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<th>[CpIrCl2]2-catalysed cyclization of 2-alkynylanilines into indoles( Main article )</th>
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<td>Author(s)</td>
<td>Kumaran, Elumalai; Leong, Weng Kee</td>
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[Cp*IrCl₂]₂-catalysed cyclisation of 2-alkynyylanilines into indoles

Elumalai Kumaran, Weng Kee Leong*

Division of Chemistry and Biological Chemistry, Nanyang Technological University, 21 Nanyang Link, Singapore 637371. Phone: +65 6592 7577. Email: chml2k@ntu.edu.sg

Abstract: [Cp*IrCl₂]₂ catalyses the cyclisation of 2-alkynyylanilines into indoles. A wide variety of substrates is tolerated. A reaction pathway involving intramolecular hydroamination is proposed.

Keywords: Catalytic hydroamination; indole; 2-alkynyylaniline; iridium

On binding to transition metals, alkynes are activated toward nucleophilic attack. This has been demonstrated with a variety of nucleophiles, including amines,¹ imines,² water,³ alcohols,⁴ phenols,⁵ halides,⁶ carboxylic acids,⁷ nitro groups,⁸ carbonyl groups⁹ and enol ethers.¹⁰ Catalytic transformation of alkynes based on such activation has been studied with a number of different metals, and intramolecular versions are very useful in providing heterocyclic compounds. In particular, inter- and intramolecular alkyne hydroamination reactions have been extensively explored because the resulting N-heterocycles have broad synthetic interest and applications.¹¹

We have previously reported that [Cp*IrCl₂]₂ (1) can activate the C≡C bond for transformations that include hydrosilylation,¹² dimerization,¹³ and C≡C bond cleavage.¹⁴ This catalyst was also found to lead to the formation of a variety of iridium amino-carbene derivatives in the presence of an alkyne and an arylamine.¹⁵ Quite surprisingly, it catalysed the formation of 2,2’-biindoles from 2-ethynyylanilines under similar reaction conditions.¹⁶ These reactions all involved terminal alkynes or alkynyl moieties, and they were proposed to proceed via initial coordination of the alkyne moiety followed by rearrangement into a vinylidene. As expected, internal 2-alkynyylanilines cannot undergo rearrangement into a
vinylidene and hence cannot form 2,2' biindoles. We have found, instead, that these undergo cyclisation to form indoles.

Complex 1 catalysed the cyclisation of 2-(2-phenylethynyl)aniline (2a) to afford 2-phenylindole (3a) in 76% yield (Scheme 1).

Scheme 1

An optimization study (Table 1) showed that the reaction was more effective in more polar solvents such as methanol or acetonitrile (entries 2-6). The catalyst loading could be effectively lowered from 5 to 2 mol% without detriment, but further lowering to 1 mol% led to a significantly lower yield (entries 2, 7 and 8). Although a number of salt additives (NaPF₆, NaBF₄, NH₄BF₄ or NH₄PF₆) were effective (entries 9-12), NaBF₄ showed the best catalytic activity; NaBF₄ itself was not catalytically active (entry 13).

Table 1. Optimization study for the intramolecular cyclization of 2a to give 3a catalysed by [Cp*IrCl₂]₂ (1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Additive (mol%)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (5)</td>
<td>-</td>
<td>Acetonitrile-d₃</td>
<td>60</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>1 (5)</td>
<td>NaBF₄ (10)</td>
<td>Acetonitrile-d₃</td>
<td>60</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>1 (5)</td>
<td>NaBF₄ (10)</td>
<td>Toluene-d₈</td>
<td>60</td>
<td>18</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>1 (5)</td>
<td>NaBF₄ (10)</td>
<td>Chloroform-d₃</td>
<td>60</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>1 (5)</td>
<td>NaBF₄ (10)</td>
<td>THF-d₈</td>
<td>60</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>1 (5)</td>
<td>NaBF₄ (10)</td>
<td>Methanol-d₄</td>
<td>60</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>1 (2)</td>
<td>NaBF₄ (4)</td>
<td>Acetonitrile-d₃</td>
<td>60</td>
<td>8</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>1 (1)</td>
<td>NaBF₄ (2)</td>
<td>Acetonitrile-d₃</td>
<td>60</td>
<td>8</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>1 (2)</td>
<td>NaBF₄ (4)</td>
<td>Acetonitrile-d₃</td>
<td>40</td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>1 (2)</td>
<td>NH₄PF₆ (4)</td>
<td>Acetonitrile-d₃</td>
<td>40</td>
<td>8</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>1 (2)</td>
<td>NH₄BF₄ (4)</td>
<td>Acetonitrile-d₃</td>
<td>40</td>
<td>8</td>
<td>83</td>
</tr>
<tr>
<td>12</td>
<td>1 (2)</td>
<td>NaPF₆ (4)</td>
<td>Acetonitrile-d₃</td>
<td>40</td>
<td>8</td>
<td>67</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>NaBF₄ (4)</td>
<td>Acetonitrile-d₃</td>
<td>40</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

aYield determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.
Similar cyclization reactions have been studied with a number of transition metals including Au,\textsuperscript{17} Pd,\textsuperscript{18} Rh,\textsuperscript{19} and others,\textsuperscript{20} although some of them have disadvantages such as higher catalyst loading,\textsuperscript{20a} high temperature,\textsuperscript{17d,8b-c,19-20} or the need for protection of the amino group.\textsuperscript{20a} Several iridium complexes have also been examined,\textsuperscript{1a,19a,21} but the functional group tolerance was tested with only two catalytic systems,\textsuperscript{1a,21b} both of which showed very limited functional group compatibility. For example, Liu et. al. reported the iridium-catalysed intramolecular cyclization of aminoalkynes,\textsuperscript{1a} but their catalyst failed with alkynylanilines containing electron-withdrawing substituents on the aniline moiety. Similarly, the catalyst reported by Fukuzawa was not effective for alkynylanilines with an electron-withdrawing substituent on the alkyne moiety.\textsuperscript{21b} Unlike these iridium-based catalytic systems,\textsuperscript{1a,21b} however, complex 1 showed good catalytic performance with a wide range of substrates; electron-donating and electron-withdrawing substituents on either the aniline or the alkyne moiety were tolerated, as were secondary (entries 14 and 15) and sterically crowded (entry 7) 2-alkynylanilines and N-protected (entry 16) alkynylanilines (Table 2). Formation of 2-trimethylsilylindole using the optimized conditions failed; this problem has been reported with some of the other catalytic systems.\textsuperscript{18c,20a,b} In our case, however, the reaction could be made to work with a slight modification of the conditions (no salt additive and with DCE as the solvent).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & R & R’ & R” & Yield (\%) \\
\hline
1 & H & & C_6H_5 & H & 3a, 90 \\
2 & 4-CH_3 & & C_6H_5 & H & 3b, 92 \\
3 & 4-(CH_3)_3 & & C_6H_5 & H & 3c, 93 \\
4 & 4-Cl & & C_6H_5 & H & 3d, 91 \\
\hline
\end{tabular}
\caption{Substrate scope study for the intramolecular cyclization catalysed by 1.}
\end{table}
As a demonstration of the utility of this reaction for the construction of more complex N-heterocycles, we also synthesized 2,2'-biindole (3q), 1,4-diindolylbenzene (3r) and 1,3,5-triindolylbenzene (3s) in good yields using this methodology (Scheme 2).

Scheme 2
The reaction presumably involves initial binding of the alkyne moiety, in a similar manner to that proposed earlier for the formation of biindoles from 2-ethynylanilines, \(^{16}\) but with the loss of a chloride to form a cationic intermediate A (Scheme 3). Formation of a cationic species is favoured by a polar environment – in the presence of a salt or in a polar solvent. Such a cationic species has been proposed earlier for a related rhodium catalytic system, \(^{1b}\) and similarly, the alkyne is asymmetrically bound (Figure S1). The third ligand L is presumably a solvent molecule or, more likely, a second N-bound alkynylaniline. Intramolecular nucleophilic attack by the aniline moiety onto the coordinated alkyne would form B; the regiochemistry of this is controlled by the bulkiness of the R group on the alkyne as well as the favourable formation of the five-membered heterocyclic ring. Loss of a proton from the aniline moiety and protonolysis at the alkenyl-iridium bond would give the indole, and recoordination of the alkynylaniline would regenerate A. We have examined this pathway computationally at the B3LYP/LanL2DZ level using density functional theory (DFT); the free energy changes (in kJ mol\(^{-1}\)) from A are also shown in Scheme 3, and are reasonable.
In conclusion, we have found that complex 1, in the presence of a salt additive, acts as an effective catalyst for the intramolecular hydroamination of internal alkynylanilines 2 to afford indoles 3. A wide variety of substrates was tolerated. The reaction pathway proposed involved initial coordination of the alkynylaniline via the alkyne moiety to a cationic intermediate, which subsequently underwent intramolecular attack by the aniline to form the indole.

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Supplementary data: Experimental procedures and characterization data for all substrates, computationally optimized structures of intermediates A and B, and $^1$H NMR and $^{13}$C NMR spectra for new compounds. This material is available free of charge via the internet at http://dx.doi.org/1.1016/j.tetlet.
References


