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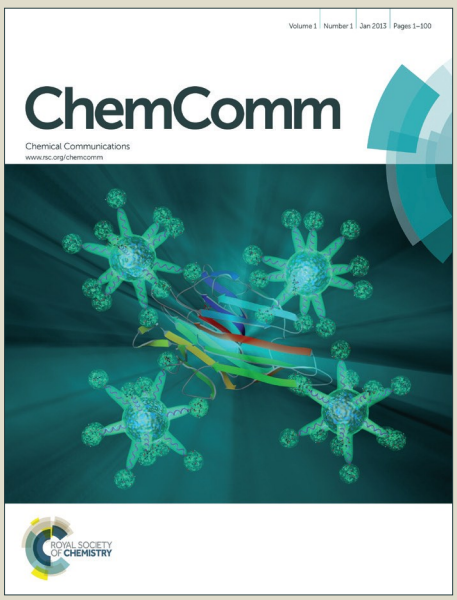

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A General Catalytic Reaction Sequence to Alkaloid-Inspired Indole Polycycles

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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.[1] 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.[2] 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.[3]

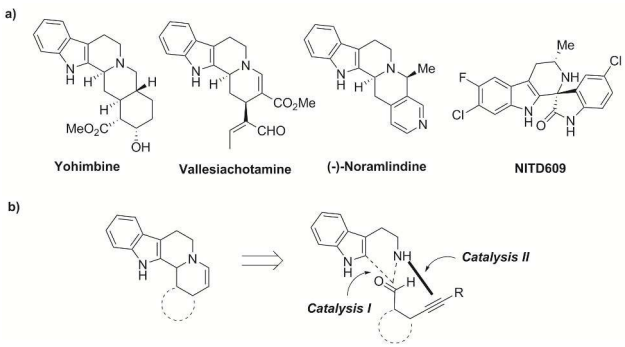


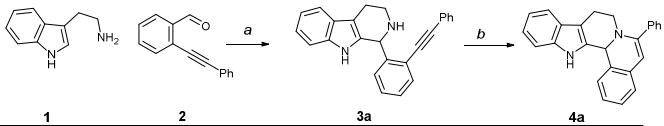
Figure 1. a) Natural and synthetic small molecules embodying the indoloquinolizines and related scaffolds; b) A general retrosynthesis of indoloquinolizines and related frameworks.

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[4] to yield tetrahydro-*β*-carbolines, which under suitable reaction conditions could undergo a hydroamination reaction[5] with the alkyne to yield the desired indoloquinolizine framework.[6] It was planned to explore different acetylenic scaffolds in the optimized general route and provide structurally diverse indole alkaloid based compounds.[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. [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[9] led us to explore $Yb(OTf)_3$ as a catalyst. Treating a mixture of tryptamine and aldehyde **2** with 10mol% of $Yb(OTf_3)$ and subjecting it to microwave irradiation provided only a very low yield of **3a** (entry 2)**.** Addition of the ionic liquid [bmim]Cl-$AlCl_3$ (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.[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.[11] While silver triflate failed to provide the intramolecular hydroamination reaction of adduct **3a**, *i.e.* a 6-*endo*-dig cyclization (step *b*) to yield **4a** (entry 5, Table 1), we examined this reaction with selected gold complexes.[12] Treatment of **3a** with $AuCl(SMe_2)$ 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 $Au(OTf)PPh_3$ in DCE enhanced the yield for **4a** substantially (entry 7, Table 1). Under these reaction conditions, $Au(PPh_3)SbF_6$ as well as $Au(III)Cl_3$ were similarly effective (entries 8-9, Table 1). Interestingly, the gold complexes (CH_3CN)[(2-biphenyl)di-adamantylphosphine]-gold(I) (**X**) and its *tert*-butyl analogue (**Y**) were found to be very effective hydromination catalysts. In DCE the gold complex (**Y**) provided a good yield of indoloquinolizine **4a** (entry 10). However, its catalytic efficiency in acetonitrile was only low and owing to the very low solubility of **Y** in toluene, no hydroamination product was observed even after 24 h of the reaction (entries 12-13). Since the catalyst **X** provided the 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.

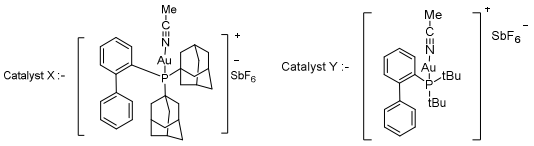
Table 1. Optimization of two step sequence leading to Indoloquinolizine **4a**



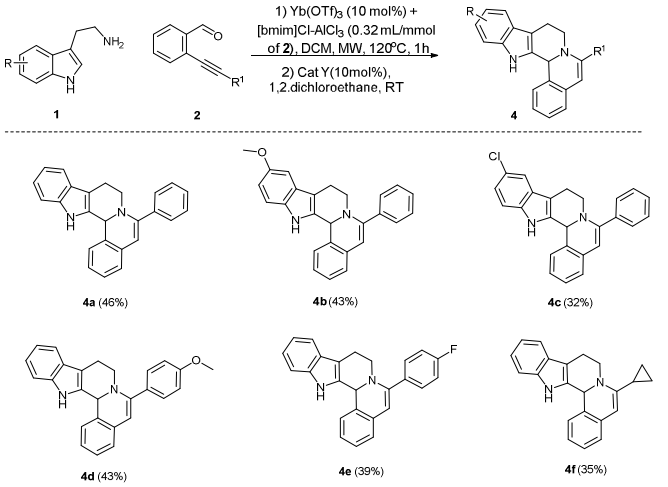
1 2 3a 4a

Entry	Catalyst (mol%) for **a**	Catalyst (10 mol%) for **b**	Solvent	Temp. (°C)	Reaction Time (h)	Yield [%][a] 3a	4a
1	TFA (100)	--	DCM	r t to 50	24	< 40	NA
2	$Yb(OTf)_3$ (10)	--	DCM	MW, 120	1	12	NA
3	$Yb(OTf)_3$ (10) + [bmim]Cl-$AlCl_3$[b]	--	DCM	r t	24	65	NA
4	**$Yb(OTf)_3$ (10) + [bmim]Cl-$AlCl_3$[b]**	--	**DCM**	**MW, 120**	**1**	**74**	NA
5	--	AgOTf	DCE	r t	1	NA	Trace
6	--	$AuCl(SMe_2)$	DCE	r t	1	NA	25
7	--	$Au(OTf)PPh_3$	DCE	r t	1	NA	40
8	--	$Au(PPh_3)SbF_6$	DCE	r t	1	NA	35
9	--	$AuCl_3$	DCE	r t	1	NA	37
10	--	**Cat. Y**	**DCE**	**r t**	**1**	NA	**62**
11	--	**Cat. X**	DCE	r t	1	NA	42
12	--	**Cat. Y**	MeCN	r t	1	NA	48
13	--	**Cat. Y**	Toluene	r t	24	NA	NR

[a]isolated yield; [b]0.32 mL/mmol of **2**; rt = room temperature; NA = not applied; NR = no reaction; MW = microwave irradiation, DCE- 1,2-dichloroethane, DCM-dichlorometahne. 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 $Yb(OTf)_3$ in the presence of [bmim]Cl-$AlCl_3$ (0.32 mL/mmol 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.[13]

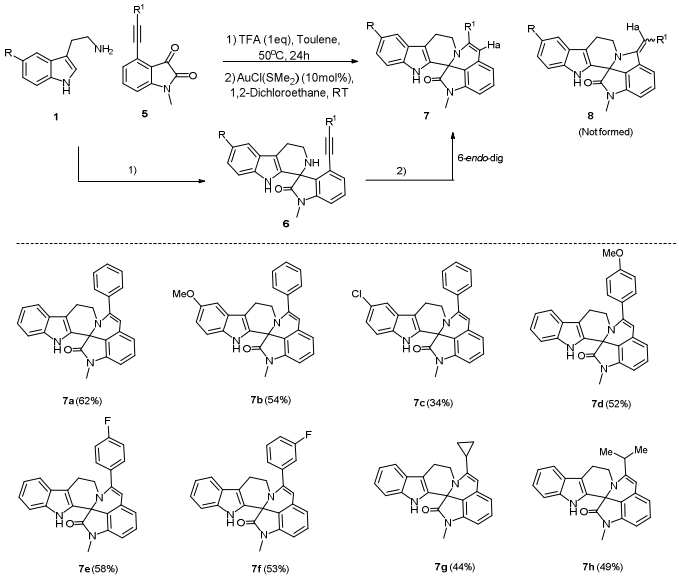


Scheme 1. Synthesis of substituted indoloquinolizines by a sequence of Pictet-Spengler cyclization and gold mediated hydroamination reactions. The yields are depicted over two reaction steps.

Having successfully established a synthesis of indoloquinolizines (**4**), we next explored the utility of the two-step protocol for the synthesis of complex, hexacyclic indoloquinolizines (**7**) which embody a spirooxindole ring-system fused to a tetrahydro-β-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.[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-β-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 $AuCl(SMe_2)$ to catalyse the hydroamination reaction and to afford the desired hexacyclic indoloquinlizine (**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-

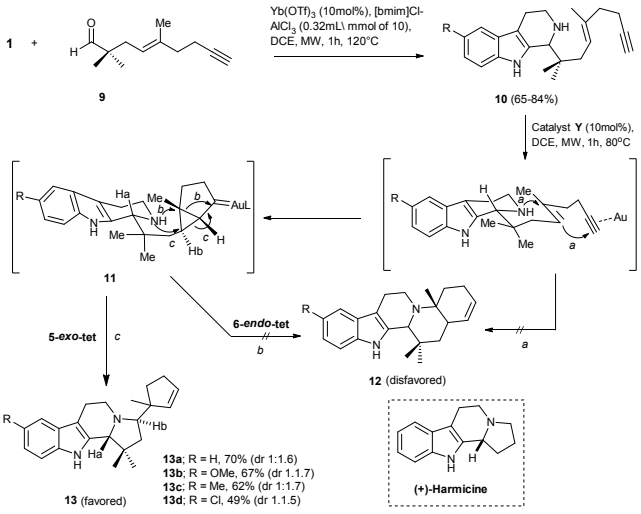
chlorotryptamine, the Pictet-Spengler cyclization failed in the presence of TFA, and we had to resort to ytterbium catalysis (Scheme 1). Both aryl and alkyl functionalized acetylenic isatines gave the desired products (**7a-h**) in good yields. Notably, the products were formed as single isomers.[13] 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 ~ δ 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 indoloquinolizines (**4**) also ruled out a 5-*exo*-dig cyclization (Scheme 1).



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

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-β-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**.[16a] 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*).[17] Under the optimized reaction conditions (Scheme 1), tryptamine and enyne aldehyde **9** yielded the Pictet-Spengler adduct **10a** in 84% yield (Scheme 3 and see the Supporting Information for details). A reaction screening for the catalytic polycyclization cascade was then attempted with the Pictet-Spengler product **10a** employing various gold complexes (see details in Supporting Table 2). $Au(PPh_3)OTf$ did not provide **12** in a reaction with **10a**. However, under these conditions a cyclization cascade lead to harmicine[18] analogue **13a** (Scheme 3) embodying a cyclopentyl ring (30% yield, see Supporting Table 2). Attempts with different Au(I) catalysts, $Au(PPh_3)NTf_2$, $AuCl(SMe_2)$, and also a Au(III) catalyst ($AuCl_3$), under different reaction conditions led only to the formation of **13a** in moderate and varying yields. Formation of cyclization product **12** was not observed (see the Supporting Information Table 3). Interestingly, catalyst **Y** was again found to be suitable for the synthesis of natural product analogues **13** when the reaction was performed in DCE and under microwave heating at 80°C. Under the optimized reaction conditions (Scheme 3), differently substituted adducts **10** underwent the cascade polycyclization and yielded the tetracyclic indoles **13** in good yields as mixtures of diastereoisomers (Scheme 3). The *syn*-configuration in the minor diastereomer of **13** was established by observation of a nOe signal between Ha and Hb. A significant difference in the chemical shift of Ha in the proton NMR spectrum of the major diastereomer thus indicates an *anti*-configuration (see the Supporting Information for details).

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[17] over a 6-*endo*-tet pathway which is in accordance with Baldwin´s rules (Scheme 3).[19]



Scheme 3. A cascade polycyclization route to hexahydro-1*H*-indolizino[8,7-*b*]indoles and a proposed reaction mechanism.

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

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.

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Notes and references

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