Present work on the Palladium-mediated direct synthesis of derivatives 4-methyl and 4-ethyl isoquinolone derivatives

Discussion
Substituted isoquinolones are important from both synthetic and application points of view. The isoquinolone moiety is found in several alkaloids and other pharmacologically important compounds.\textsuperscript{180-193} Isoquinolones have been employed as useful intermediates in the synthesis of indenoisoquinolines, protoberberines, and dibenzoquinolizines. These are of much interest in medicinal chemistry. Due to their biological and pharmacological importance, several methods have been reported for the synthesis of isoquinoline derivatives.\textsuperscript{194-199} Only few methods have utilized palladium catalyst. Palladium-catalyzed\textsuperscript{200,201} reactions have been extensively used for carboannulation\textsuperscript{202-205} and heteroannulation\textsuperscript{206-215} processes. Several research groups have reported the synthesis of aromatic heterocycles via palladium-catalyzed annulation of internal alkynes\textsuperscript{216,217} Others have shown that palladium-catalyzed cyclizations are valuable synthetic tools for the preparation of a wide variety of heterocycles using vinylic compounds, terminal alkynes, allenes and other substrates. In continuation of our work on palladium catalyzed cyclization\textsuperscript{153,155,218} we report here a straightforward protocol for the synthesis of hitherto unreported substituted isoquinolone derivatives.

The Heck precursors 414a-g were synthesized in one step by the reaction between N-allyl derivative of the corresponding amines (413) with 2-iodobenzoylchloride in anhydrous DCM in the presence of triethylamine and a catalytic amount of DMAP as outlined in Scheme 98.

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme98.png}
\end{center}

\textit{Scheme 98. Reagents and reaction condition} (i) 2-iodobenzoylchloride anhydrous CH\(_2\)Cl\(_2\), Et\(_3\)N, cat DMAP (cat) rt.
When the intramolecular Heck reaction was carried out with substrate 414a in the presence of 10 mol% of Pd(OAc)$_2$ as a catalyst, KOAc (2.5 eq) as a base and tetrabutyl ammonium bromide as a promoter in DMF at about 80°C for 1 h we obtained the corresponding N-substituted 4-methyl isoquinolone derivative 415a in 90% yield (Table 16).

Table 16: Cyclization of 414a to 415a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst $^b$</th>
<th>Base $^c$</th>
<th>Solvent</th>
<th>Yield of 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>KOAc</td>
<td>DMF</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>Cs$_2$CO$_3$</td>
<td>DMF</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>Et$_3$N</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>KOAc</td>
<td>CH$_3$CN</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>PdCl$_2$</td>
<td>KOAc</td>
<td>DMF</td>
<td>45</td>
</tr>
</tbody>
</table>

$^a$Tetrabutylammonium bromide (TBAB) was used as a promoter. All the reactions were performed at 80°C for 1-1.3 h.
$^b$10 mol% of catalyst was used
$^c$2.50 equiv of base was used. NR = No reaction

We have examined the influence of factors such as nature of the base, solvent, catalyst and the temperature on the formation of the cyclized product 415a. With increase of the temperature the yield of the product decreases due to extensive decomposition of the starting material. We have also examined the influence of the base like Cs$_2$CO$_3$, K$_2$CO$_3$, triethyl amine. KOAc proved to be the most effective base for cyclization. Changing the solvent neither reduced the reaction time nor improved the yield of the reaction. Use of low-boiling solvent such as CH$_3$CN did not give any cyclized product. We have also examined the effect of PdCl$_2$ as a catalyst, and in this case the reaction is found to be very slow. However, we obtained the same product 415a in low yield. Results are summarized in table 16.

Substrates 414b-e were treated similarly with Pd(OAc)$_2$ and KOAc in DMF for 1-1.3 h to afford different N-substituted 4-methyl isoquinolone
derivatives (Table 17) and the substrates 414f-g gave the corresponding N-
substituted 4-ethyl isoquinolone derivatives (Table 17, entry 6 & 7).
However, when the reaction was carried out with N-allyl-2-iodo-benzamide 
(414h) no cyclized product was obtained, instead it afforded the deiodinated 
product (416) (Scheme 99).

Table 17. Summarized results of the Heck reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>Time(h)</th>
<th>Product</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>414a</td>
<td>1</td>
<td>415a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>414b</td>
<td>11</td>
<td>415b</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>414c</td>
<td>11</td>
<td>415c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>414d</td>
<td>12</td>
<td>415d</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>414e</td>
<td>13</td>
<td>415e</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>414f</td>
<td>1</td>
<td>415f</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>414g</td>
<td>12</td>
<td>415g</td>
<td>70</td>
</tr>
</tbody>
</table>
Usually a ligand such as PPh$_3$ is necessary\textsuperscript{219} for carrying out this type of palladium-mediated Heck cyclization. However, no ligand is needed for achieving this type of reaction, reported here. Mechanistically, these reactions appear to proceed as depicted in Scheme 100.

In conclusion we have achieved an expedious synthesis of hitherto unreported N-substituted 4-methyl and 4-ethyl isoquinolone derivatives through a ligand free palladium mediated intramolecular Heck cyclization.