Yield, 37%; R_f 0.80 (10:1 hexanes/ethyl acetate); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 2.43 (2 H, m, allylic), 3.21 (2 H, m, CH\(_2\)N), 4.20 (1 H, s, NH), 5.17 (1 H, d, \(J = 10.2\) Hz, terminal vinyl, cis to the internal vinylic hydrogen), 5.22 (1 H, d, \(J = 17.2\) Hz, terminal vinyl, trans to the internal vinylic hydrogen), 5.84 (1 H, m, internal vinyl), 6.43 (1 H, t, \(J = 7.8\) Hz, aryl),
6.54 (1 H, d, \(\mathbf{J} = 7.8 \text{ Hz}, \text{aryl}\)), 7.20 (1 H, m, aryl), 7.64 (1 H, d, \(\mathbf{J} = 7.8 \text{ Hz}, \text{aryl}\)); IR (neat) 3480 (N-H) cm\(^{-1}\); m/z calcd for \(\text{C}_{10}\text{H}_{12}\text{NI}\) 273.00145; found, 273.00161.

**Compound 34**

Yield, 43%; \(R_f\) 0.80 (10:1 hexanes/ethyl acetate); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.71 (3 H, d, \(\mathbf{J} = 7.2 \text{ Hz}, \text{CH}_3\)), 2.43-2.49 (2 H, m, allylic), 3.17-3.24 (2 H, m, \(\text{CH}_2\text{N}\)), 4.22 (1 H, s, NH), 5.46 (1 H, m, vinyl, cis), 5.69 (1 H, vinyl, cis), 6.45 (1 H, t, \(\mathbf{J} = 7.8 \text{ Hz}, \text{aryl}\)), 6.59 (1 H, d, \(\mathbf{J} = 7.5 \text{ Hz}, \text{aryl}\)), 7.22 (1 H, t, \(\mathbf{J} = 7.8 \text{ Hz}, \text{aryl}\)), 7.66 (1 H, d, \(\mathbf{J} = 7.8 \text{ Hz}, \text{aryl}\)); IR (neat) 3395 (NH), 1000 (C=C, cis) cm\(^{-1}\); m/z calcd for \(\text{C}_{11}\text{H}_{14}\text{NI}\), 287.01710; found 287.01688.

**Compound 48**

Yield, 66%; \(R_f\) 0.48 (15:1 hexanes/ethyl acetate); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.16 (4 H, d, \(\mathbf{J} = 6.9 \text{ Hz}, \text{allylic}\)), 5.18 (2 H, d, \(\mathbf{J} = 10.2 \text{ Hz}, \text{terminal vinyl, cis to the internal vinylic hydrogen}\)), 5.25 (2 H, d, \(\mathbf{J} = 17.4 \text{ Hz}, \text{terminal vinyl, trans to the internal vinylic hydrogen}\)), 5.86-5.99 (2 H, m, internal vinyl), 6.96 (1 H, t, \(\mathbf{J} = 7.8 \text{ Hz}, \text{aryl}\)), 7.34 (1 H, t, \(\mathbf{J} = 7.5 \text{ Hz}, \text{aryl}\)), 7.58 (1 H, d, \(\mathbf{J} = 7.6 \text{ Hz}, \text{aryl}\)), 7.84 (1 H, d, \(\mathbf{J} = 7.8 \text{ Hz}, \text{aryl}\)); IR (neat) 3085 (C-H) cm\(^{-1}\); m/z calcd for \(\text{C}_{13}\text{H}_{16}\text{NI}\) 313.03275; found, 313.03224.
Preparation of compound 15 from 14a

Compound 14a (0.518 g, 2 mmol) was treated with a large excess (1.5 ml) of acetic anhydride at room temperature. After two days, the reaction as indicated by TLC was complete. The crude mixture was washed with water and extracted with ether. The ether layer was concentrated and the residual acetic acid was removed under vacuum. The product which was a light yellow oil was used without further purification:
yield, ~100% (0.600 g); \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 1.80 (3 H, s, CH\(_3\)), 3.60 (2 H, m, allylic), 5.06 (1 H, d, \( J = 18 \) Hz, terminal vinyl, trans to the internal vinylic hydrogen), 5.11 (1 H, d, \( J = 10.2 \) Hz, terminal vinyl, cis to the internal vinylic hydrogen), 5.89 (1 H, m, internal vinyl), 7.09 (1 H, t, \( J = 7.5 \) Hz, aryl), 7.19 (1 H, d, \( J = 9.0 \) Hz, aryl), 7.40 (1 H, t, \( J = 7.8 \) Hz, aryl), 7.95 (1 H, d, \( J = 7.8 \) Hz, aryl); IR (neat) 1740 (C=O) cm\(^{-1}\); m/z calcd for C\(_9\)H\(_{10}\)NI (M\(^+\)-COCH\(_3\)), 257.9779; found 257.9780.

Synthesis of compound 21 from ortho-iodoacetanilide

Sodium hydride (50%, 0.121 g, 2.52 mmol) was placed in a round bottom flask and washed with hexanes (three times). The residue was kept under vacuum to remove the remaining hexanes. The flask was flushed with nitrogen and cooled to 0°C. THF (9 ml) was slowly added to the flask with constant stirring under nitrogen. The ortho-iodoacetanilide (0.471 g, 1.8 mmol) dissolved in 2 ml of THF was slowly added to the sodium
hydride-THF mixture. After the evolution of hydrogen had ceased, methyl 4-bromocrotonate (Aldrich) (0.390 g, 2.16 mmol) was added dropwise to the solution. The mixture was allowed to warm to room temperature and stirred at that temperature overnight. The reaction mixture was extracted with ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded the crude product which was purified by column chromatography using 1:1 hexanes/ethyl acetate as eluent: 33% yield (0.215 g); R_f 0.38 (1:1 hexanes/ethyl acetate); ^1H NMR (CDCl_3), δ 1.82 (3 H, s, COCH_3), 3.68-3.84 (1 H, m, buried under OCH_3 absorption, allylic), 3.73 (3 H, s, OCH_3), 4.99 (1 H, dd, J_1 = 15.6 Hz, J_2 = 3.6 Hz, allylic), 5.87 (1 H, d, J = 15.9 Hz, vinyl, trans), 6.92-7.02 (1 H, m, vinyl, trans), 7.10 (1 H, t, J = 7.5 Hz, aryl), 7.21 (1 H, d, J = 7.8 Hz, aryl), 7.44 (1 H, br t, J = 7.0 Hz, aryl), 7.95 (1 H, d, J = 7.8 Hz, aryl); IR (neat) 1720 N (C=O), 1665 (C=O) cm^{-1}; m/z calcd for C_{13}H_{14}NO_3I 359.00185; found, 359.00156.

Preparation of compounds 19, 20, and 49

The procedure for the synthesis of compound 20 is representative. To a mixture of ortho-iodoaniline (0.22 g, 1 mmol) and cinnamoyl chloride (0.166 g, 1 mmol) was added 2 ml of THF. The solution was stirred at room temperature. Triethylamine (0.101 g, 1 mmol) was added dropwise to the
solution and the mixture was stirred for 16 hours. Water was then added to the solution and the product was extracted with three portions of ether. The combined ether extracts were washed with dilute aqueous hydrochloric acid and dried with anhydrous magnesium sulfate. Evaporation of the solvent yielded the crude amide (0.337 g, 94%). The crude product was dissolved in a minimum amount of boiling chloroform. The solution was allowed to cool to room temperature and hexanes were added dropwise to the solution until the first few crystals were seen. The solution was placed in a freezer overnight. The amide was obtained in 73% (0.254 g) recrystallized yield; mp 154°C; $^1$H NMR (CDCl$_3$) $\delta$ 6.59 (1 H, d, $\tau$ = 15.6 Hz, vinyl, trans), 6.85 (2 H, br t, $\tau$ = 7.8 Hz, aryl), 7.34-7.40 (4 H, m, aryl), 7.55-7.58 (2 H, m, aryl), 7.64 (1 H, s, NH), 7.75-7.80 (2 H, m, aryl and vinyl), 8.37 (1 H, d, $\tau$ = 8.1 Hz, aryl); IR (CH$_2$Cl$_2$) 3380 (NH), 1685 (C=O) cm$^{-1}$; m/z calcd for C$_{15}$H$_{12}$INO, 348.99590; found, 348.99637.

Compound 19

Yield, 80% (46% recrystallized); mp 100°C; $^1$H NMR (CDCl$_3$) $\delta$ 5.58 (1 H, dd, $\tau_1$ = 10.2 Hz, $\tau_2$ = 1.2 Hz, terminal vinyl, cis to the internal vinylic hydrogen), 6.30 (1 H, dd, $\tau_1$ = 17.0 Hz, $\tau_2$ = 1.2 Hz, terminal vinyl, trans to the internal vinylic hydrogen), 6.86 (1 H, ddd, $\tau_1$ = $\tau_2$ = 7.7 Hz, $\tau_3$ = 1.4 Hz, aryl), 7.59 (1 H, s, NH), 7.79 (1 H, dd, $\tau_1$ = 9 Hz, $\tau_2$ = 1.4 Hz, aryl), 8.34 (1 H, d, $\tau$ = 7.8 Hz, aryl); IR (CH$_2$Cl$_2$)
3380 (NH), 1690 (C=O) cm$^{-1}$; m/z calcd for C$_9$H$_8$NOI 272.96507; found, 272.96471.

**Compound 47**

Yield, 99% (recrystallized yield, 84%); mp 176°C; $^1$H NMR (CDCl$_3$) $\delta$ 4.61 (2 H, d, $J$ = 6.0 Hz, benzylic), 6.09 (1 H, s, NH), 6.42 (1 H, d, $J$ = 15.6 Hz, vinyl), 6.99 (1 H, br t, $J$ = 7.8 Hz, aryl), 7.26-7.52 (7 H, m, aryl), 7.67 (1 H, d, $J$ = 15.6 Hz, vinyl), 7.84 (1 H, d, $J$ = 7.8 Hz, aryl); IR (CHCl$_3$) 3440 (NH), 1665 (C=O), 1625 (C=C) cm$^{-1}$; m/z calcd for C$_{16}$H$_{14}$NOI 363.01202; found 363.01196.

**Preparation of compounds 35 and 50**

The procedure for the synthesis of compound 35 is representative. Vinylacetic acid (0.225 g, 2.5 mmol) was added to dry ether (15 ml) kept at 0°C under nitrogen. To this mixture was slowly added oxalyl chloride (0.32 g, 2.5 mmol) dissolved in 5 ml of ether and the mixture was stirred at 0°C overnight. This is to make sure that all of the acid has been converted to the corresponding acid chloride [in the preparation of the acid halide leading to compound 50 excess (15 equivalents) oxalyl chloride was used]. 2-Iodoaniline (0.440 g, 2 mmol) was dissolved in THF (10 ml) and cooled to 0°C. Triethylamine (0.202 g, 2 mmol) was added slowly and the resulting mixture was stirred at 0°C for ten minutes. The acid halide (in ether) was slowly added to the mixture by a
canula or a syringe under nitrogen (it should be noted that excess oxalyl chloride used in the other procedure was removed under vacuum before addition to the ortho-iodoaniline). The resulting mixture was stirred at 0°C and allowed to warm to room temperature after two hours. The crude reaction mixture was poured into water and extracted with ether. The ether extract was dried over magnesium sulfate. After removal of ether under vacuum, the crude product was recrystallized from chloroform/hexanes mixture: crude yield, 91% (0.523 g); recrystallized yield, 43%; mp 86°C; \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.63 (1 H, s, NH), 3.24 (2 H, d, \( J = 7.2 \) Hz, allylic), 5.40 (1 H, d, \( J = 10.0 \) Hz, terminal vinyl, cis to the internal olefinic hydrogen), 5.42 (1 H, d, \( J = 17.7 \) Hz, terminal vinyl, trans to the internal olefinic hydrogen), 6.02-6.13 (1 H, m, internal vinyl), 6.84 (1 H, t, \( J = 7.5 \) Hz, aryl), 7.34 (1 H, t, \( J = 7.8 \) Hz, aryl), 7.77 (1 H, d, \( J = 7.8 \) Hz, aryl), 8.25 (1 H, d, \( J = 8.1 \) Hz, aryl); IR (CH\(_2\)Cl\(_2\)) 3250 (NH), 1690 (C=O) cm\(^{-1}\); m/z calcd for \( \text{C}_{10}\text{H}_{10}\text{NOI} \), 286.98072; found, 286.98089.

Compound 50

Yield, 98% (recrystallized yield, 65%); mp 105°C; \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 4.10 (2 H, br t, \( J = 5.7 \) Hz, allylic), 5.22 (1 H, br d, \( J = 10.2 \) Hz, terminal vinyl, cis to the internal vinylic hydrogen), 5.33 (1 H, br d, \( J = 17.1 \) Hz, terminal vinyl, trans to the internal vinyl), 7.10 (1 H, br t, \( J = 8.1 \) Hz, aryl), 7.33-7.43 (2 H, m, aryl), 7.87 (1 H, d, \( J = 8.1 \) Hz, aryl); IR
The same procedure was used except for a minor modification. Triethylamine was used in excess (10 equivalents) in order to neutralize a minor amount of the contaminated cinnamyl hydrochloride present in the cinnamylamine.\textsuperscript{55} Yield, 52\% (recrystallized); mp 136°C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 4.28 (2 H, br t, J = 6.9 Hz, CH\textsubscript{2}), 5.90 (1 H, br s, NH), 6.29-6.38 (1 H, m, vinyl, trans), 6.68 (1 H, d, J = 16 Hz, vinyl, trans), 7.14 (1 H, t, J = 7.5 Hz, aryl), 7.25-7.47 (7 H, m, aryl), 7.89 (1 H, d, J = 7.8 Hz, aryl); IR (CHCl\textsubscript{3}) 3440 (NH), 1670 (C=O) cm\textsuperscript{-1}; m/z calcd for C\textsubscript{16}H\textsubscript{14}NIO 363.01202; found 363.01229.

Preparation of compound 47 from ortho-iodobenzyl alcohol

To a mixture of ortho-iodobenzyl alcohol (0.468 g, 2 mmol) and triethylamine (0.202 g, 2 mmol) in dichloromethane (10 ml) at 0°C, was slowly added methanesulfonyl chloride (0.240 g, 2.1 mmol). The resulting mixture was allowed to stir at 0°C for two hours. The crude mixture was washed with water and extracted with ether. After drying the ether extracts over anhydrous magnesium sulfate, the volatile solvents were removed on a rotary evaporator and the crude mesylate was used immediately without further purification. The crude mesylate
was dissolved in THF (10 ml) and cooled to 0°C. To this solution was added excess allylamine (1.71 g, 30 mmol) and the resultant mixture was allowed to warm to room temperature overnight. The crude reaction was poured into water and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and the crude yellow oil was purified by column chromatography using 6:1 hexanes/ethyl acetate as eluent: yield, 91% (0.497 g); \( R_f \) 0.14 (6:1 hexanes/ethyl acetate); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.71 (1 H, s, NH), 3.28 (2 H, d, \( J = 6.0 \) Hz, allylic), 3.81 (2 H, s, benzylic), 5.13 (1 H, d, \( J = 10.2 \) Hz, terminal vinyl, cis to the internal vinylic hydrogen), 5.22 (1 H, d, \( J = 15.6 \) Hz, terminal vinyl trans to the internal vinylic hydrogen), 5.91-6.01 (1 H, m, internal vinyl), 6.95 (1 H, t, \( J = 7.5 \) Hz, aryl), 7.28-7.39 (2 H, m, aryl), 7.82 (1 H, d, \( J = 7.8 \) Hz, aryl); IR (neat) 3300 (NH) cm\(^{-1}\); m/z calcd for C\(_{10}\)H\(_{12}\)NI 273.00145; found 273.0063.

**Compound 52**

The synthesis of compound 52 was achieved as above except for minor modifications. Potassium carbonate (one equivalent) was used in order to neutralize any accompanying cinnamyl amine hydrochloride. Cinnamyl amine was used in a three fold excess; yield, 52%; \( R_f \) 0.18 (3:1 hexanes/ethyl acetate); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.88 (1 H, s, NH), 3.45 (2 H, d, \( J = 6 \) Hz, allylic), 3.87 (2 H, s, benzylic), 6.31-6.38 (1 H, m, vinyl, trans), 6.57 (1 H, d, \( J = 16 \) Hz, vinyl, trans), 6.96 (1 H, t,
\[ J = 7.8 \text{ Hz, aryl}, \ 7.19-7.41 \ (7 \ H, \ m, \ aryl), \ 7.83 \ (1 \ H, \ d, \ J = 7.8 \text{ Hz, aryl}); \ \text{IR (neat) } 3310 \ (\text{NH}), \ 3060 \ (\text{C-H}) \ \text{cm}^{-1}; \ m/z \ \text{calcd for } C_{16}H_{16}NI 349.03275; \ \text{found } 349.03244. \]

**Preparation of compounds 2, 10, 23-24, 26-29, 37-38, 53-57**

The procedure for the synthesis of compound 2 is representative. Palladium acetate (1.12 mg, 0.005 mmol); sodium carbonate, triethylamine or sodium acetate (0.625 mmol); and tetra-n-butylammonium chloride (69.5 mg, 0.25 mmol) were placed in a culture tube equipped with a stirrer and a screw cap. A solution of compound 17a (65 mg, 0.25 mmol) in DMF (0.4 ml) was slowly added with stirring under a stream of nitrogen via a 1 ml syringe. The syringe was further rinsed with 0.10 ml of DMF and added slowly to the reaction mixture (in cases where the starting halides are solids, their dissolution in DMF prior to addition is not necessary). The tube was sealed after the addition and the reaction, which was usually over in a day with Na\textsubscript{2}CO\textsubscript{3} was monitored by TLC. After a day, the reaction mixture was diluted with ether and washed with brine and water. The ether extracts were dried over anhydrous magnesium sulfate and concentrated under vacuum to yield the crude product. The crude product was dissolved in a minimum amount of ethyl acetate or chloroform and filtered through a short (three inches) silica gel column using 15:1 hexanes/ethyl acetate as eluent. Compound 2 was obtained in 97% yield (sodium carbonate was the base used): mp 94°C
(lit.\textsuperscript{56} mp 95-96°C); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 2.35 (3 H, s, CH\textsubscript{3}), 6.88-7.69 (6 H, m, aryl and N-H). Compared with \textsuperscript{1}H NMR spectrum in ref. 57.

**Compound \textsuperscript{10}**

Yield, 81%; \(R_f\) 0.33 (30:1 hexanes/ethyl acetate); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 2.32 (3 H, s, CH\textsubscript{3}), 3.72 (3 H, s, NCH\textsubscript{3}), 6.81 (1 H, s, aryl), 7.10 (1 H, t, \(J = 7.6\) Hz, aryl), 7.26 (2 H, m, aryl), 7.56 (1 H, d, \(J = 9.3\) Hz, aryl); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 137.20, 126.56, 121.51, 118.99, 118.60, 110.28, 109.02 (all aryl), 32.50 (NCH\textsubscript{3}), 9.55 (CH\textsubscript{3}); IR (neat) 3100 (C-H) cm\textsuperscript{-1}; m/z calcd for C\textsubscript{10}H\textsubscript{11}N (M\textsuperscript{+}-H) 144.0812; found 114.0811.

**Compound 21**

Yield, 90%; \(R_f\) 0.60 (2:1 hexanes/ethyl acetate); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 2.23 (3 H, s, CH\textsubscript{3}), 2.62 (3 H, s, COCH\textsubscript{3}), 7.09 (1 H, s, aryl), 7.32 (3 H, m, aryl), 7.57 (1 H, d, \(J = 9.2\) Hz, aryl); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 168.07 (C=O), 135.97, 131.51, 125.14, 123.36, 122.22, 118.79, 118.34 and 116.57 (all aryl), 23.88 and 9.61 (aliphatic); IR (neat) 1710 (C=O) cm\textsuperscript{-1}; m/z calcd for C\textsubscript{11}H\textsubscript{11}NO 173.0842; found 173.0844.

**Compound 24**

Yield, 29% (slightly impure by GC); \(R_f\) 0.55 (30:1 hexanes/ethyl acetate); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 2.49 (2 H, m, allylic), 2.86 (2 H, br t, \(J = 15\) Hz, CH\textsubscript{2}CN), 5.93-5.99 (1 H, m, vinyl), 6.39 (1 H, br d, \(J = 11.7\) Hz, vinyl), 7.11 (2 H, m, aryl), 7.49 (1
H, m, aryl), 7.76 (1 H, s, NH); IR (CHCl₃) 3490 (NH) cm⁻¹; m/z calcd for C₁₂H₉N 167.0735; found 167.0735.

Compound 26

Yield, 65%; Rₓ 0.49 (30:1 hexanes/ethyl acetate); ^1H NMR (CDCl₃) δ 1.29 (6 H, s, CH₃'s), 3.29 (2 H, s, CH₂), 3.65 (1 H, br s, NH), 6.62 (1 H, d, J = 7.5 Hz, aryl), 6.72 (1 H, t, J = 7.5 Hz, aryl), 6.98-7.03 (2 H, m, aryl); ^1³C NMR (CDCl₃) δ 127.31, 122.00, 118.80, 109.64 (all aryl), 61.79 (CH₂N), 41.86 and 27.69 (aliphatic); IR (neat) 3480 (NH) cm⁻¹; m/z calcd for C₁₀H₁₃N 147.1048; found 147.1048. Anal. calcd for C₁₀H₁₃N: C, 82.38; H, 8.88. Found C, 82.45; H, 8.37.

Compound 27

Yield, 97% (recrystallized yield, 84%); mp 176-178°C (lit. mp 175-176°C); ^1H NMR (CDCl₃) δ 6.84-6.94 (2 H, m, aryl), 7.19-7.25 (2 H, m, aryl), 7.41-7.50 (3 H, m, aryl), 7.62-7.69 (3 H, m, aryl), 7.85 (1 H, s, vinyl), 9.06 (1 H, s, NH); note: integration from δ 7.19-7.69 could not be determined accurately. It is possible that there are two isomers; ^1³C NMR (CDCl₃) δ 170.58 (C=O), 141.99, 140.08, 137.40, 135.00, 131.97, 130.44, 129.89, 129.58, 129.32, 128.95, 128.64, 128.25, 127.91, 123.05, 121.77, 119.28, 110.36, 109.75; IR (CHCl₃) δ 3460 (NH), 1705 (C=O) cm⁻¹; m/z calcd for C₁₅H₁₁NO 221.08407; found 221.0836.
Compound 28

Yield, 20%; Rf 0.35 (2:1 hexanes/ethyl acetate); 1H NMR (CDCl3) δ 2.63 (3 H, s, COCH3), 3.74 (3 H, s, OCH3), 3.74 (2 H, s, CH2, buried under the singlet due to OCH3), 7.26-7.40 (2 H, m, aryl), 7.45 (1 H, s, aryl), 7.52 (1 H, d, J = 6.9 Hz, aryl), 8.43 (1 H, d, J = 8.1 Hz, aryl); IR (neat) 1735 (C=O), 1680 (C=O) cm⁻¹; m/z calcd for C13H13NO3 231.0875; found 231.0877.

Compound 29

Yield, 73%; Rf 0.24 (10:1 hexanes/ethyl acetate); 1H NMR (CDCl3) δ 1.33 (3 H, t, J = 7.5 Hz, CH3), 2.78 (2 H, q, J = 7.5 Hz, CH2), 6.93 (1 H, s, aryl), 7.08-7.20 (2 H, m, aryl), 7.31 (1 H, d, J = 7.8 Hz, aryl), 7.61 (1 H, d, J = 7.8 Hz, aryl), 7.84 (1 H, br s, NH); 13C NMR (CDCl3) δ 136.49, 127.48, 121.90, 120.45, 119.09, 118.96, 118.86, 111.07 (all aryl), 18.40 and 14.52 (aliphatic); IR (neat) 3420 (NH), 3050 (C-H) cm⁻¹; m/z calcd for C10H11N 145.08915; found 145.08919.

Compound 376

Yield, 97%; Rf 0.30 (5:1 hexanes/ethyl acetate); 1H NMR (CDCl3) δ 2.65 (3 H, s, CH3), 7.15 (1 H, br d, J = 7.0 Hz, aryl), 7.40-8.22 (4 H, m, aryl), 8.75 (1 H, d, J = 7.2 Hz, aryl); compared with 1H NMR spectrum in ref. 57.
Compound 38

Yield, 55%; Rf 0.29 (5:1 hexanes/ethyl acetate); 1H NMR (CDCl₃) δ 1.40 (3 H, t, J = 7.5 Hz, CH₃), 3.12 (2 H, q, J = 7.5 Hz, CH₂), 7.25 (1 H, d, J = 4.2 Hz, aryl), 7.56 (1 H, dt, J₁ = 7.2 Hz, J₂ = 1.4 Hz, aryl), 7.70 (1 H, br t, J = 7.5 Hz, aryl), 8.04 (1 H, d, J = 8.7 Hz, aryl), 8.12 (1 H, d, J = 8.4 Hz, aryl), 8.82 (1 H, d, J = 4.5 Hz, aryl); 13C NMR (CDCl₃) 150.31, 149.89, 148.21, 130.21, 128.92, 127.47, 126.24, 123.39, 119.77 (all aryl), 25.03 and 14.03 (aliphatic); IR (neat) 3060, 3030 (C-H) cm⁻¹; m/z calcd for C₁₅H₁₂N 157.08915; found 157.08890.

Compound 53

Yield, 39%; Rf 0.30 (2:1 hexanes/ethyl acetate); 1H NMR (CDCl₃) δ 2.62 (3 H, s, CH₃), 7.60 (1 H, t, J = 8.1 Hz, aryl), 7.74 (1 H, t, J = 7.8 Hz, aryl), 7.93-7.98 (2 H, m, aryl), 8.37 (1 H, s, aryl), 9.11 (1 H, s, aryl); 13C NMR (CDCl₃) δ 151.15, 143.00, 135.40, 130.13, 128.27, 128.09, 127.21, 126.88, 123.14 (all aryl), 15.78 (aliphatic); IR (neat) 3080 (C-H) cm⁻¹; m/z calcd for C₁₀H₉N 143.07353; found 143.07327. Anal. calcd for C₁₀H₉N: C, 83.94; H, 6.29. Found C, 83.72; H, 6.40.

Compound 54

Yield, 39%; Rf 0.18 (1:1 hexanes/ethyl acetate); mp 195-198°C; 1H NMR (CDCl₃) δ 4.47 (2 H, d, J = 4.5 Hz,
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benzylic), 6.79 (1 H, br s, NH), 7.07-7.38 (7 H, m, vinyl and aryl), 7.64 (1 H, d, J = 1.5 Hz, aryl), 7.71 (2 H, d, J = 7.2 Hz, aryl); $^{13}$C NMR (CDCl$_3$) δ 167.28 (C=O), 136.68, 136.04, 135.53, 132.09, 130.22, 129.31, 128.41, 127.91, 127.89, 127.47, 125.14, 124.01 (aryl and vinyl), 45.00 (benzylic); IR (CHCl$_3$) 3405 (NH), 1670 (C=O) cm$^{-1}$; m/z calcd for C$_{16}$H$_{13}$NO 235.09972; found 235.09915. Anal. calcd for C$_{16}$H$_{13}$NO: C, 81.74; H 5.57. Found C, 81.93; H, 5.34.

Compound 55

Yield, 58%; R$_f$ 0.18 (1:1 hexanes/ethyl acetate); mp 157-159°C (lit. 60 mp 173°C); $^1$H NMR (CDCl$_3$) δ 2.25 (3 H, s, CH$_3$), 6.99 (1 H, s, aryl), 7.46-7.70 (3 H, m, aryl), 8.42 (1 H, d, J = 7.2 Hz, aryl), 11.64 (1 H, s, OH); $^{13}$C NMR (CDCl$_3$) δ 164.06, 138.50, 132.48, 127.82, 126.53, 126.13, 125.43, 123.33, 112.46 (all aryl), 15.30 (aliphatic); IR (CH$_2$Cl$_2$) 3050 (OH), 1650 (C=N) cm$^{-1}$; m/z calcd for C$_{10}$H$_9$NO 159.06842; found 159.06816. Anal. calcd for C$_{10}$H$_9$NO: C, 75.50; H, 5.66. Found C, 75.30; H, 5.97.

Compound 57

Yield, 33%; R$_f$ 0.17 (1:1 hexanes/ethyl acetate); $^1$H NMR (CDCl$_3$) δ 4.05 (2 H, s, allylic), 6.92 (1 H, s, vinyl), 7.20-7.62 (8 H, m, aryl), 8.45 (1 H, d, J = 8.1 Hz, aryl), 11.61 (1 H, s, NH); $^{13}$C NMR (CDCl$_3$) δ 139.12, 137.75, 132.52, 128.67, 127.95, 126.86, 126.59, 126.53, 126.43, 126.35, 123.52
and 115.53 (aryl and vinyl), 35.60 (allylic); IR (CHCl₃) 3400 (N-H), 1650 (C=O) cm⁻¹; m/z calcd for C₁₆H₁₃NO 235.09972; found 235.09990. Anal. calcd for C₁₆H₁₃NO: C, 81.74; H, 5.57. Found C, 80.41; H, 5.58.

Preparation of compound 58 from ortho-iodophenol

In a round bottom flask was added potassium carbonate (0.304 g, 2.2 mmol), ortho-iodophenol (0.440 g, 2 mmol), acetone (5 ml) and 4-bromo-1-butene. The mixture was refluxed for 24 hours under nitrogen. After cooling, the reaction mixture was poured into water (30 ml) and extracted with ether. The ether extract was dried and concentrated under vacuum. The residue was purified by column chromatography using 10:1 hexanes/ethyl acetate as eluent. Compound 58 was obtained in 55% (0.302 g) isolated yield: Rf 0.65 (10:1 hexanes/ethyl acetate); ¹H NMR (CDCl₃) δ 2.82 (2 H, q, J = 6.6 Hz, allylic), 4.25 (2 H, t, J = 6.6 Hz, OCH₂), 5.32 (1 H, d, J = 10.2 Hz, terminal vinyl, cis to the internal vinylic hydrogen), 5.40 (1 H, br d, J = 17.1 Hz, vinyl, trans to the internal vinylic hydrogen), 6.10-6.22 (1 H, m, internal vinyl), 6.89 (1 H, dt, J₁ = 7.5 Hz, J₂ = 1.2 Hz, aryl), 6.99 (1 H, dd, J₁ = 7.2 Hz, J₂ = 1.5 Hz), 7.44-7.50 (1 H, m, aryl), 7.96 (1 H, dd, J₁ = 7.8 Hz, J₂ = 1.5 Hz, aryl); IR (neat) 3060 (C-H) cm⁻¹; m/z calcd for C₁₀H₁₁lOI 273.98547; found 273.98505.
The two isomers, compounds 59 and 60 (ratio 1.1:1) were obtained by the palladium-catalyzed cyclization (see the procedure outlined for the synthesis of compound 2) of compound 58: yield, 68%; Rf 0.65 (10:1 hexanes/ethyl acetate); $^1$H NMR (CDCl₃) δ 2.03 (3 H, s, CH₃), 2.69 (2 H, t, J = 5.4 Hz, allylic hydrogens of isomer 59), 4.25 (2 H, t, J = 5.7 Hz, OCH₂ of isomer 59), 4.75 (2 H, m, OCH₂ of isomer 60), 4.90 (1 H, br s, vinyl hydrogen of isomer 59), 5.52 (1 H, br s, vinyl hydrogen of isomer 59), 5.58 (1 H, m, vinyl hydrogen of isomer 60), 6.79-7.20 (7 H, m, aryl hydrogens of both isomers), 7.59 (1 H, d, J = 7.5 Hz, aryl hydrogen of one of the two isomers); IR (neat) 3050 (C-H) cm⁻¹; GC/MS (isomer 59) 146 (M⁺), 131; (isomer 60) 146 (M⁺), 131 (M⁺-CH₃, base peak).
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PART III. ORGANOPALLADIUM APPROACHES TO CARBOCYCLES
ORGANOPALLADIUM APPROACHES TO CARBOCYCLES

Our success in the synthesis of heterocyclic aromatic compounds via palladium(0) catalysts prompted us to extend this methodology toward the synthesis of aromatic carbocycles, particularly naphthalenes and naphthols. There are many natural products such as tetracyclic antibiotics that contain the naphthalene ring system.

As a model study, we decided to apply our best cyclization conditions to the following systems (compounds 1-4). The synthesis of compounds 1 and 2 was achieved in a straightforward manner starting from ortho-iodobenzyl alcohol (Scheme 1). Thus, ortho-iodobenzyl alcohol was converted to ortho-iodobenzenaldehyde by treatment with 1.5 equivalents of pyridinium chlorochromate (PCC) in CH$_2$Cl$_2$ at room temperature for two hours.$^1$ Upon treatment of the Grignard reagent derived from 4-bromo-1-butene with o-iodobenzenaldehyde in ether at 0°C, compound 1 was obtained in a 67% isolated yield.
Compound 2 was prepared by the PCC oxidation of compound 1. Compound 3 was prepared by the treatment of o-iodobenzaldehyde with the Grignard reagent derived from 5-iodo-cis-2-pentene (prepared from 3-pentyl-l-ol by standard methods as outlined in equation 1). The yield of compound 3 was fairly low (15%).
The following methods were employed in the synthesis of compound 4, but all of them were unsuccessful (eqs. 2-4).

\[
\begin{align*}
\text{CH}_2\text{OR} & \quad \text{MgBr} & \quad \text{many products} \\
0^\circ \text{C}, \text{ ether} & \\
R = \text{Ms, p-tosyl}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{Br} & \quad \text{MgBr} & \quad \text{mostly bibenzyl products} \\
0^\circ \text{C}, \text{ ether} & 
\end{align*}
\]

Thus, when either the methanesulfonate or tosylate of o-iodobenzyl alcohol were treated with the Grignard reagent made from 4-bromo-l-butene, many products were obtained (eq. 2). However, when o-iodobenzyl bromide was treated with the same Grignard reagent, mostly bibenzyl products were obtained. When the organocuprate derived from the Grignard reagent of 4-bromo-l-butene was treated with o-iodobenzyl bromide, a bibenzyl coupled product was obtained exclusively. At this
stage, further attempts were not carried out in the synthesis of compound 4.

The three best bases (Et$_3$N, NaOAc and Na$_2$CO$_3$ as bases) reported in the previous section were chosen for the Pd-catalyzed cyclization of compounds 1-3. The attempted conditions and the products obtained from compounds 1-3 are listed in Table 1.

When compound 1 was subjected to the usual cyclization at room temperature (in the presence of Pd(OAc)$_2$ and one equivalent of n-Bu$_4$NCl in DMF), compound 5 was isolated as the only product with all three bases. Surprisingly, not even a trace of the expected 6-membered ring alcohol or 1-methylnaphthalene (the product of cyclization and subsequent dehydration), could be seen (eq. 5). This observation can be explained by the following scheme (Scheme 1). Thus, initial isomerization of the olefinic bond in substrate 1, followed by cyclization would yield compound 5. The reaction proceeds in excellent yields as indicated in Table 1. The olefinic stereochemistry in the product could not be determined by $^1$H NMR spectral
Table 1. Pd-Catalyzed Cyclization of Compounds 1-3

<table>
<thead>
<tr>
<th>Base</th>
<th>Reaction temp.</th>
<th>Reaction time</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(°C)</td>
<td>(days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et₃N</td>
<td>RT</td>
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<td><img src="image5" alt="Product 5" /></td>
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<td><img src="image6" alt="Product 6" /></td>
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<td></td>
<td></td>
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<td><img src="image7" alt="Product 7" /></td>
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</tr>
<tr>
<td>Et₃N</td>
<td>RT</td>
<td>1</td>
<td><img src="image5" alt="Product 5" /></td>
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</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Base</th>
<th>Reaction temp. (°C)</th>
<th>Reaction time (days)</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
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<tr>
<td>NaOAc</td>
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<td>6</td>
<td>47</td>
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<td>10</td>
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<td></td>
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<tr>
<td>Na₂CO₃</td>
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<td>1</td>
<td>no products</td>
<td>-</td>
</tr>
<tr>
<td>NaOAc</td>
<td>80</td>
<td>1</td>
<td>no products</td>
<td>-</td>
</tr>
<tr>
<td>Et₃N</td>
<td>80</td>
<td>1</td>
<td>6</td>
<td>49</td>
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<td>Na₂CO₃</td>
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<tr>
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</tr>
<tr>
<td>Et₃N</td>
<td>80</td>
<td>2</td>
<td>8</td>
<td>78</td>
</tr>
</tbody>
</table>
studies, although both $^{13}$C NMR and $^1$H NMR spectra revealed the presence of only one isomer.

Compound 2 undergoes cyclization smoothly to yield a mixture of two products, compounds 6 (the product of initial cyclization) and 7 (the product formed from double bond migration after initial cyclization) at room temperature. The desired compound 7 could not be obtained exclusively. Separation of the two isomers was accomplished by flash column chromatography. The combined yield of the two compounds (6 and 7) was quite good with Et$_3$N and Na$_2$CO$_3$ serving as bases. At 80°C, Et$_3$N yielded compound 6 exclusively in a 49% yield; the other two bases yielded polymeric products.

Compound 3 undergoes cyclization at 80°C with all three bases. Even here, cyclization of the starting material seemed to occur after initial internal migration of the double bond. The product 8 (one stereoisomer) was isolated in very high yields with all three bases.
The cyclization reactions reported above yielded an aromatic product with only one substrate. As these reactions did not look promising in the synthesis of polycyclic aromatics, further studies were not carried out.
EXPERIMENTAL SECTION

Equipment

Proton NMR spectra were recorded on a Nicolet NT-300 spectrometer. $^{13}$C NMR spectra were recorded on a Nicolet NT-300 (operating at 75 MHz for carbon nuclei) spectrometer. Infrared spectra were recorded on a Perkin-Elmer spectrometer. Mass spectral data were obtained on an MS-50 high resolution mass spectrometer.

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. N,N-Dimethylformamide (DMF) was distilled over calcium hydride. Methylene chloride was distilled over phosphorous pentoxide. Ortho-iodobenzaldehyde was prepared from commercially available ortho-iodobenzyl alcohol (Aldrich) by the method reported by Corey. Ether was distilled over CaH$_2$.

Preparation of compounds 1 and 3

The procedure for the synthesis of compound 1 is representative of that used to prepare compound 3. To a dry round bottom flask equipped with a side arm and a reflux condenser was added powdered magnesium metal (100 mg, 4.1 mmol) and 4 ml of freshly distilled ether. To this mixture, under nitrogen, was added 4-bromobutene (0.27 g, 2 mmol) and ethylene dibromide (0.316 g, 2 mmol) dissolved in 1 ml of
ether. After the exothermic reaction had subsided, the flask was cooled to 0°C in an ice bath, and ortho-iodobenzaldehyde (0.402 g, 1.73 mmol) slowly added. The mixture was stirred at 0°C for 30 minutes and allowed to warm to room temperature for an additional 30 minutes. The mixture was then quenched with brine and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and concentrated to give the crude product. The product was purified by column chromatography over silica gel using 5:1 hexanes/ethyl acetate as eluent. Compound 1 was obtained in 67% yield (0.334 g):

\[ R_f \quad 0.40, \quad 5:1 \text{hexanes/ethyl acetate}; \quad ^1H \text{ NMR (CDCl}_3\text{)} \delta 1.68-1.87 (3 \text{H, m, CH}_2 \text{ and OH}), 2.22-2.29 (2 \text{H, m, allylic}), 4.89-4.93 (1 \text{H, m, benzylic}), 4.99-5.12 (2 \text{H, m, terminal vinyl}), 5.85-5.95 (1 \text{H, m, internal vinyl}), 6.96 (1 \text{H, t, J} = 7.8 \text{ Hz, aryl}), 7.37 (1 \text{H, t, J} = 7.5 \text{ Hz, aryl}), 7.51 (1 \text{H, d, J} = 7.8 \text{ Hz, aryl}), 7.80 (1 \text{H, d, J} = 7.5 \text{ Hz, aryl}); \text{IR (neat) 3380 (OH), 3060 (C-H) cm}^{-1}; \text{m/z, calcd for C}_{11}H_{13}O 288.0013; \text{found 288.00133.}

**Compound 3**

Fifteen percent yield; \[ R_f \quad 0.40, \quad 5:1 \text{hexanes/ethyl acetate}; \quad ^1H \text{ NMR (CDCl}_3\text{)} \delta 1.60-1.84 (5 \text{H, m, aliphatic}), 2.10 (1 \text{H, br s, OH}), 2.23-2.30 (2 \text{H, m, allylic}), 4.88-5.00 (1 \text{H, m, benzylic}), 5.48-5.54 (2 \text{H, m, vinyl, cis}), 6.96 (1 \text{H, t, J} = 7.5 \text{ Hz, aryl}), 7.36 (1 \text{H, t, J} = 7.5 \text{ Hz, aryl}), 7.52 (1 \text{H, d, J} = 7.8 \text{ Hz, aryl}), 7.80 (1 \text{H, d, J} = 7.8 \text{ Hz, aryl}); \text{IR (neat)}
3380 (OH), 3050 (C-H) cm$^{-1}$; m/z calcd for C$_{12}$H$_{15}$O 302.0014; found 302.00142.

**Compound 2**

Pyridinium chlorochromate (0.353 g, 1.64 mmol) was suspended in methylene chloride (3 ml) and the benzylic alcohol 1 (0.313 g, 1.09 mmol) dissolved in 1 ml of dichloromethane was rapidly added at room temperature. The reaction, which was monitored by thin layer chromatography, was complete after six hours. The black reaction mixture was diluted with ether, the solvent was decanted, and the black solid was washed twice with ether. The product (compound 2) was isolated simply by filtration of the organic extracts through Florisil and evaporation of the solvent at reduced pressure. Yield 95% (0.294 g); $^1$H NMR (CDCl$_3$) $\delta$ 2.49 (2 H, br q, $J = 6.6$ Hz, allylic), 3.00 (2 H, t, $J = 7.2$ Hz, COCH$_2$), 5.00-5.12 (2 H, m, terminal vinyl), 5.83-5.93 (1 H, m, internal vinyl), 7.09-7.15 (1 H, m, aryl), 7.34-7.41 (2 H, m, aryl), 7.91 (1 H, d, $J = 8.1$ Hz, aryl); IR (neat) 3070 (C-H), 1695 (C=O) cm$^{-1}$; m/z calcd for C$_{11}$H$_{11}$O 285.98547; found 285.98559.

**Pd-catalyzed cyclization of compounds 1-3 leading to carbocycles 5, 6, 7 and 8**

The cyclizations were carried out as outlined in the experimental section of the preceding section.
Compound 5

Eighty-four percent yield, \( R_f \) 0.18, 5:1 hexanes/ethyl acetate. \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.96 (1 H, s, OH), 2.09 (3 H, br q, \( J = 1.6 \) Hz, CH\(_3\)), 2.53 (2 H, m, allylic), 4.71 (1 H, m, benzylic), 5.78 (1 H, m, vinyl), 7.24-7.39 (4 H, m, aryl); \(^1^3\)C NMR (CDCl\(_3\)) \( \delta \) 137.14, 134.39, 131.81, 128.28, 127.43, 126.66, 123.42, 121.94 (aryl and vinyl), 68.19 (benzylic), 32.70 (allylic) and 19.14 (CH\(_3\)); IR (neat) 3370 (OH), 3050 (C-H) cm\(^{-1}\); m/z calcd for C\(_{11}\)H\(_{12}\)O 160.0888; found, 160.0884. Anal. calcd for C\(_{11}\)H\(_{12}\)O: \( % \) C, 81.56; H, 7.47. Found C, 81.23; H, 7.45.

Compound 6

Sixty-four percent yield; \( R_f \) 0.45, 6:1 hexanes/ethyl acetate; \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 2.74-2.79 (2 H, m, allylic), 2.83-2.88 (2 H, m, COCH\(_2\)), 5.27 (1 H, br s, vinyl), 5.58 (1 H, br s, vinyl), 7.39 (1 H, t, \( J = 8.1 \) Hz, aryl), 7.54 (1 H, dt, \( J_1 = 6.6 \) Hz, \( J_2 = 1.6 \) Hz, aryl), 7.65 (1 H, d, \( J = 7.2 \) Hz, aryl), 8.15 (1 H, dd, \( J_1 = 7.8 \) Hz, \( J_2 = 1.5 \) Hz, aryl); \(^1^3\)C NMR (CDCl\(_3\)) \( \delta \) 197.61, 127.17, 124.74, 111.55 (aryl and vinyl), 39.37 and 32.54 (aliphatic); IR (neat) 3080 (C-H), 1680 (C=O) cm\(^{-1}\); m/z calcd for C\(_{11}\)H\(_{10}\)O 158.07317; found 158.07298. Anal. calcd for C\(_{11}\)H\(_{10}\)O: \( % \) C, 83.58; H, 6.38. Found C, 83.42; H, 6.42.
Compound 7

Forty-nine percent yield; R_f 0.32, 6:1 hexanes/ethyl acetate; ^1H NMR (CDCl_3) δ 2.60 (3 H, s, CH_3), 5.35 (1 H, br s, OH), 6.70 (1 H, d, J = 7.5 Hz, aryl), 7.12 (1 H, d, J = 7.5 Hz, aryl), 7.47-7.56 (2 H, m, aryl), 7.93 (1 H, d, J = 7.8 Hz, aryl), 8.21 (1 H, d, J = 7.8 Hz, aryl); ^13C NMR (CDCl_3) δ 149.96, 133.59, 126.63, 126.24, 126.12, 124.91, 124.66, 124.23, 122.09, 108.18 (all aryl), 18.82 (CH_3); IR (neat) 3580 (OH), 3040 (C-H) cm^-1; m/z calcd for C_{11}H_{10}O 158.07317; found 158.07321. Anal. calcd for C_{11}H_{10}O: %C, 83.58; %H, 6.38. Found %C, 83.74; %H, 6.42.

Compound 8

Ninety-one percent yield; R_f 0.22, 6:1 hexanes/ethyl acetate; ^1H NMR (CDCl_3) δ 1.18 (3 H, t, J = 7.2 Hz, CH_3), 1.82 (1 H, br s, OH), 2.47-2.57 (4 H, m, allylic), 4.67-4.74 (1 H, m, benzylic), 5.79 (1 H, m, vinyl), 7.23-7.42 (4 H, m, aryl); ^13C NMR (CDCl_3) δ 133.74, 133.64, 128.24, 127.34, 126.75, 123.16, 119.89 (aryl and vinyl), 68.29 (benzylic), 32.67 and 25.23 (allylic), 13.00 (CH_3); IR (neat) 3340 (OH), 3060 (C-H) cm^-1; m/z calcd for C_{12}H_{14}O 174.10447; found 174.10485. Anal. calcd for C_{12}H_{14}O: %C, 82.80; %H, 8.04. Found %C, 82.76; %H, 7.89.
REFERENCES

SUMMARY

Organopalladium approaches to interphenylene prostaglandin analogs, heterocycles and carbocycles have been examined. Three new prostaglandin analogs, a number of heterocycles and carbocycles have been synthesized. In particular, our synthetic approaches to heterocyclic compounds have been very successful and this methodology can be explored further in the synthesis of complex, biologically active natural products.
I would like to thank my major professor, Dr. Richard C. Larock, for his guidance and support during the course of this work. I would also like to thank my family for their encouragement and support. I would like to thank John Walling, Steven Ilkka, David Leuck, James Macias, John Price, Dean Stinn and all the members in the Larock research group for the innumerable discussions and suggestions that were helpful during the course of this work. In addition, I would like to thank my wife, Linda, for her support and encouragement during the course of this work. Finally, I would like to thank Mrs. Nancy Qvale for an excellent job in preparing this dissertation.