Construction of Cyclopenta[b]indol-1-ones by a Tandem Gold(I)-Catalyzed Rearrangement/Nazarov Reaction and Application to the Synthesis of Bruceolline H

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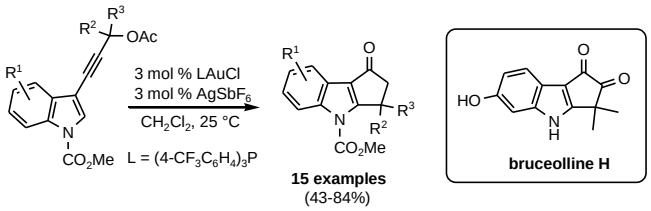
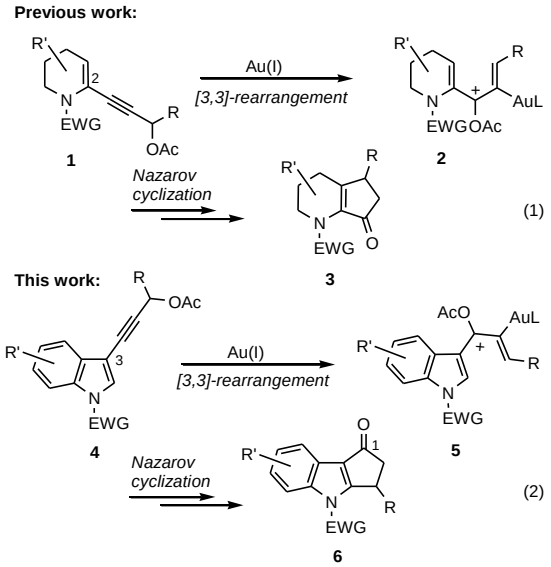
Supporting Information Placeholder



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) catalysis[3] 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 processes,[7] 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 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).

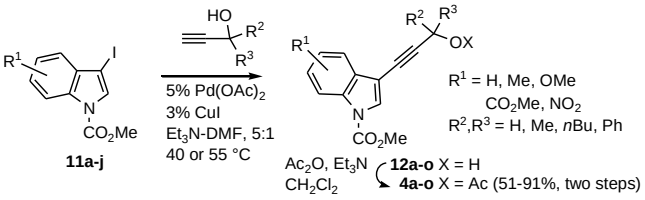
Table 1. Reaction of 4a over various catalysts[a]

entry	ligand L	anion (X^-)	time (h)	**6a** (%)[b]	**10a** (%)[b]
1	Ph_3P	SbF_6^-	6	94 (79)[c]	6
2	$(4\text{-}CF_3C_6H_4)_3P$	SbF_6^-	2	98 (83)[c]	2
3	*c*Hex_3P	SbF_6^-	22	77	23
4	*t*-Bu_3P	Tf_2N^-	24	37	3
5	*c*HexJohnPhos	SbF_6^-	24	31	traces
6	(2,4-di-*t*-$BuC_6H_3O)_3P$	SbF_6^-	1.5	79 (73)[c]	-
7	$(4\text{-}CF_3C_6H_4)_3P$	Tf_2N^-	4	99	1
8	$(4\text{-}CF_3C_6H_4)_3P$	TfO^-	2	96	4
9[d]	$(4\text{-}CF_3C_6H_4)_3P$	$BARF^-$	4	-	-

[a]Reactions carried out by premixing 3 mol % of both LAuCl and AgX in CH_2Cl_2 for 20 min at 25 °C and then adding the substrate (0.2 mmol); [b]Conversion measured by ^{1}H NMR; [c]Yield after chromatography; [d]3 mol % of NaBARF (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was used.

Monitoring the reaction by ^{1}H NMR (Figure 1) revealed that the reaction was complete in two hours when ligand L1 [$(4\text{-}CF_3C_6H_4)_3P$] and $AgSbF_6$ as the source of the non-coordinating anion were used, providing cyclopenta[b]indole **6a** in 83% yield (Table 1, entry 2). Interestingly, while monitoring the reaction, we could not observe any NMR signal associated to acetate **8a** (Scheme 2), formed after the cyclization process, due to its immediate transformation into final compound **6a**.[12] With $AgSbF_6$ (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 1. Preparation of substrates 4.



With ligand L2 (Ph_3P) the reaction was slower, being the conversion into **6a** about 94% after 6 hours (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 electronrich ligands were used (L3 = *c*Hex_3P, L4 = *t*-Bu_3P, and L5 = *c*HexJohnPhos), 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 electronpoor phospine L1, a phospite 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.

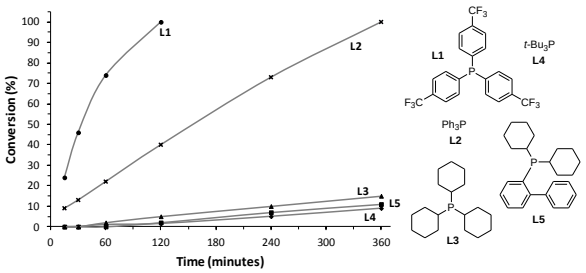
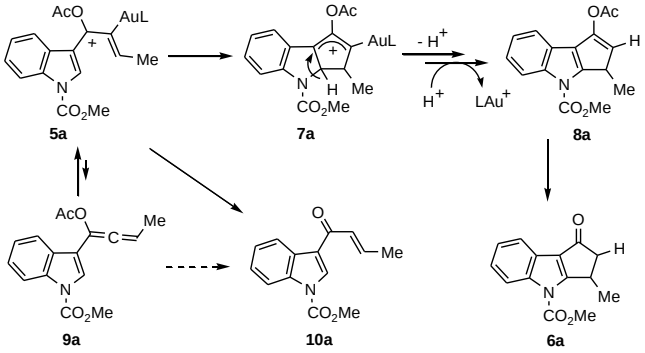


Figure 1. Effect of phosphine ligands on the reaction rate.

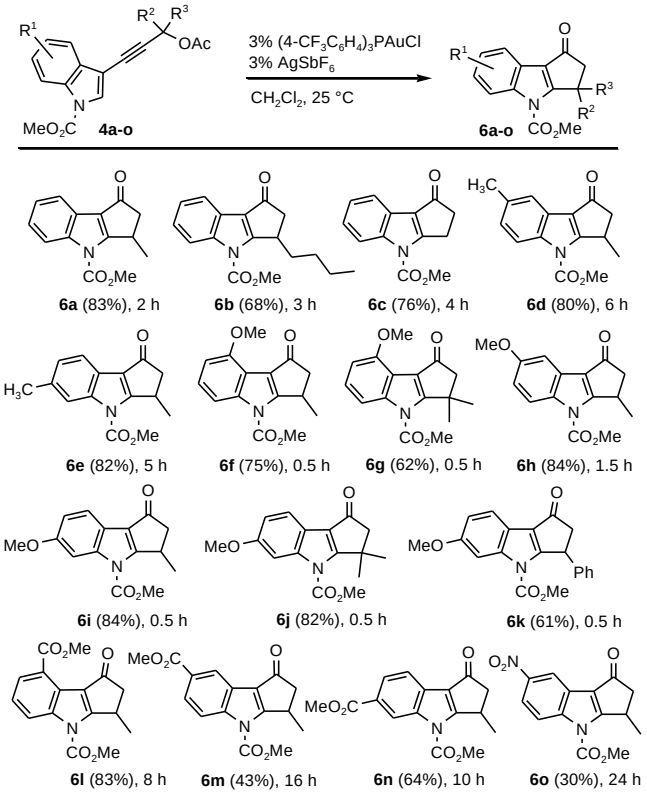
Less important was the role of the counterion: using ligand L1, the reaction rates were approximately the same with SbF_6^- (entry 2) and TfO^- (entry 8) and slightly lower (conversion complete in 4 h) with Tf_2N^- (entry 7). Only with $BARF^-$ (entry 9) the starting material was recovered unreacted.

Scheme 2. The postulated pathways.



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 conditions[13] 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 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-CO_2Me-substituted substrates **4i** and **4n**, respectively, in the presence of 3 mol % of the catalyst. Monitoring the reaction by ^{1}H 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.

Scheme 3. Scope of the reaction.



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 oxyallyl 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 Ph_3PAu^+ 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 acetate rearrangement proceeds with a low activation barrier (ΔG_{act} = 8.6 kcal/mol) and in a slightly exergonic fashion (ΔG_{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 (ΔG_{act} = 14.8 kcal/mol) in accordance to our experimental observations. Next deprotonation and 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 electronrich, and disfavored by EWGs. On the other hand, the striking accelerating effect by electronpoor 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 electronrich 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** (ΔG_{react} = +8.1 kcal/mol, see 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 (ΔG_{react} = +31.7 kcal/mol, see SI for full treatment)[17] and, moreover, we never detected, while monitoring the reactions by ^{1}H NMR, any signal associated to 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]

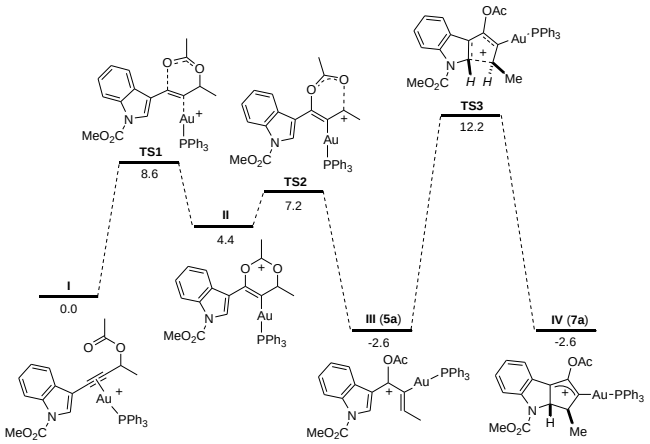
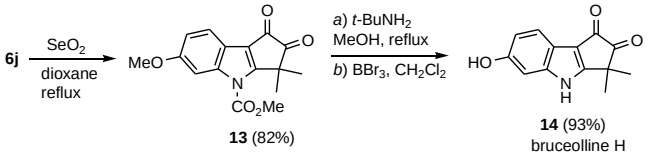


Figure 2. Computed reaction profile for the reaction of **4a**. Energies are in kcal/mol.

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) was first converted into the corresponding diketo derivative **13** (82%) by using SeO_2 in refluxing dioxane.[2b] Sequential N-deprotection[19] and O-demethylation[20] completed the synthesis of this product, which was obtained in 69% overall yield from the corresponding 3-iodoindole. ^{1}H and ^{13}C NMR spectra of **14** were identical to those reported for the natural product.[1a]

Scheme 4. Synthesis of bruceolline H.



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

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Notes

The authors declare no competing financial interest.

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