This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
A General Catalytic Reaction Sequence to Alkaloid-Inspired Indole Polycycles

Adithi Danda\textsuperscript{a,b}, Kamal Kumar\textsuperscript{a,b,*} and Herbert Waldmann\textsuperscript{a,b,*}

A catalytic two-step reaction sequence was developed to access a range of complex heterocyclic frameworks based on biorelevant indole/oxindole scaffolds. The reaction sequence includes a catalytic Pictet-Spengler cyclization followed by a Au(I) catalyzed intramolecular hydroamination of acetylenes. A related cascade polycyclization of a designed β-carboline embodying a 1,5-enyne group yields analogues of the alkaloid harmicine.

The synthesis of natural product-inspired compound collections draws inspiration from the structural frameworks of natural product classes in order to imbibe the inherent biological relevance associated with these evolutionary selected scaffolds. Among the various natural product classes indole alkaloids and related heterocycles are of major interest since they represent a large class of compounds endowed with manifold bioactivities. Synthetic access to a broad range of complex molecular frameworks is usually hampered by the lack of general synthesis protocols. In fact, synthesis optimization of the core-scaffolds is the most time consuming and challenging task in building a compound collection. Consequently, concise and general synthesis routes that could rapidly and efficiently build up a range of complex molecular frameworks, in particular, based on natural product structures are very much desired.

In an attempt to generate a compound collection based on the indoloquinolizine and related scaffolds which occur widely in the alkaloid world (for representative examples see Figure 1a), we devised the reaction sequence shown in Figure 1b. Acetylenic aldehydes and tryptamines were expected to cyclize in a Pictet-Spengler reaction\textsuperscript{4} to yield tetrahydro-β-carbolines, which under suitable reaction conditions could undergo a hydroamination reaction\textsuperscript{5} with the alkyne to yield the desired indoloquinolizine framework.\textsuperscript{6} It was planned to explore different acetylenic scaffolds in the optimized general route and provide structurally diverse indole alkaloid based compounds.\textsuperscript{7}

In the initial experiments aimed at identifying a catalyst suitable to accelerate the sequence of imine formation and Pictet-Spengler cyclization (step a), we employed tryptamine (1) and o-2-phenylethynyl benzaldehyde (2) as model substrates. Treatment of the starting materials with one equivalent of trifluoroacetic acid (TFA) led to formation of Pictet-Spengler adduct 3a in less than 20% yield. Heating the reaction mixture to 50°C for 24 h almost doubled the yield of 3a (entry 1, Table 1).

The use of ytterbium complexes for hydroamination reactions has also been described.\textsuperscript{10} However, under the optimized conditions for the Pictet-Spengler cyclization (step a), we employed tryptamine (1) and o-2-phenylethynyl benzaldehyde (2) as model substrates.\textsuperscript{8} Treatment of the starting materials with one equivalent of trifluoroacetic acid (TFA) led to formation of Pictet-Spengler adduct 3a in less than 20% yield. Heating the reaction mixture to 50°C for 24 h almost doubled the yield of Pictet-Spengler adduct 3a (entry 1, Table 1).

However, the substantial amount of substrate/product decomposition was observed that rendered the purification of 3a very difficult. The literature precedence that ytterbium complexes can catalyse Pictet-Spengler cyclizations\textsuperscript{2} led us to explore Yb(OTf)\textsubscript{3} as a catalyst. Treating a mixture of tryptamine and aldehyde 2 with 10mol% of Yb(OTf)\textsubscript{3} and subjecting it to microwave irradiation provided only a very low yield of 3a (entry 2). Addition of the ionic liquid [bmim]Cl-AlCl\textsubscript{3} (0.32 mL/mmol of tryptamine) to the reaction mixture at room temperature enhanced the yield of 3a to 65% (entry 3). Under microwave heating conditions, the yield for 3a further improved to 74% and the reaction was complete within one hour. The use of ytterbium complexes for hydroamination reactions has also been described.\textsuperscript{10} However, under the optimized conditions for the Pictet-Spengler cyclization (entry 4, Table 1), formation of the hydroamination product 4a was not observed. Owing to their alkynophilicity, gold and other coinage metal complexes have
emerged as highly useful catalysts for addition and cyclization reactions involving diverse nucleophiles and alkynes.\textsuperscript{11} While silver triflate failed to provide the intramolecular hydroamination reaction of adduct 3a, \textit{i.e.} a 6-endo-dig cyclization (step b) to yield 4a (entry 5, Table 1), we examined this reaction with selected gold complexes.\textsuperscript{12} Treatment of 3a with AuCl(SMe\textsubscript{2}) in dichloroethane (DCE) at room temperature provided only 25\% yield for the indoloquinolizine 4a and even after heating the reaction mixture to 50° C the reaction did not go to completion. Resorting to gold(I) phosphine complex Au(OTf)PPh\textsubscript{3} in DCE enhanced the yield for 4a substantially (entry 7, Table 1). Under these reaction conditions, Au(PPh\textsubscript{3})SbF\textsubscript{3} as well as Au(II)Cl\textsubscript{3} were found to be very effective hydromination catalysts. In DCE the gold complex (Y) provided a good yield of indoloquinolizine 4a only in moderate yield (entry 11, Table 1), we chose the gold complex Y for the hydroamination reaction of the Pictet-Spengler adducts.

### Table 1. Optimization of two step sequence leading to Indoloquinolizine 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Reaction Time (h)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA (100)</td>
<td>DCM</td>
<td>rt to 50</td>
<td>24</td>
<td>&lt; 40</td>
</tr>
<tr>
<td>2</td>
<td>Yb(OTf)\textsubscript{3} (10 mol%)</td>
<td>DCM</td>
<td>MW, 120</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Yb(OTf)\textsubscript{3} (10 mol%) + [bmim][Cl-AlCl\textsubscript{3}]</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Yb(OTf)\textsubscript{3} (10 mol%) + [bmim][Cl-AlCl\textsubscript{3}]</td>
<td>DCM</td>
<td>MW, 120</td>
<td>1</td>
<td>74</td>
</tr>
</tbody>
</table>

\textsuperscript{a}isolated yield; \textsuperscript{b}0.32 mL/mmoll of 2; rt = room temperature; NA = not applied; NR = no reaction; MW = microwave irradiation, DCE= 1,2-dichloroethane, DCM=dichloromethane. All reactions for the hydroamination step b were performed at 0.1 mmol scale in 2 mL of solvent.

Thus, a two-step reaction sequence was established to synthesise indoloquinolizines 4 in which a mixture of 1 and 2 with Yb(OTf)\textsubscript{3} in the presence of [bmim][Cl-AlCl\textsubscript{3}] (0.32 mL/mmoll of tryptamine) in DCM was subjected to microwave irradiation at 120° C for 1.0 h to yield the Pictet-Spengler cyclization products 3 followed by treatment of the pure adducts 3 with the gold catalyst Y (10 mol%) at room temperature to afford the desired indoloquinolizines 4 (Scheme 1). The product 4a was easily purified by flash column chromatography. These reaction conditions were then applied to differently substituted tryptamines (1) and different acetylenic aromatic aldehydes (2) leading to a set of indoloquinolizines 4 via the two-step reaction sequence (Scheme 1). Under the optimized conditions, the reaction sequence tolerates various tryptamines with electron-rich and poor aromatic ring and affording the corresponding indoloquinolizines in moderate to good yields (Scheme 1). Acetylenic aldehydes carrying electron-rich and -poor aryl moieties on the acetylene were equally effective in the reaction sequence. Pleasingly, benzaldehyde with acetylene substituted with a cyclopropyl group also afforded the corresponding indoloquinolizine (4f) in moderate yield (Scheme 1). Notably, tryptamines with electron-poor functional groups, for instance, 5-chloro-tryptamine are very poor substrates for the Pictet-Spengler cyclization and thereby cannot yield the desired indoloquinolizines (4c) in acceptable yields. However, under the conditions of the developed protocol, 4c was obtained in moderate yield over two steps which demonstrate the synthetic value of the catalytic reaction sequence.\textsuperscript{13}

![Scheme 1. Synthesis of substituted indoloquinolizines by a sequence of Pictet-Spengler cyclization and gold mediated hydroamination reactions. The yields are depicted over two reaction steps.](image)

Having successfully established a synthesis of indoloquinolizines (4), we next explored the utility of the two-step protocol for the synthesis of complex, hexacyclic indoloquinolizine (7) which embody a spirooxindole ring-system fused to a tetrahydro-b-carboline ring. To this end, instead of acetylenic aldehydes (2), acetylenic isatines (5) were employed with tryptamines (Scheme 2).

Isatines have been successfully employed in similar cyclization reactions.\textsuperscript{14} However, acetylenic isatines have not been explored for the synthesis of complex natural product-inspired scaffolds. Pleasingly, the reaction between tryptamine and 5a proceeded smoothly in the presence of TFA in toluene at 50° C to provide the desired tetrahydro-b-carboline (6a, Scheme 2, see details in the Supporting Table 1) and did not require catalysis by ytterbium salts. However, we realized that the hydroamination step in the sequence did not proceed as desired under the previously optimized reaction conditions. A limited reaction screening led us to employ 10 mol\% of AuCl(SMe\textsubscript{2}) to catalyse the hydroamination reaction and to afford the desired hexacyclic indoloquinolizine (6a) in 76\% yield (see Supporting Table 1).

Under these conditions for the two-step protocol variation of the tryptamines (1) as well as acetylenic isatines (5) delivered a set of hexacyclic indoloquinolizines (7) with good overall yields over two synthetic steps (Scheme 2). Only in the case of 5-
chlorotryptamine, the Pictet-Spengler cyclization failed in the presence of TFA, and we had to resort to ytterbium catalysis (Scheme 1). Both aryl and alkyl functionalized acetylenic isatines gave the desired products (7a-h) in good yields. Notably, the products were formed as single isomers.25 Apparently the gold mediated 6-endo-dig cyclization was preferred over a 5-exo-dig cyclization that would lead to highly ring-strained spiro-products (8, Scheme 2). Furthermore, in the proton NMR spectra for 7g-h, the enamine proton Ha appears as singlet at \( \delta 5.27 \) ppm which clearly suggests formation of a six-membered ring. In the 5-exo-dig cyclization products 8g-h, the allylic coupling would have resulted in splitting of the signal for Ha (Scheme 2 and see details in the Supporting Information). Infact, a similar observation for cyclization products 1). In 5-endo homo-dig cyclization the Ha proton would have again resulted in a singlet (Scheme 2).

Supporting Information). In fact, a similar observation for cyclization product 1) also ruled out a 5-endo dig cyclization was preferred over a 5-exo-dig cyclization that would lead to highly ring-strained spiro-products (7a-h). The chemical shift of Ha in the proton NMR spectrum of the major diastereomer of 13a was found to be 5.27 ppm which clearly suggests formation of a six-membered ring. In the 5-exo-dig cyclization products 8g-h, the allylic coupling would have resulted in splitting of the signal for Ha (Scheme 2 and see details in the Supporting Information).

Selective activation of acetylenes in enyne substrates opens up interesting opportunities for rapid construction of complex polycycles.15 Carboxylic acids and electron-rich phenols have successfully been employed as nucleophiles in gold-mediated polycyclization of 1,5-enynes.16 The conspicuous absence of electron-rich indoles as nucleophiles in this reaction intrigued us to investigate the cascade polycyclization of 1,5-enyne appended tetrahydro-\( \beta \)-carboline 10 (Scheme 3). A successful polycyclization reaction of 10 would ensure a rapid access to indole-derived polycycles of higher structural complexity. We assumed that the activation of the alkyne in the Pictet-Spengler adduct 10 by gold complexes might trigger an addition of the olefin and concomitant addition of the secondary amine in 10 to a more-stabilized carbocation i.e. the methyl-substituted carbon of the olefin (pathway a) to provide yohimbane alkaloid scaffold 12.16c Alternatively, a stepwise process involving the nucleophilic opening of the cyclopropyl gold carbene 11 formed by addition of the olefin to the gold-activated alkyne, may yield either scaffold 12 (pathway b) or the harmicine analogue 13 (pathway c). The selective formation of harmicine analogues 13 suggests that the ring-closure by addition of the secondary amine in a 5-exo-tet mode was favoured over a 6-endo-tet pathway which is in accordance with Baldwin’s rules (Scheme 3).19

Our results indicate that the polycyclization cascade was a stepwise process that occurs via the cyclopropyl gold carbene intermediate 11. Mechanistically, we assume that a gold mediated 6-endo-dig cyclization leads to the formation of cyclopropane gold complex 11. The selective formation of harmicine analogues 13 suggests that the ring-closure by addition of the secondary amine in a 5-exo-tet mode was favoured over a 6-endo-tet pathway which is in accordance with Baldwin’s rules (Scheme 3).19

Conclusions
In conclusion, we have developed a general two-step catalytic synthetic access to a range of indole alkaloid-inspired complex molecular frameworks. Conditions were optimized for a sequence of Pictet-Spengler cyclization followed by the hydroamination of acetylenes to afford diverse and complex indoloquinolizines. We also discovered a Au(I) catalyzed cascade polycyclization providing access to structurally

---

**Scheme 2.** A two-step protocol to highly complex and hexacyclic indoloquinolizines embodying spirooxindole ring-system (6). The yields are depicted over two reaction steps.

**Scheme 3.** A cascade polycyclization route to hexahydro-[1f]-indolizino[8,7-b]indoles and a proposed reaction mechanism.
complex analogues of the natural product harmicine. The methodology developed gives practical and efficient access to complex small molecules and may find advantageous applications in the synthesis of alkaloids and compound collections inspired by their structures.

Acknowledgements
This work was supported by the Ministry of Innovation, Science, Research and Technology of North Rhine-Westphalia and Europäischer Fonds für Regionale Entwicklung and by the European Research Council under the European Union’s Seventh Framework Programme (FP7/2007-2013; ERC Grant 268309 to H.W.).

Notes and references
5. Some decomposition of the indololoquinozolines was observed over normal silica gel columns and therefore the fast flash column chromatography was employed to purify the indole polycycles, in particular compounds 4 and 7.
10. One composition of the indololoquinozolines was observed over normal silica gel columns and therefore the fast flash column chromatography was employed to purify the indole polycycles, in particular compounds 4 and 7.
12. Some decomposition of the indololoquinozolines was observed over normal silica gel columns and therefore the fast flash column chromatography was employed to purify the indole polycycles, in particular compounds 4 and 7.