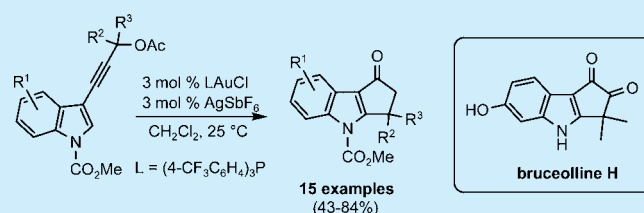


Construction of Cyclopenta[*b*]indol-1-ones by a Tandem Gold(I)-Catalyzed Rearrangement/Nazarov Reaction and Application to the Synthesis of Bruceolline HDina Scarpi,[†] Martina Petrović,[†] Béla Fiser,[‡] Enrique Gómez-Bengoa,[‡] and Ernesto G. Occhiato*,[†][†]Dipartimento di Chimica "U. Schiff", Università degli Studi di Firenze, Via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy[‡]Departamento de Química Orgánica I, Universidad del País Vasco/UPV-EHU, Manuel de Lardizabal 3, Donostia-San Sebastián 20018, Spain

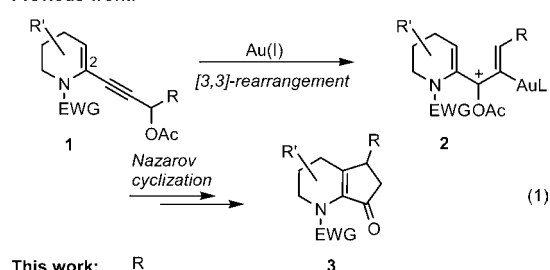
S Supporting Information

ABSTRACT: A tandem gold(I)-catalyzed rearrangement/Nazarov reaction of enynyl acetates which efficiently provides cyclopenta[*b*]indol-1-ones as useful precursors for the synthesis of natural and bioactive compounds is described. The synthetic potential of the methodology is demonstrated by the first total synthesis of bruceolline H.

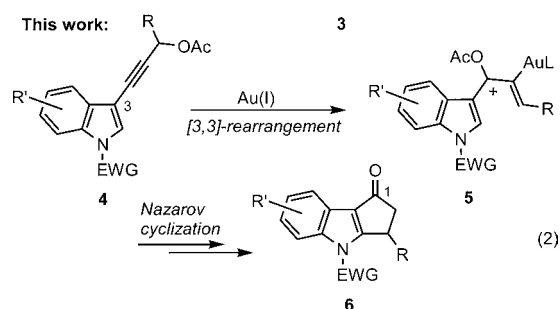


The development of new methods for the synthesis of cyclopenta[*b*]indoles is a widely explored research area, as those structures are commonly found in many natural and biologically active compounds.^{1,2} In particular, gold(I) catalysis³ has emerged in the past few years as a powerful tool for the pentannulation of indoles and other N-heterocycles.⁴ Cyclization reactions triggered by electrophilic activation of an unsaturated side chain of the heterocycle,⁵ sequential gold(I)-catalyzed hydroamination/cyclization reactions,⁶ and cascade gold(I)-catalyzed rearrangement/cyclization processes⁷ have all successfully been employed for the pentannulation of indoles. As a part of our studies on the synthesis of cyclopenta-fused heterocycles by the Nazarov reaction,^{8,9} we recently reported that N-heterocycles **1** bearing a propargylic ester moiety at position 2 (eq 1), undergo, in the presence of a gold(I) catalyst, a tandem process which forms pentannulated heterocycles **3** under remarkably mild conditions.^{7a} The process entails, as the key steps, the gold(I)-catalyzed [3,3]-sigmatropic rearrangement of the propargylic acetate, which generates requisite pentadienyl cation **2**, and the Nazarov cyclization of the latter.¹⁰ 5-Acyloxy 1,3-enynes **4** in which an indole ring bears the propargylic moiety at position 3 (eq 2) are instead unexplored substrates for this gold-catalyzed cascade process. To date, the gold(I)-catalyzed pentannulation of 3-substituted indoles has involved 3-allenylindoles,^{5c,d} 3-prop-2-ynyl-1*H*-indoles,¹¹ 3-allenones,^{5b} and 3-acyloxy 1,4-enynes,^{7b} but the behavior under gold catalysis of substrates **4** is unknown. The process would lead to the formation of cyclopenta[*b*]indoles **6** with a substitution pattern on the five-membered ring which would allow an easy entry to the bruceollines^{1a,b} and other natural products possessing the cyclopenta[*b*]indol-1-one nucleus.^{1e,f,2} Herein we report that the gold(I)-catalyzed reaction of enynyl acetates **4** provides in high overall yield target cyclopenta[*b*]indol-1-ones **6**, which are obtained in just five steps from commercially available starting material, and demonstrate the

Previous work:



This work:



synthetic potential of the methodology by the first total synthesis of bruceolline H, a natural compound whose isolation from *Brucea mollis* was first reported in 2011.^{1a}

An examination of different ligands and gold(I) counterions was first undertaken to find the best reaction conditions with model substrate **4a** ($R^1, R^2 = H, R^3 = Me$, Scheme 1).

Monitoring the reaction by ¹H NMR (Figure 1) revealed that the reaction was complete in 2 h when ligand L1 [(4-CF₃C₆H₄)₃P] and AgSbF₆ as the source of the noncoordinating anion were used, providing cyclopenta[*b*]indole **6a** in 83% yield (Table 1, entry 2). Interestingly, while monitoring the

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Scheme 1. Preparation of Substrates 4

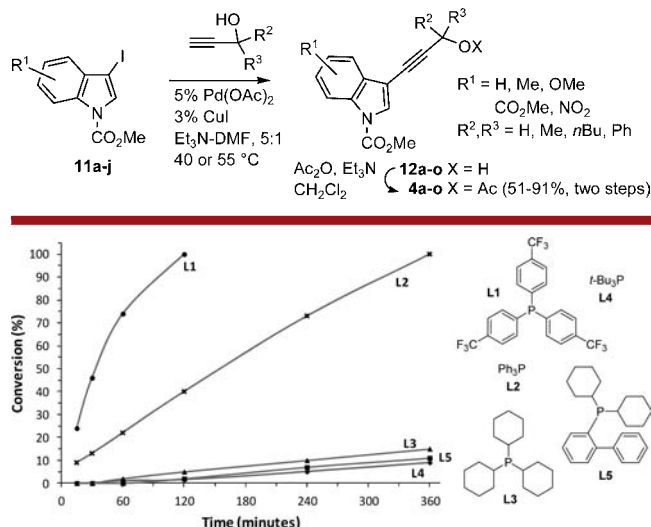


Figure 1. Effect of phosphine ligands on the reaction rate.

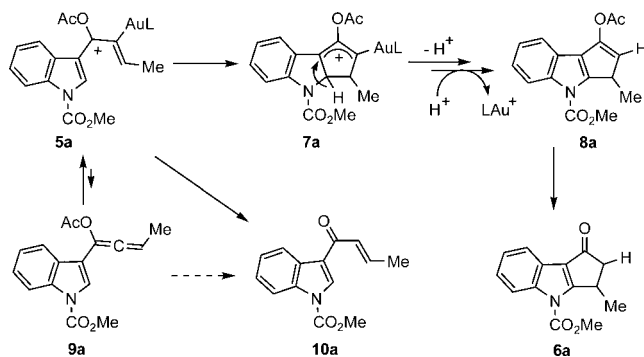
Table 1. Reaction of 4a over Various Catalysts^a

entry	ligand L	anion (X ⁻)	time (h)	6a ^b (%)	10a ^b (%)
1	Ph ₃ P	SbF ₆ ⁻	6	94 (79) ^c	6
2	(4-CF ₃ C ₆ H ₄) ₃ P	SbF ₆ ⁻	2	98 (83) ^c	2
3	cHex ₃ P	SbF ₆ ⁻	22	77	23
4	<i>t</i> -Bu ₃ P	Tf ₂ N ⁻	24	37	3
5	cHexJohnPhos	SbF ₆ ⁻	24	31	traces
6	(2,4-di- <i>t</i> -BuC ₆ H ₃ O) ₃ P	SbF ₆ ⁻	1.5	79 (73) ^c	
7	(4-CF ₃ C ₆ H ₄) ₃ P	Tf ₂ N ⁻	4	99	1
8	(4-CF ₃ C ₆ H ₄) ₃ P	TfO ⁻	2	96	4
9 ^d	(4-CF ₃ C ₆ H ₄) ₃ P	BARF ⁻	4		

^aReactions carried out by premixing 3 mol % of both LAuCl and AgX in CH₂Cl₂ for 20 min at 25 °C and then adding the substrate (0.2 mmol); ^bConversion measured by ¹H NMR; ^cYield after chromatography; ^d3 mol % of NaBARF (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was used.

reaction, we could not observe any NMR signal associated with acetate 8a (Scheme 2), formed after the cyclization process, due to its immediate transformation into final compound 6a.¹² With AgSbF₆ (3 mol %) alone, the reaction did occur but the conversion was only 6% after 2 h, thus showing that the Au(I) complex is the real catalyst for this process.

Scheme 2. Postulated Pathways

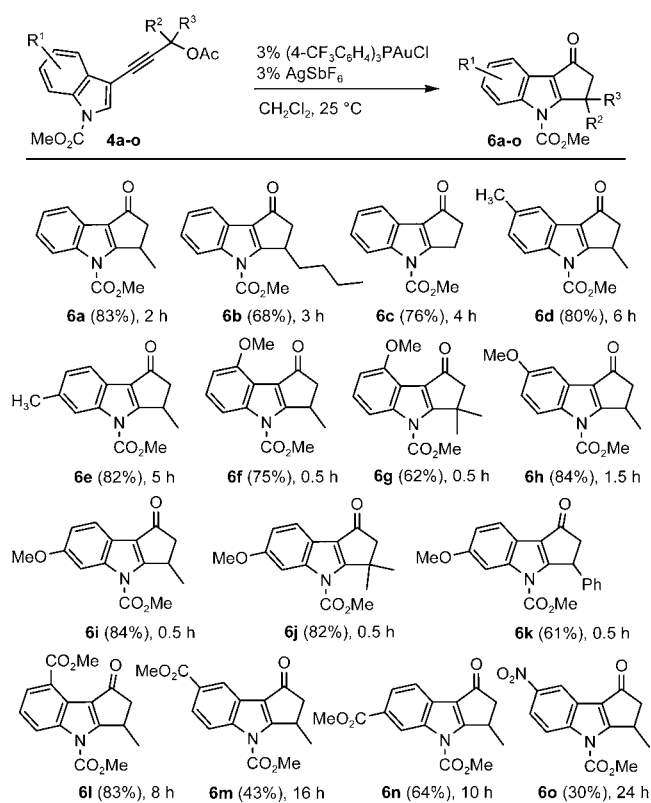


With ligand L2 (Ph₃P) the reaction was slower, with conversion into 6a about 94% after 6 h (entry 1). In this case, we also observed the formation of a certain amount (6%) of α,β -unsaturated compound 10a (Scheme 2) as a 3:1 *E/Z* isomeric mixture. When more electron-rich ligands were used (L3 = cHex₃P, L4 = *t*-Bu₃P, and L5 = cHexJohnPhos), the reaction was very slow, with only partial conversions even after 24 h and the formation of higher (up to 23%) relative amounts of α,β -unsaturated compound 10a (entries 3–5). Given the marked effect of electron-poor phosphine L1, a phosphite ligand was used (entry 6), but although the reaction was slightly faster, a lower yield than with L1 was obtained because of the formation of unidentified side products.

Less important was the role of the counterion: using ligand L1, the reaction rates were approximately the same with SbF₆⁻ (entry 2) and TfO⁻ (entry 8) and slightly lower (conversion complete in 4 h) with Tf₂N⁻ (entry 7). Only with BARF⁻ (entry 9) was the starting material recovered unreacted.

The scope of the reaction was investigated with a series of differently substituted enynyl acetates 4 and ligand L1. To this end, *N*-protected 3-iodoindoles 11a–j (Scheme 1), bearing various electron-withdrawing and electron-donating groups, were coupled to alkyn-3-ols under Sonogashira conditions¹³ to provide, after *O*-acetylation of alcohols 12a–o, requisite substrates 4a–o in good to excellent overall yields (51–91%, unstable when neat). The outcome of the tandem reaction varied with the electronic properties of the substituent on the indole ring (Scheme 3) with EWGs (in 4l–o) lowering both the reaction rate and conversion into the Nazarov product. In the cases of 4m and 4o, bearing an EWG at position 5, a particularly high amount of the corresponding α,β -unsaturated compound was also obtained (37 and 50%, respectively). With

Scheme 3. Scope of the Reaction



ED groups, the isolated yields of cyclopenta[*b*]indolones **6** were good to excellent and reaction rates very high, especially with methoxy-substituted substrates **4f–k** (generally less than 1 h for a complete conversion). To further confirm the effect of the indole substituent,¹⁴ a competition experiment was carried out on a 1:1 mixture of 6-MeO- and 6-CO₂Me-substituted substrates **4i** and **4n**, respectively, in the presence of 3 mol % of the catalyst. Monitoring the reaction by ¹H NMR revealed the almost immediate conversion (less than 15 min) of the substrate with the ED group on the ring into **6i**, whereas substrate **4n** was completely converted into **6n** in 4 h.

The formation of α,β -unsaturated ketone **10a** (Scheme 2) and its relative increase when the cyclization becomes very slow suggest that the Nazarov cyclization of intermediate **5a** to form oxallyl cation **7a** is the rate-determining step of the whole process. Whereas with N-heterocycles **1** (eq 1) the cyclization was a fast process,^{7a} a computational study carried out on substrate **4a** and Ph₃PAu⁺ as the cationic gold species, in fact, resulted in the cyclization of pentadienyl cation **5a** being the rate-limiting step of the tandem reaction (Figure 2). The

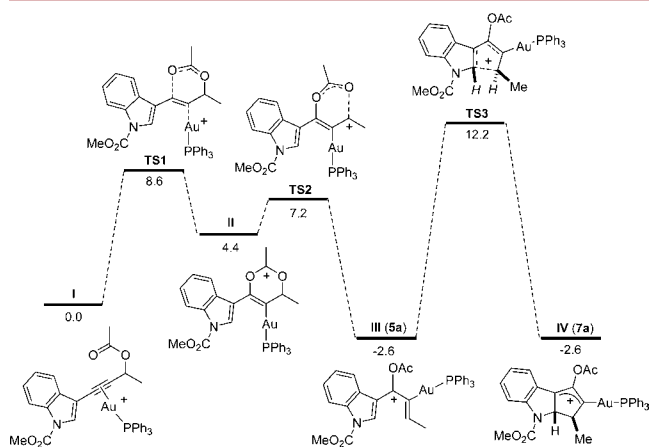


Figure 2. Computed reaction profile for the reaction of **4a**. Energies are in kcal/mol.

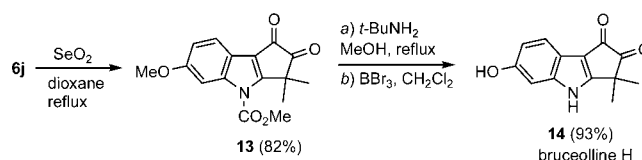
acetate rearrangement proceeds with a low activation barrier ($\Delta G_{\text{act}} = 8.6$ kcal/mol) and in a slightly exergonic fashion ($\Delta G_{\text{react}} = -2.6$ kcal/mol) to form intermediate **III** (i.e., **5a**). The next cyclization step, from **III** to **IV** (i.e., **7a**), has the highest activation barrier ($\Delta G_{\text{act}} = 14.8$ kcal/mol) in accordance to our experimental observations. Next, deprotonation/protodeauration of **IV** is highly exergonic (-19.6 kcal/mol), ensuring the irreversibility of the overall process.¹⁵ On these grounds, the effect of the indole substituents and gold ligands on the reaction rate can be easily explained: on one hand, the electrophilic attack by the cationic side chain is favored by electron-donating substituents which make the indole ring in intermediate **III** more electron rich and disfavored by EWGs. On the other hand, the striking accelerating effect by electron-poor gold ligands could be justified by a more electrophilic, and thus more reactive, allylic side chain.¹⁶ Accordingly, in an experiment carried out with 4-MeO-substituted compound **4f** and the electron-rich gold ligand L3, conversion into **6f** was much slower (7 vs 0.5 h with L1).

Concerning the formation of **10a** (Scheme 2), this should directly derive from **5a** ($\Delta G_{\text{react}} = +8.1$ kcal/mol, see the SI), but dissociation of LAu⁺ from **5a** to provide **10a** through

acetyloxy allene intermediate **9a** could be a possible pathway, too. Allene **9a**, moreover, could cyclize under gold(I) catalysis to give pentannulated indole **6a**.^{5d} However, the formation of allene **9a** from **5a** was calculated to be extremely disfavored ($\Delta G_{\text{react}} = +31.7$ kcal/mol, see the SI for full treatment),¹⁷ and moreover, we never detected, while monitoring the reactions by ¹H NMR, any signal associated with allene **9a**. Thus, we can reasonably rule out deauration of **5a** to form **9a** as the main pathway toward both **10a** and **6a**. Finally, a classical Lewis acid assisted Nazarov cyclization of **10a** into **6a** under the reaction conditions can be excluded, too.¹⁸

To demonstrate the usefulness of the methodology, the synthesis of bruceolline H was carried out. While the synthesis of unsubstituted bruceollines has been described,² bruceolline H has been isolated quite recently and its synthesis never reported.^{1a} To this end, cyclopenta[*b*]indolone **6j** (Scheme 4)

Scheme 4. Synthesis of Bruceolline H



was first converted into the corresponding diketo derivative **13** (82%) by using SeO₂ in refluxing dioxane.^{2b} Sequential N-deprotection¹⁹ and O-demethylation²⁰ completed the synthesis of this product, which was obtained in 69% overall yield from the corresponding 3-iodoindole. ¹H and ¹³C NMR spectra of **14** were identical to those reported for the natural product.^{1a}

In summary, we have shown that the tandem gold(I)-catalyzed rearrangement/Nazarov reaction of enynyl acetates **4** efficiently provides cyclopenta[*b*]indol-1-ones as useful precursors for the synthesis of natural and bioactive compounds. A variety of substituents on the indole core are tolerated, and their effect on the reaction rate is consistent with the cyclization being the rate-determining step, as it is the remarkable influence of the gold(I) ligands. The synthetic potential of the methodology is demonstrated by the first total synthesis of bruceolline H.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01990.

Experimental procedures and spectroscopic data of all new compounds and details of the computational studies (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ernesto.occhiato@unifi.it.

Notes

The authors declare no competing financial interest.

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