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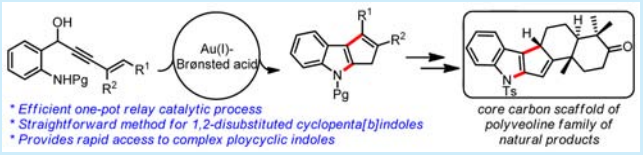
One-Pot Relay Gold(I) and Brønsted Acid Catalysis: Cyclopenta[*b*]annulation of Indoles via Hydroamination/Nazarov-Type Cyclization Cascade of Enynols

Seema Dhiman and S. S. V. Ramasastry*

Organic Synthesis and Catalysis Lab, Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Sector 81, S. A. S. Nagar, Manuali PO, Punjab 140306, India

Supporting Information

ABSTRACT: An expedient relay gold(I) and Brønsted acid catalyzed hydroamination/Nazarov cyclization of 1-(2-aminophenyl)pent-4-en-2-ynols for the synthesis of various polyfunctionalized cyclopenta[*b*]indoles is described. The synthetic utility of this method has been demonstrated by the synthesis of a few unprecedented pentacyclic indoles and indole−steroidal hybrids. Further, the new methodology has been successfully applied to the enantioselective synthesis of core carbon structure of the polyveoline family of natural products.

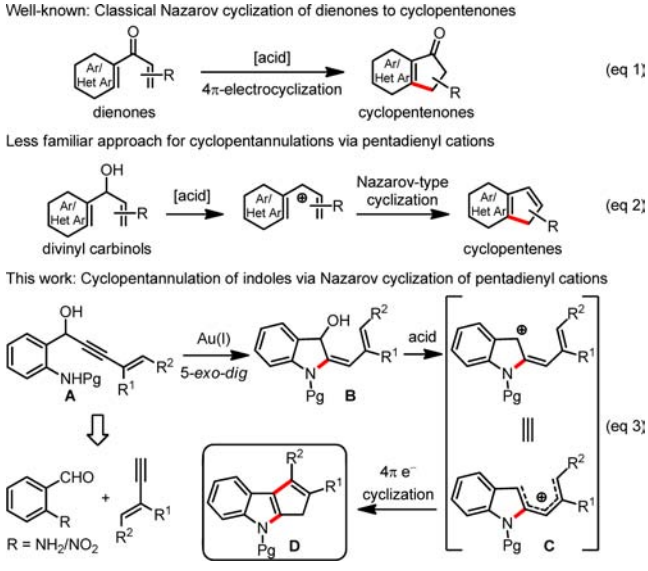


Gold-catalyzed transformations have attracted tremendous attention in recent years owing to their exceptional ability to activate π-systems of alkynes, allenes, and alkenes toward nucleophilic attacks.[1] Most of these methods provide access to several complex structural motifs under extremely mild conditions which were previously inaccessible through traditional synthetic transformations. In particular, relay gold catalytic processes were demonstrated to exhibit great potential in rapidly assembling intricate chemical structures often associated with pot, step, and atom economy.[2]

Cyclopenta[*b*]indoles undoubtedly are privileged substructures owing to the occurrence of several bioactive natural products and discovery of many medicinally significant compounds.[2i,3] Among several elegant approaches for the construction of this skeleton, the Nazarov reaction[4] is undoubtedly one of most versatile and efficient methods. However, most of the Nazarov cyclizations leading to cyclopentenes exploit the 4π-electrocyclizations of dienone systems extensively (Scheme 1, eq 1). Surprisingly, Nazarov-type cyclizations of pentadienyl cations (originating from the respective divinyl carbinols) for the synthesis of cyclopentannulated aryls and heteroaryls are rather scarce (Scheme 1, eq 2).[5] Toward this, we have initiated a program for the rapid assemblage of pentadienyl cationic systems through gold-mediated cascade processes from easily accessible starting compounds which should eventually lead to the cyclopentannulation of indoles.

It was envisaged that 2-aminophenyl enynols **A** could undergo Au(I)-catalyzed 5-*exo*-*dig* cyclization (hydroamination) to form 2-allylidene indolinols **B**. Further, under acidic conditions, indolinols **B** could generate the pentadienyl cations **C**, which potentially undergo a 4π-electrocyclization leading to the formation of cyclopenta[*b*]annulated indoles **D** (Scheme 1, eq 3).

Scheme 1. Our Strategy for the Synthesis of Cyclopenta[*b*]indoles via Nazarov-Type Cyclization



Since 1-(2-aminophenyl)pent-4-en-2-ynols **A** are underexplored substrates, especially never being employed in a gold-catalyzed process, and since modular access to this class can be achieved from readily available 2-amino or 2-nitro benzaldehydes and enynes (Scheme 1, eq 3), this method thus can be a short and efficient strategy for the synthesis of cyclopentannulated indoles. Herein, we delineate our efforts toward the development of a novel synthetic strategy aimed at the construction of 1,2-disubstituted cyclopenta[*b*]indoles from

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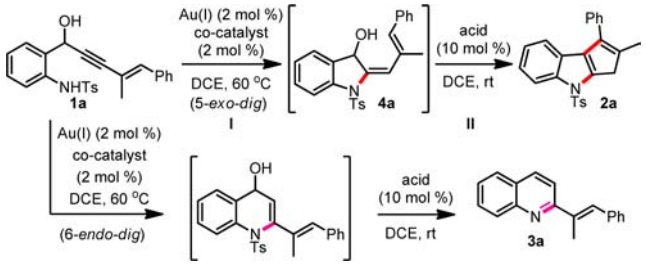
enynols **A** facilitated by the 4π-electrocyclization of rather uncommon pentadienyl cations with Au(I) and Brønsted acid as promoters of the two cyclization events.[6]

In order to validate the mechanistic hypothesis proposed in Scheme 1, eq 1,[7] the enynol **1a** was chosen as the model substrate.[8] In light of our previous success with a Au(I)−TfOH relay catalytic system for the cyclopentannulation of heteroaryls,[2i] we chose this catalyst system in the preliminary evaluation. Gratifyingly, reaction of **1a** under the prototypical conditions furnished the desired product **2a** in 74% yield along with an easily separable quinoline **3a**[9] (in 8% yield) (Table 1, entry 1). With the intention of further improving the efficiency of the reaction, various base, solvent, gold precatalysts, and acid combinations were investigated, and the results are compiled in Table 1.

Table 1. Optimization of Reaction Parameters[a,b]



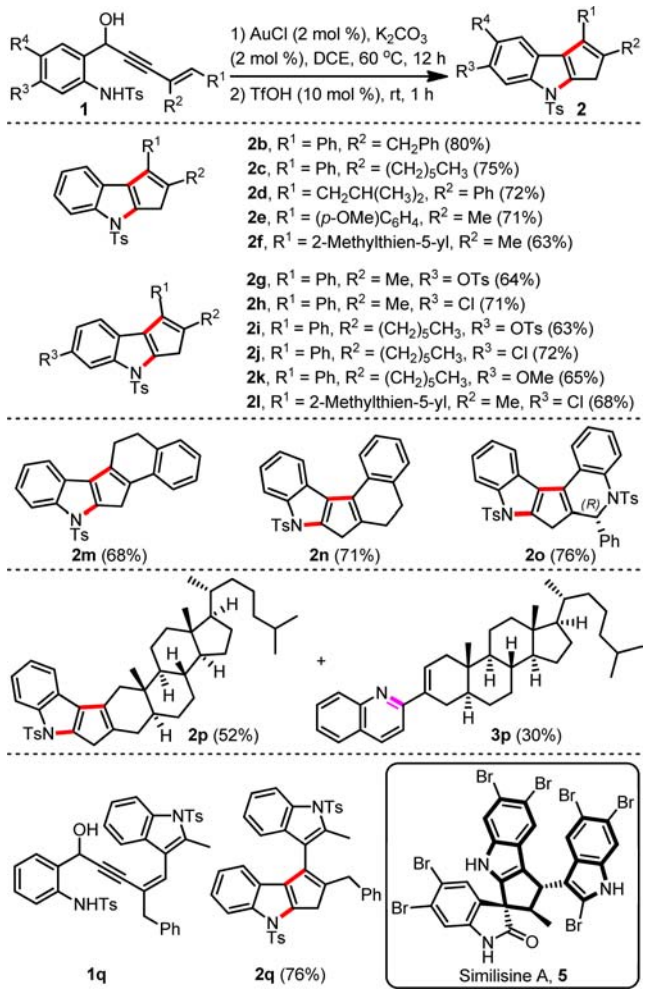
entry	catalyst	co-catalyst	acid	time (h)	**2a**, yield[c] (%)
1	AuCl	K_2CO_3	TfOH	13	74
2	AuCl	Na_2CO_3	TfOH	13	60
3	AuCl	Et_3N	TfOH	13	38
4	AuCl	AgOTf	TfOH	48	–
5	PPh_3AuCl	$AgSbF_6$	TfOH	48	–
6[d]	AuCl	K_2CO_3	TfOH	15	57
7[e]	AuCl	K_2CO_3	–	48	–
8[f]	AuCl	K_2CO_3	TfOH	13	–
9	AuCl	K_2CO_3	$HClO_4$	16	64
10	PPh_3AuCl	K_2CO_3	TfOH	26	56
11	AuCl	K_2CO_3	TMSOTf	16	70
12	AuCl	K_2CO_3	$Bi(OTf)_3$	60	43
13	AuCl	K_2CO_3	$In(OTf)_3$	60	49
14	AuCl	K_2CO_3	$BF_3.OEt_2$	13	67
15	AuCl	K_2CO_3	$AgSbF_6$	60	36
16[g]	$AuCl_3$	K_2CO_3	TfOH	30	36
17	Ipr AuCl	K_2CO_3	TfOH	30	59
18	AgOAc	–	TfOH	14	68

[a]A 5 mL glass vial was filled with **1a** (0.1 mmol), Au(I) catalyst (0.002 mmol), co-catalyst (0.002 mmol), and solvent (1 mL), and stirred at 60 °C. Upon disappearance of **1a** (by TLC), an acid (0.01 mmol) was added at room temperature (rt) and stirring continued at rt until **4a** disappeared (by TLC). [b]6−10% of the quinoline **3a** also formed in cases where step I worked. [c]Isolated yield after column chromatography. [d]Toluene as solvent. [e]When THF was used as solvent, even step I did not work. [f]Step II at 60 °C. [g]6 mol % of base.

Although initial success was obtained from a Au(I)/base combination, subsequent attempts to improve the yield with different inorganic or organic bases were discouraging (Table 1, entries 2 and 3). Commonly employed Au(I)/Ag(I) combinations[10] were surprisingly unproductive (Table 1, entries 4 and 5), and the addition of a catalytic amount of TfOH generated only a complex mixture. A brief solvent screening or performing step II at an elevated temperature delivered no promising improvements (Table 1, entries 6−8). After realizing the inefficiency of the Brønsted acids other than TfOH in step II (Table 1, entry 9), we opted to investigate the influence of Lewis acids. However, among several Lewis acids screened, except TMSOTf and BF_3·OEt_2, the others provided **2a** in poor yields (Table 1, entries 11−15). Other attempts provided only moderate success (Table 1, entries 16−18).

With the optimal conditions in hand, we next focused on investigating the substrate scope. Toward this, a diverse range of 1-(2-aminophenyl)pent-4-en-2-ynols **1b−q** were prepared and subjected to the optimized conditions. The results are summarized in Scheme 2. Overall, the relay catalytic process

Scheme 2. Substrate Scope[a,b]



[a]A 5 mL glass vial was filled with **1** (0.1 mmol), AuCl (0.002 mmol), K_2CO_3 (0.002 mmol), and 1,2-dichloroethane (1 mL) and stirred at 60 °C. Upon disappearance of **1** (by TLC), TfOH (0.01 mmol) was added at room temperature (rt) and stirring continued at rt until **4** disappeared (by TLC). [b]Isolated yield after column chromatography.

was realized to be very general and efficient, and a wide range of cyclopentannulated indoles **2b−q** could be rapidly assembled in good to excellent yields. Varied amounts (<10%) of the respective quinolines (**3**) were also usually isolated. In general, consistent reaction times were observed irrespective of the electronic or steric factors involved. Scheme 2 outlines the tolerable substituents across the aryl ring (R^1 and R^2), which can be electron-donating as well as electron-withdrawing (such

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as −OMe, −Cl, and −OTs). Regarding the olefin, a variety of alkyl, aryl, and heteroaryl substituents (R^3 and R^4) were well-tolerated under the reaction conditions.

An attractive feature of this method lies in its ability to readily assemble natural product like complex pentacyclic indoles **2m−o**. Among them, the structure of **2o** was confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information for details).[11] The present strategy thus could pave the way for the easy synthesis of their complex analogues which may find suitable applications in medicinal chemistry and also in materials science.

Next, we targeted the synthesis of indole-steroidal conjugates since indoles and steroids are well-established privileged scaffolds, and therefore, synthesis of indole−steroidal hybrids can offer potential opportunities to validate their biological properties.[12] Toward this, the cholesteryl enynol **1p**[13] was synthesized and was subjected to the optimized conditions. Along with the desired product **2p** in 52% yield, the respective quinoline **3p** (in 30% yield) was also isolated. Nevertheless, a novel entry for the previously unknown indole steroidal hybrids has been established.

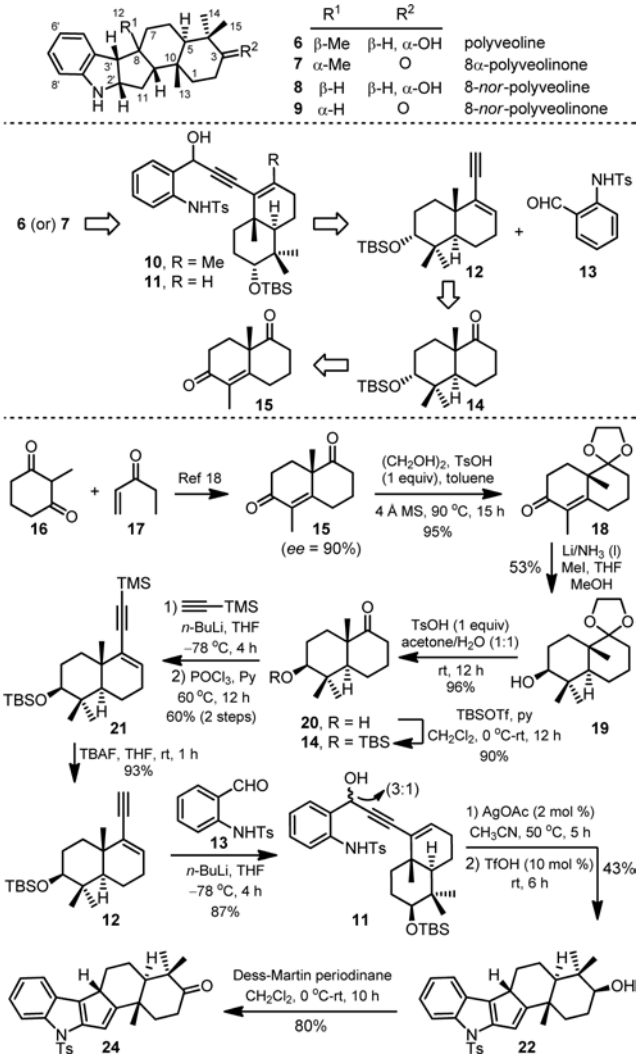
In an attempt to synthesize the bis-indole fragment present in the polybrominated spiro-trisindole natural product similisine A (**5**)[14] employing this method, enynol **1q** was prepared. Reaction of **1q** under the optimized conditions furnished the bis-indole derivative **2q**, which represents the partial structure of the tris-indole natural product similisine A (**5**).

In order to further demonstrate the synthetic utility of our method, we have undertaken the enantioselective synthesis of the core carbon skeleton of the polyveoline family of natural products. The first member of this family, polyveoline **6**, was isolated in 1978,[15a] and the latest member, 8α-polyveolinone **7**, was isolated in 2014.[15b] Despite the presence of complex molecular architectures associated with interesting biological activity profiles,[15b,16] surprisingly, no total synthesis of any member of polyveoline family has been reported thus far.[17]

Retrosynthetic analysis depicted in Scheme 3 readily identified the enynol **10** as a suitable precursor for the synthesis of the complete carbon framework of either **6** or **7**. However, since the preliminary results pertaining to Au(I)-mediated reaction of enynols such as **10** where the olefin is *tetrasubstituted* generated only the respective quinolines, we targeted the synthesis of the carbon skeleton present in 8-nor-polyveoline **8** and 8-nor-polyveolinone **9**. For this purpose, enynol **11** serves as a suitable retrosynthetic precursor which can be readily obtained from the enyne **12** and the amino benzaldehyde **13**. The enyne **12** can be obtained from the ketone **14**, which in turn can be easily derived from the Wieland−Miescher ketone analogue **15**.

To begin with, commercially available 2-methylcyclohexane-1,3-dione **16** was converted via the Wieland−Miescher analogue **15**[18] into the strategic intermediate **14**.[19] Treatment of **14** with TMS-acetylene followed by $POCl_3$-mediated dehydration generated the enyne **21** in 60% yield over two steps. Selective deprotection of TMS group in **21** was accomplished by TBAF in excellent yield. With the key intermediate **12** in hand, we next attempted the synthesis of the desired enynol **11**. Thus, addition of lithiated **12** to the aldehyde **13** generated the enynol **11** in 87% yield as a 3:1 diastereomeric mixture, an inconsequential aspect in the succeeding steps. Ag(I)-catalyzed hydroamination followed by TfOH-catalyzed Nazarov-type cyclization furnished the TBS-deprotected pentacyclic indole **22** in 43% yield along with 51% of the respective quinoline **23**.[20] Dess−Martin oxidation of the alcohol **22** resulted in the formation of ketone **24**. Indoles **22** and **24** possess the complete carbon framework present in 8-nor-polyveoline **8** and 8-nor-polyveolinone **9**.

Scheme 3. Enantioselective Synthesis of the Core Carbon Scaffolds of 8-Nor-polyveoline 8 and 8-Nor-polyveolinone 9



In conclusion, we have successfully demonstrated a practical and efficient relay catalytic system for indole cyclopentannulations of 1-(2-aminophenyl)pent-4-en-2-ynols which involves a cascade Au(I)-catalyzed hydroamination and Brønsted acid catalyzed 4π-electrocyclization sequence. We have validated the generality of this method toward the synthesis of complex natural product like structures and indole steroidal conjugates. Further studies to extend the scope of this method for the buildup of scaffold diversity and elaboration toward the enantioselective total synthesis of bioactive natural products are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and characterization data for all new compounds (^{1}H NMR, ^{13}C NMR) (PDF)
X-ray crystal structure of **2o** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: ramsastry@iisermohali.ac.in.

Notes

The authors declare no competing financial interest.

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(20) Au(I)-catalyzed reaction of **11** surprisingly generated only the quinoline **23** in 84% yield (see the Supporting Information). Among several other conditions tested, AgOAc delivered the required product **22** in 43% yield. See:. Susanti, D.; Koh, F.; Kusuma, J. A.; Kothandaraman, P.; Chan, P. W. H. *J. Org. Chem.* **2012**, *77*, 7166.

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