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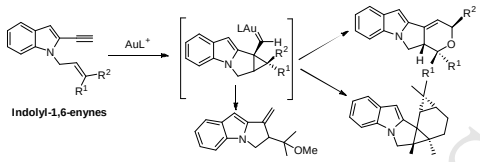

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ABSTRACT

A gold (I) catalyzed cycloisomerization of indolyl-1,6-enynes *via* 5-*exo*-dig cyclization is reported. The reaction passes through an intermediate whose fate can be steered to yield different indole polycyclic scaffolds through various intra- and intermolecular cyclization reactions. One of the key transformations of indolyl-1,6-enynes was a formal [2+2+2] cycloaddition reaction with various aldehydes to afford natural product-like tetracyclic indoles.

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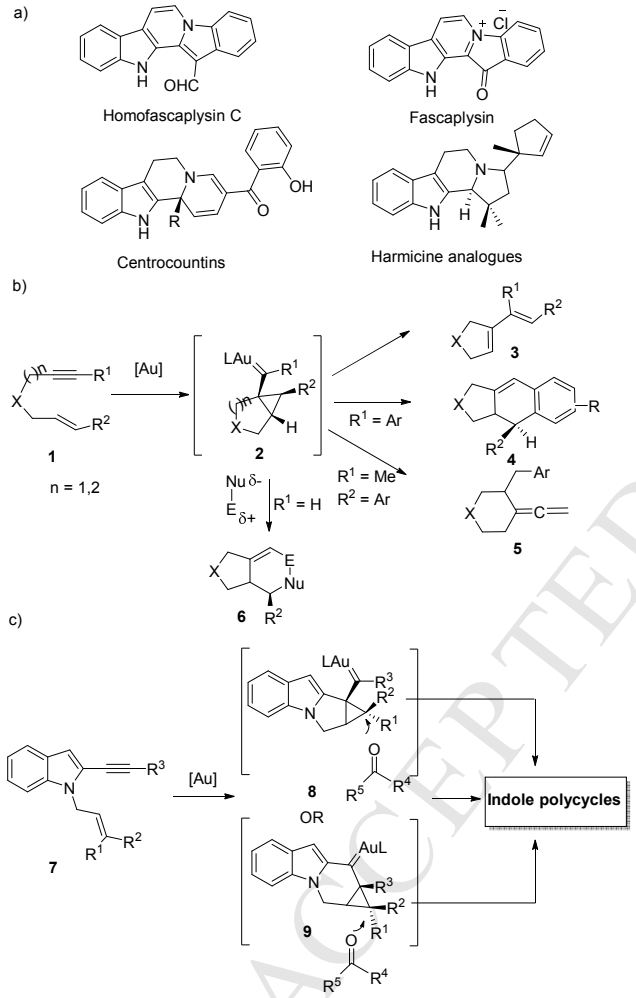
1. Introduction

Organic synthesis plays a vital role in medicinal and chemical biology discoveries by providing novel small molecule modulators of different biological functions.[1-7] Therefore, there is a constant need to unravel new chemical transformations for the synthesis of complex and novel molecular scaffolds.[8-11] In particular, chemical transformations that could yield scaffolds resembling structural features of natural products are highly desired.[12-15] In this context, we have been exploring different chemical reactivity to access privileged indole scaffold based polycyclic frameworks and derived compound collections.[16-23] For instance, an enantioselective routes to indolo-quinolizines catalyzed by chiral Lewis acids was developed affording novel mitotic modulators.[24] Recently, we also employed gold(I) mediated polycyclization reaction to build analogues of Harmicine natural product (Scheme 1a).[25]



Scheme 1. a) Indole natural product analogues and derived polycycles; b) gold mediated cycloisomerizations leading to complex scaffolds; c) indolyl-1,6-enynes as substrates to build diverse indole polycycles via gold mediated transformations.

Gold(I) catalyzed cycloisomerization reactions are efficient transformations that have been extensively explored on 1,*n*-enyne (*n* = 5-7) substrates affording a range of diverse molecules (Scheme 1b).[26-33] While these rearrangements have often yielded carbo- and oxa- heterocycles, formation of aza-heterocycles has been less explored. Enyne cycloisomerization reactions often pass through cyclopropyl gold carbene intermediates (**2**).[34-36] In the absence of external nucleophiles, 1,6- and 1,7-enynes frequently deliver dienes (**3**, Scheme 1b).[37] Only in a few cases did enyne cycloisomerizations yield structurally complex compound classes if additional modulating external nucleophiles were absent.[5-7] For instance, Echavarren et al used highly electrophilic gold (I) catalysts to perform a [4+2] cycloaddition of 1,6-enynes leading to molecules of type **4** (Scheme 1b).[38] We could successfully transform 1,7-enynes under different reaction conditions into either a scaffold similar to **4** or into an exocyclic allenic framework (**5**, Scheme 1b).[39] In order to explore and harness the potential of gold(I)-catalyzed cycloisomerization of enynes for the synthesis of complex molecular frameworks with privileged indole ring-system,[40-44] we designed the 1,6-enynes **7**. Indolyl-enynes **7** upon gold activation can lead to either a 5-*exo*-dig cyclization affording cyclopropyl gold(I) carbene intermediates (**8**) or a 6-*endo*-dig cyclization yielding intermediate **9**. Identifying the reaction conditions that selectively yield one of these intermediates could provide an opportunity for the synthesis of polycyclic indoles by various intra- and intermolecular cyclization reactions. For instance, on the one hand, the intermediates **8** or **9** themselves can rearrange to provide novel cyclic molecules and on the other hand molecular rearrangements can also be triggered by the addition of nucleophilic carbonyl compounds affording complex indole polycycles.[26] Here we present the gold(I)-catalyzed intra- and intermolecular cyclization reactions of enynes **7** and their potential in the synthesis of diverse and privileged complex molecular structures (Scheme 1c).

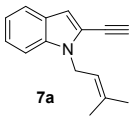
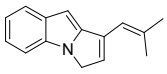
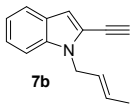
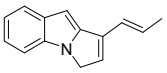
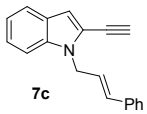
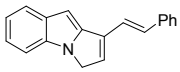
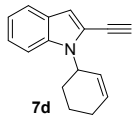
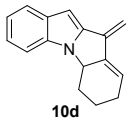
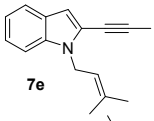
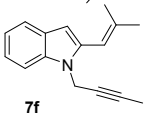
2. Results and Discussion

The synthesis of indolyl enynes **7** was carried out by means of conventional methods (see the Supporting Information) from commercially available indole 2-carboxylic acid. A successful gold catalysis process requires a good balance of both the electrophilic nature of ligands to enhance the alkynophilicity as well as back-donating ability to release the catalyst in the catalytic cycle in a facile manner. Based on the extensive literature about 1,6-enyne cycloisomerization reactions and our experience in this chemistry,[39,45,46] we focused on four different gold catalysts representing two classes of ligands, i.e. *N*-heterocyclic carbenes and phosphines and with different electronic and steric properties (**A**-**D**). The gold(I) complexes with **A**-**D** were also prepared by means of known procedures.[47-53] While the cycloisomerization of enyne **7** *via* the cyclopropyl gold carbene intermediate **8** or **9** would remain competitive reaction in intermolecular nucleophilic addition of carbonyl function, the cycloisomerization was first analyzed separately in the absence of any nucleophile with the four catalysts **A**-**D** (Table 1).

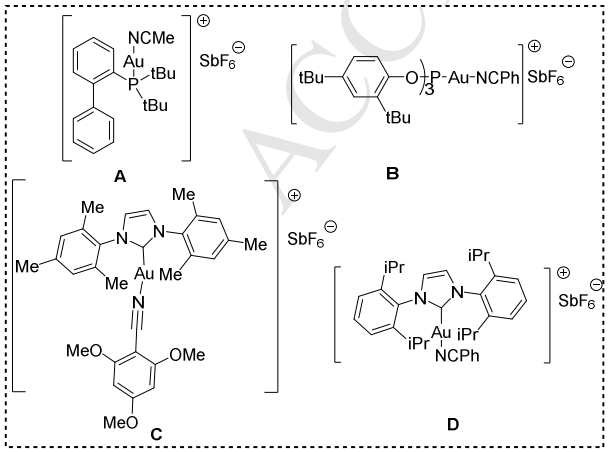
Among the set of chosen catalysts **A**-**D**, gold complex **B** is the most electrophilic, and hence also the most reactive. These characteristics often lead to lower selectivity. Catalyst **A** is less electrophilic than **B**, but more than carbene gold(I) complexes **C** or **D**. Catalysts **C** and **D** being less electrophilic might take longer to complete the reactions, however, may offer better chemo- and stereoselectivities. Different electronic and steric properties of these catalysts would nevertheless provide a better understanding of the reaction mechanism.

Table 1. Gold catalyzed cycloisomerization reaction of enynes **7**.

7 10

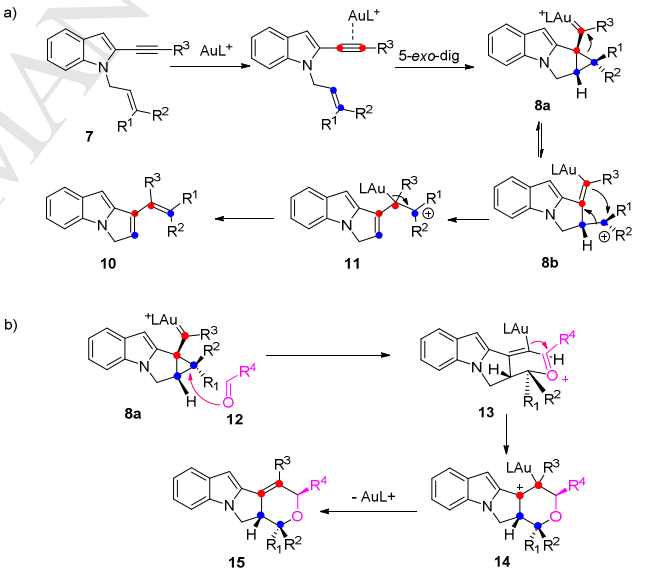
No.	Enyne 1	Cat.	Reaction Time (h)	Yield (%)[a]	Product 10
1.	 7a	A	1	82	 10a
2.	7a	B	3	--[b]	10a
3.	7a	C	3	79	10a
4.	7a	D	3	--[b]	10a
5.	 7b	A	1	--[c]	 10b
6.	 7c	A	10	80	 10c
7.	 7d	A	10	>60[c]	 10d
8.	 7e	A	24	NR	--
9.	 7f	A	24	NR	--

a: isolated yields; *b*: mixture of inseparable products formed; *c*:isolated as a mixture with another product that could not be separated. NR = no reaction observed.



Differently substituted indole enynes **7a-f** were treated with gold complexes **A**-**D** (Table 1). In all cases, when the reaction did occur, the tricyclic indoles (**10**) which are products from the *exo*-dig pathway were formed (Scheme 1c). The yields for the cycloisomerization of enyne **7a** to afford the tricyclic indole **10a** were high using catalyst **A** or **C**, whereas in other cases **10a** was formed along with inseparable impurities (entries 1-4, Table 1). In case of mono-substituted olefins, methyl substitution in **7b** led to a mixture of different products including the cyclization product **10b**. Phenyl substitution in **7c** was well tolerated and product **10c** was isolated in excellent yield (entry 6). Enyne **7e** with a cyclic olefin did react to provide the cyclization product **10e** in high yield; however, the product isolation was extremely difficult (entry 7). In agreement with literature,[54] no reaction occurred with enynes supporting substituted alkynes (Table 1, entries 8-9) even after 24 h at room temperature, clearly suggesting to use terminal acetylenes for further complexity generating transformations using gold(I) catalysis with indolyl-enynes.

The reaction mechanism for cycloisomerization of 1,6-enynes **7** catalyzed by gold(I) is summarized in Scheme 2. The reaction begins with an *exo*-dig cyclization of the olefin to the acetylene to form the *anti*-cyclopropyl gold carbenes **8a** and **8b** which evolve to provide single cleavage dienes as only the alkene is cleaved in the process (Scheme 2a). We assume that a substitution on alkyne (R^3) might sterically disfavor the formation of cyclopropane gold carbene **8a** as observed in the case of **7e-f** (Table 1).



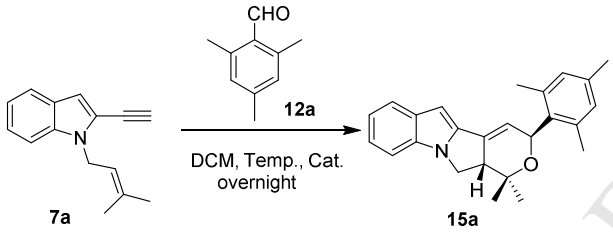
Scheme 2. a) Proposed reaction mechanism for cyclo-isomerization of enyne **1** to scaffold **10**. b) Predicted formation of tetracyclic indoles **15** in a formal [2+2+2] cycloaddition reaction.

With the information that enynes **7** under gold(I) catalytic reaction conditions follow an *exo*-dig cyclization, we assumed that aldehydes as *O*-nucleophiles would likewise add to the intermediate **8** and further rearrangement would deliver complex indole scaffolds. Plausibly, attack of an aldehyde on the cyclopropane ring would form an oxonium cationic intermediate **13** that cyclizes to form a tetracyclic intermediate **14** in a stereoselective manner (Scheme 2b).[26] The gold(I) catalyst leaves the catalytic cycle of this formal [2+2+2] cycloaddition reaction to finally yield the complex tetracyclic indole **15** (Scheme 2b).

Gold complex **A** was identified as suitable catalyst delivering the intermediate cyclopropyl gold intermediate to which an aldehyde could attack and lead to a formal [2+2+2]

cycloaddition reaction adduct **15.** However, the less electrophilic catalyst **C** also had been reported to effectively catalyze such intermolecular reactions.[55,43] Therefore, reaction conditions to afford cycloadducts **15** were optimized with both gold complex **C** as well as **A** (Table 2). At room temperature, catalyst **C** led to only 21% of the desired product **15a** and the tricyclic indole **10a** was the major product (entry 1, Table 2). We envisaged that decreasing the reaction temperature might slow down the intramolecular cyclization and thereby favor the intermolecular reaction in the presence of excess of aldehyde as nucleophile. Indeed, when the reaction was conducted with catalyst **C** at 0 °C using 5 equivalents of aldehyde, the desired product **15a** was obtained in 70% yield along with **10a** as minor product (entry 2). Using 3 equivalents of aldehyde reduced the yield for **15a** (entry 3). Also, further reducing the temperature was detrimental to the yield of **15a** (entries 4-5, Table 2) as the reaction was not complete even after 48 h. The same reaction optimization was performed with the catalyst **A** (entries 6-11, Table 2). Interestingly, with catalyst **A** the reaction was still very efficient even at low temperatures like -30 or -70°C (entries 7-11) affording the cycloaddition product **15a** as the major product and in very good yields. The best result was obtained when catalyst **A** was used at -70 °C, and with 3 equivalents of the aldehyde **12a** leading to **15a** in 65% yield (Table 2, entry 10).

Table 2. A formal [2+2+2] cycloaddition reaction between enyne **1a** and aldehyde **12a**.

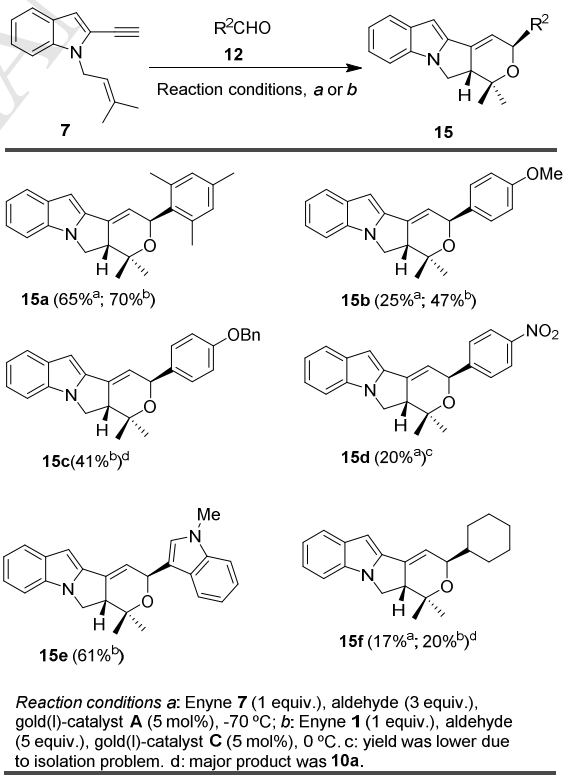


Entry	Cat. (mol%)	Temp. (°C)	12a (equiv.)	Yield 15a (%)[a]
1.	C (5)	rt	5	21
2.	**C (5)**	**0**	**5**	**70**
3.	C (5)	0	3	62
4.	C (5)	-30	5	55[b]
5.	C (5)	-70	5	50[b]
6.	A (5)	0	3	20
7.	A (5)	-30	3	63
8.	A (3)	-70	3	43
9.	A (10)	-70	3	40
10.	**A (5)**	**-70**	**3**	**65**
11.	A (5)	-70	5	62

a) Yield of isolated product. b) The reaction was not complete even after 48 h.

The gold catalyzed intermolecular formal [2+2+2] cycloaddition reaction was further extended to more aldehydes to explore the scope of the reaction (Scheme 3). Reaction conditions optimized with both the catalysts were applied. Electron-rich aromatic aldehydes performed better than electron-poor ones affording the desired adducts **15a-c** in moderate to very good yields (Scheme 3). With electron-deficient *p*-nitrobenaldehyde only a lower yield of adduct **15d** could be recorded, primarily because of its tedious purification from excess of aldehyde used in the reaction. Indole 2-carbaldehyde was also successfully employed as representative heterocycle in the cycloaddition reaction to give cycloadduct **15e** in high yield. Interestingly, cyclohexanal as a representative alkyl aldehyde also provided the desired tetracyclic indole **15f**, *albeit* in lower yield (Scheme 3). The main product in this case was the single cleavage product **10a**. Although, some other heterocyclic aldehydes like 2-furaldehyde did provide corresponding cycloaddition products (LC-MS), they could not be isolated from impurities formed as well as excess of aldehyde used in the reactions. For the same purification problem, isolated yields of several adducts are lower than for instance, in case of mesityl aldehyde in which case the product could be easily isolated.

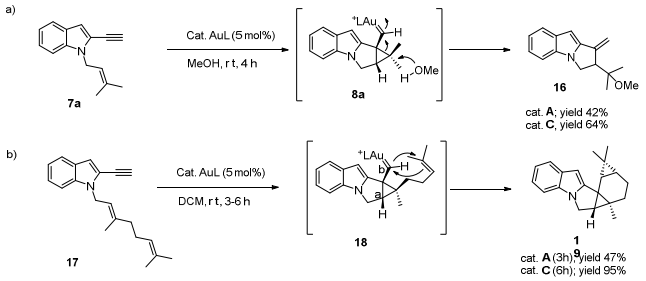
The origin of the complete diastereoselectivity for **15a-f** stems from the stereospecific formation of *anti*-cylopropane gold carbene complex **8a** to which oxo-nucleophile (**12**) adds in a Markovnikov manner leading to a carbocationic intermediate **13** which undergoes Prins type stereospecific cylization to afford the adduct **15** as single diastereoisomer (Scheme 2b).[26]



Scheme 3. Scope of the gold(I) catalyzed [2+2+2] cyclo-addition reaction between enyne **7** and various aldehydes **12**.

The successful application of enyne cycloisomerization in trapping aldehydes as nucleophiles raised our curiosity to test other nucleophiles in both inter- and intramolecular fashion. To this end, the indole enyne **7a** was treated under the optimized reaction conditions with methanol as solvent and external nucleophile and led to formation of tricyclic indole

16. Catalyst **C** provided better yield for **16** than catalyst **A** (Scheme 4a). It seems that addition of methanol to cyclopropane gold carbene intermediate opens up the ring followed by proto-deauration to yield the compound **16** (Scheme 4a).



Scheme 4. Inter- and intramolecular nucleophilic additions to cyclopropyl gold carbene intermediate of indole-enynes.

Methanol is a simple and relatively hard nucleophile as compared to aldehydes and therefore had only limited scope to modulate the intermediate **8a** into further novel frameworks. To access further molecular complexity *via* gold mediated cycloisomerization and by trapping the gold cyclopropane carbene intermediate, an extended diene-yne **17** was employed. Our curiosity was to observe a novel mode of addition of extended olefin that might happen either to cyclopropane (*a* in **18**) causing a ring-expansion or to the gold carbene center (*b* in **18**) leading to further complex and novel molecular scaffolds. Under the catalysis of **A** or **C**, in DCM and at room temperature, the dienyne **17** was cleanly transformed into a pentacyclic indole scaffold embodying two cyclopropane rings (**19**, Scheme 4b). Clearly, the reaction happens *via* addition of terminal olefin to gold carbene that further eliminates the gold catalyst forming another cyclopropane ring. Thus, while addition of a relatively hard *O*-nucleophile attacked the cyclopropane ring, the olefin preferred the gold-carbene center indicating a rather carbocationic nature of the intermediate **18** (and **8**). Further experiments might be required to shed more light on the nature of gold carbene complex **8**.

3. Conclusions

In conclusion, we have disclosed gold(I) mediated intra- and intermolecular transformations of indole based 1,6-enynes to build complex and novel indole scaffolds. A formal [2+2+2] cycloaddition reactions of indole based 1,6-enynes 7 with various aldehydes was employed as a key reaction leading to tetracyclic indoles supporting a dihydropyran ring. Successful formation of natural product-like tetracyclic indoles **15** was achieved by employing catalytic phosphine or NHC-gold complexes **A** and **C**. In addition, cycloisomerization of enynes **7** afforded the tricyclic indoles **10** that support a diene system amenable to further cycloaddition reactions to deliver further complex indoles. These gold(I) mediated divergent synthesis may find applications in designing privileged structure based scaffold synthesis.

4. Experimental Section

4.1. General

Unless otherwise noted, chemicals were obtained from Aldrich, Acros, or Alfa Aesar and were used without further purification. Reactions were carried out in standard glassware using anhydrous solvents. ^{1}H and ^{13}C NMR spectroscopic data were recorded on a Varian Mercury VX 400 or Varian 500-inova 500 spectrometer at RT unless stated otherwise. NMR spectra were calibrated to the solvent signals of $CDCl_3$, $(CD_3)_2CO$, or CD_3CN. Enantiomeric resolution was performed using a Dionex UltiMate 2000 HPLC with a 10mm Daicel IC column. HRMS-(FAB) MS were taken on Finnigan MAT MS 70. HRMS-ESI were measured on an Accela HPLC-System (HPLC column 50/1 Hypersil GOLD1.9 µm) with an LTQ Orbitrap mass spectrometer from Thermo Scientific. (ESI)-MS were measured by using an Agilent 1100 series binary pump to ether with a reversed-phase HPLC column (Macherey-Nagel). TLC was performed on Merck silica gel 60 F254 aluminum sheet. For flash chromatography silica gel from Baker (40-70 µm) was used. MPLC was performed using an Isco sq16 with prepacked cartridges (30 µm, spherical silica gel) from Interchim were used. Melting points were recorded on Büchi Melting points B-540 apparatus and are uncorrected.

4.1.1. General procedure for the synthesis of 1,6-enynes

To a freshly prepared solution of indole-2-carbaldehyde (5 mmol) in anhydrous DMF (35 mL) was added under argon Cs_2CO_3 (15 mmol) and the corresponding allyl bromide (2 mmol). The mixture was stirred overnight at 65 °C. The reaction mixture was diluted with EtOAc (35 mL) and washed with water (5 x 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by flash chromatography (petroleum ether, 100%) afforded the desired products as oils. Then, CBr_4 (11 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C. PPh_3 (22 mmol) was added and the color of the reaction turned orange. After stirring the mixture for 10 minutes at 0 °C, the corresponding *N*-substituted indole 2-carbaldehyde (5 mmol) was added dropwise at 0 °C. After stirring for another 1.5 h, the reaction mixture was diluted with pentane (50 mL), filtered through a Celite plug and the solvent removed under reduced pressure to yield the corresponding 2-(2,2-dibromovinyl)-*N*-substituted-indole (100% yield) that was directly used in the next step. 5 mmol of this indole was dissolved in anhydrous THF (50 mL) under argon atmosphere and cooled to -78 °C. *n*BuLi in hexane (10 mmol) was added dropwise. The color of the reaction turned from yellow to orange. After stirring at -78°C for 2 h, the reaction mixture was gradually warmed to room temperature (5 h). The reaction was quenched by adding saturated aqueous solution of NH_4Cl (5 mL) at 0 °C, extracted with Et_2O (3 x 50 mL), the combined organic layers dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash chromatography (100:1, petroleum ether/ethyl acetate) afforded the 1,6-enynes.

*4.1.1.1. 2-Ethynyl-1-(3-methylbut-2-en-1-yl)-1H-indole (**7a**)*

^{1}H NMR (400 MHz, acetone-d_6) δ 7.56 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.37 (ddd, *J* = 8.3, 1.7, 0.8 Hz, 1H), 7.22 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.07 (tt, *J* = 10.4, 2.2 Hz, 1H), 6.80 (d, *J* = 0.6 Hz, 1H), 5.26 (ddd, *J* = 6.6, 4.1, 1.4 Hz, 1H), 4.91 (d, *J* = 6.7 Hz, 2H), 4.16 (s, 1H), 1.92 – 1.88 (m, 3H), 1.73 – 1.66 (m, 3H); **^{13}C NMR** (101 MHz, acetone-d_6) δ 134.9, 130.1, 127.7, 126.2, 123.3,

123.1, 119.1, 118.2, 115.8, 113.3, 110.3, 109.8, 26.1, 19.3. **HRMS-ESI** calcd. for $C_{15}H_{16}N$ $[M+H]^+$: 210.1283. Found: 210.13029.

*4.1.1.2. 1-Cinnamyl-2-ethynyl-1H-indole (**7c**)*

^{1}H NMR (400 MHz, acetone-d_6): δ 7.59 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.49 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.19 (m, 2H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.87 (d, *J* = 0.7 Hz, 1H), 6.54 – 6.39 (m, 2H), 5.09 (dd, *J* = 17.2, 5.0 Hz, 2H), 4.18 (s, 1H); **^{13}C NMR** (101 MHz, acetone-d_6): δ 136.8, 136.7, 132.1, 128.7, 127.9, 127.4, 126.6, 125.1, 123.5, 121.2, 120.5, 110.5, 108.5, 85.1, 75.3, 46.1; **HRMS-ESI** calcd. for $C_{19}H_{16}N$ $[M+H]^+$: 258.1277. Found: 258.1284.

*4.2. General procedure for cyclization of 1,6-enynes to tricyclic indoles **10***

To a round bottom flask and under argon atmosphere was added 1,6-enyne **7** (1 mmol), in DCM (1 mL) followed by addition of the catalyst A (5 mol%). The reaction mixture was stirred at room temperature till completion (tlc, table 1). The solvent was removed and the product was purified by flash chromatography with pentane as eluent.

*4.2.1. 1-(2-Methylprop-1-en-1-yl)-3H-pyrrolo-[1,2-a]indole (**10a**)*

^{1}H NMR (400 MHz, acetone-d_6): δ 7.47 (d, *J* = 7.50 Hz, 1H), 7. 44 (d, *J* = 7.49 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 2.9 Hz, 1H), 7.11 (dt, *J* = 8.6, 4.3 Hz, 1H), 6.40 (d, *J* = 2.9 Hz, 1H), 6.10 (s, 1H), 3.81 (s, 1H), 1.88 (s, 3H), 1.87 (s, 3H); **^{13}C NMR** (101 MHz, acetone-d_6): δ 134.9, 130.1, 127.7, 126.2, 123.3, 123.1, 119.1, 118.2, 115.8, 113.3, 110.3, 109.8, 26.1, 19.3; **HRMS-ESI** calcd. for $C_{15}H_{16}N$ $[M+H]^+$: 210.1283. Found: 210.1299.

*4.3. General procedure for the formal [2+2+2+] cyclo-addition between indole enyne **7a** and aldehydes*

Method A: To a dried schlenk and under argon atmosphere was added the enyne (0.36 mmol, 1 eqv.) and of the corresponding aldehyde (3 eqv.) in DCM (2.0 mL). The mixture was then cooled to -70 °C (15 min.) and catalyst **A** (5 mol%) was added. The mixture was stirred overnight and warmed gradually to room temperature. The violet colored crude reaction mixture was directly concentrated and product was purified by column chromatography using pentane as eluent.

Method B: To a dried schlenk and under argon atmosphere was added the enyne (0.36 mmol, 1 eqv.) and the corresponding aldehyde (5 eqv.) DCM (2.0 mL). The mixture was then cooled to 0 °C (15 min.) and catalyst **C** (5 mol%) was added. The mixture was stirred overnight and warmed gradually to room temperature. The violet colored crude reaction mixture was directly concentrated and product was purified by column chromatography using pentane as eluent.

*4.3.1. 3-Mesityl-1,1-dimethyl-1,3,11,11a-tetrahydropyrano[4',3':3,4]pyrrolo[1,2-a]indole (**15a**)*

^{1}H NMR (400 MHz, acetone-d_6): δ 7.53 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.01 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.84 (s, 2H), 6.46 (s, 1H), 6.10 (t, *J* = 2.6 Hz, 1H), 5.80 (dd, *J* = 3.9, 2.5 Hz, 1H), 4.53 (dd, *J* = 9.6, 9.0 Hz, 1H), 3.79 (dd, *J* = 9.8, 8.8 Hz, 1H), 3.69 (ddd, *J* = 11.8, 7.8, 3.5 Hz, 1H), 2.40 (s, 7H), 2.24 (s, 3H), 1.43 (s, J = 5.8 Hz, 4H), 1.38 (s, 4H); **^{13}C NMR** (101 MHz, acetone-d_6) δ141.6, 137.4, 136.9, 133.8, 133.5, 133.3, 129.9, 129.6, 121.4, 121.2, 121.1, 119.7, 119.2, 109.9, 91.4, 73.9, 69.7, 50.9, 45.0, 20.2, 19.8, 18.8; **HRMS-ESI** calcd. for $C_{25}H_{28}NO$ [M+H]+: 358.2165. Found: 358.2168.

*4.3.2. 3-(4-Methoxyphenyl)-1,1-dimethyl-1,3,11,11a-tetrahydropyrano[4',3':3,4]pyrrolo-[1,2-a]indole(**15b**)*

^{1}H NMR (400 MHz, acetone-d_6): δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.47 (s, 1H), 6.16 (s, 1H), 5.31 (s, 1H), 4.51 (t, *J* = 9.4 Hz, 1H), 3.80 (s, 3H), 3.76 (d, *J* = 9.8 Hz, 1H), 3.68 (t, *J* = 8.4 Hz, 1H), 1.44 (s, 3H), 1.34 (s, 3H); **^{13}C NMR** (101 MHz, acetone-d_6): δ 159.7, 154.4, 134.1, 133.4, 129.0, 125.7, 121.6, 121.4, 120.9, 119.9, 114.9, 114.0, 110.1, 91.8, 73.9, 73.5, 70.7, 55.0, 51.6, 45.1, 18.7; **HRMS-ESI** calcd. for $C_{23}H_{24}NO_2$ $[M+H]^+$: 346.1802. Found: 346.1805.

*4.3.3. 3-(4-(Benzyloxy)phenyl)-1,1-dimethyl-1,3,11,11a-tetrahydropyrano[4',3':3,4]pyrrolo-[1,2-a]indole(**15d**)*

^{1}H NMR (400 MHz, acetone-d_6): δ 7.53 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.43 – 7.35 (m, 4H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.03 - 6.99 (m, 3H), 6.47 (s, 1H), 6.16 (t, *J* = 3.0 Hz, 1H), 5.31 (t, *J* = 3.0 Hz, 1H), 5.15 (s, 2H), 4.51 (t, *J* = 9.3 Hz, 1H), 3.78 (t, *J* = 8.8 Hz, 1H), 3.67 (ddd, *J* = 11.7, 8.6, 3.1 Hz, 1H), 1.44 (s, 3H), 1.34 (s, 3H); **^{13}C NMR** (101 MHz, acetone) δ 159.4, 142.2, 138.5, 135.0, 134.5, 134.0, 130.0, 129.5, 129.3, 128.6, 128.6, 128.3, 122.1, 121.9, 121.3, 120.4, 115.6, 110.6, 92.3, 74.5, 74.0, 70.5, 52.1, 45.6, 19.2; **HRMS-ESI** calcd. for $C_{29}H_{28}NO_2$ $[M+H]^+$: 422.2115. Found: 422.2114.

*4.4. Addition of methonol as nucleophile to Indole-enyne **1a***

To a dried schlenk and under argon atmosphere was added the enyne (0.36 mmol, 1 eqv.) in methanol (1.5 mL) at room temperature, followed by addition of catalyst **A** or **C** (5 mol%). The mixture was stirred for 4h when the reaction was complete (tlc). The crude reaction mixture was directly concentrated and product was purified by column chromatography using pentane as eluent.

*4.4.1. 2-(2-Methoxypropan-2-yl)-1-methylene-2,3-dihydro-1H-pyrrolo[1,2-a]indole (**16**)*

^{1}H NMR (400 MHz, acetone-d_6): δ 7.51 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.08 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 7.00 (tt, *J* = 7.1, 1.0 Hz, 1H), 6.46 (s, 1H), 5.69 (s, 1H), 5.30 (s, 1H), 4.25 (ddd, *J* = 10.9, 3.3, 1.1 Hz, 1H), 4.16 (ddd, *J* = 9.6, 7.9, 1.1 Hz, 1H), 3.69 (d, *J* = 7.9 Hz, 1H), 3.25 (br s, 3H), 1.28 (s, 3H), 0.97 (s, 3H); **^{13}C NMR** (101 MHz, acetone-d_6) δ 140.2, 133.5, 133.3, 121.2, 121.1, 119.7, 114.9, 109.9, 108.4, 90.6, 76.7, 54.0, 48.6, 44.8, 21.6, 20.9; **HRMS-ESI** calcd. for $C_{16}H_{20}NO$ $[M+H]^+$: 242.1542. Found: 242.1539.

4.5. *Synthesis of hexacyclic indole (**19**)*

To the enyne **17** (0.09 mmol) in a dried schlenk under argon atmosphere was added catalyst **A** or **C** (5 mol%) in DCM (1 mL) and orange colored reaction mixture was stirred for 3-6 h. After completion of the reaction (tlc), the concentrated mixture was purified by column chromatography to obtain the product **19**. Notably, we observed that freshly purified starting material **17** performed better and any impurity with enyne could drastically reduce the yield of the product.

*4.5.1. 1,1,3a-Trimethyl-1,1a,2,3,3a,3b,4,10c-octahydrocyclopropa[5'',6'']benzo[1'',2'':1',3']cyclopropa[1',2':3,4]pyrrolo[1,2-a]indole (**19**)*

^{1}H NMR (400 MHz, acetone-d_6): δ 7.43 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.16 (s, 1H), 4.24 (dd, *J* = 11.2, 6.1 Hz, 1H), 3.96 (d, *J* = 11.0 Hz, 1H), 1.91 – 1.74 (m, 2H), 1.81 (s, 1H, overlaped), 1.37 – 1.27 (m, 2H), 1.26 (s, 3H), 1.17 (s, 3H), 1.04 (d, *J* = 8.8 Hz, 1H), 0.85 (dd, *J* = 13.3, 8.3 Hz, 1H), 0.64 (s, 3H); **^{13}C NMR** (101 MHz, acetone-d_6): δ147.4, 145.7, 133.2, 132.7, 120.1, 120.0, 118.9, 108.4, 93.9, 43.1, 40.0, 33.2, 30.5, 28.1, 23.1, 22.3, 18.2, 16.4, 13.7. **HRMS-ESI** calcd. for $C_{20}H_{24}N$ $[M+H]^+$: 278.1902. Found: 278.1910.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://.....

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