EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201500462

Annulated N-Heterocycles by Tandem Gold(I)-Catalyzed [3,3]-Rearrangement/Nazarov Reaction of Propargylic Ester Derivatives: an Experimental and Computational Study

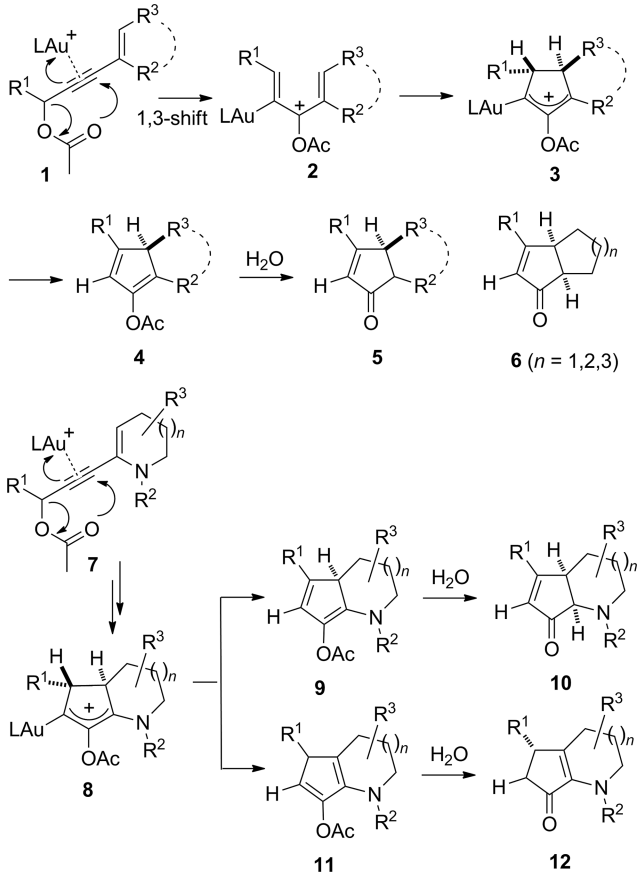
Martina Petrović,[a] Dina Scarpi,[a] Béla Fiser,[b] Enrique Gómez-Bengoa,[b] and Ernesto G. Occhiato*[a]

Keywords: Homogeneous catalysis / Gold / Annulation / Enynes / Nitrogen heterocycles

The gold(I)-catalyzed tandem rearrangement/Nazarov reaction of propargylic ester derivatives is a useful strategy for the synthesis of cyclopenta-fused N-heterocyclic structures present in many natural compounds. Readily available lactams are converted into enol phosphates and triflates and coupled to propargyl alcohols under Sonogashira conditions. After acetylation, the gold-catalyzed rearrangement of the enynyl acetates readily occurs when using 3–5 mol-% of a gold(I) catalyst. The rearrangement generates a divinyl cation which undergoes a 4π electrocyclization (Nazarov reaction) leading to the target compound in good to excellent yield. This process has been studied in details both experimentally and computationally to understand the influence of both the reaction conditions and substrate structural features on the reaction rate and regioselectivity, as well as the torquoselectivity in the ring closure step. A series of examples illustrates at the end the scope of the reaction.

Introduction

The widespread presence of the 2-cyclopentenone moiety in natural products has always been a stimulus for synthetic organic chemists to find new methods for efficiently building this structure, with a varying degree of substitution and control of the stereochemistry.[1] Among the many approaches to 2-cyclopentenones, the Nazarov reaction ranks as one of the most important and versatile since the requisite 4π electron pentadienyl cation can be generated not only from classical dienones but also from a steadily increasing variety of unconventional substrates or processes,[2] including gold-catalyzed transformations.[3,4] Suitably assembled propargylic esters are particularly useful as substrates for the Nazarov reaction, since the transition metal-catalyzed migration of the carboxylic group to any of the two unsaturated positions leads to competent pentadienyl cations. 5-Acyloxy-1,3-enynes **1** in particular (Scheme 1), undergo – under remarkably mild conditions – a gold(I)-catalyzed [3,3]-rearrangement to pentadienyl cations **2** which, after Nazarov reaction and eventual protodeauration, provide acetyloxy-substituted cyclopentadiene products **4**. Hydrolysis (in situ or after work-up) of the latter leads to the target cyclopentenones **5**.[5] This strategy



Scheme 1. Sequential gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction of 5-acyloxy-1,3-enynes **1** (above) and **7** (below).

[a] Dipartimento di Chimica "U. Schiff", Università degli Studi di Firenze,
Via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy
E-mail: ernesto.occhiato@unifi.it
www.egocch.it/
[b] Departamento de Química Orgánica I, Universidad del País Vasco/UPV-EHU,
Manuel de Lardizabal 3, 20018 Donostia-San Sebastián, Spain
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500462.

successfully provides cyclopenta-fused carbacycles **6** when the enyne double bond is embedded in a five-, six- and seven-membered ring (Scheme 1).[5a,5b,6] Our interest in the synthesis of cyclopenta-fused heterocycles by the Nazarov reaction,[7] as well as in gold-catalysis,[8a] prompted us to investigate if the same approach could still furnish annulated systems when embodying the same double bond into *N*-heterocycles as **7** (Scheme 1).

This in fact would represent a new synthetic approach to molecular structures (e.g. [1]pyrindines, annulated pyrrolines and azepines) present in many natural compounds (Figure 1),[9] some of which (e.g. cephalotaxine and roseophilin) already synthesized via some of the Nazarov reaction variants.[10]

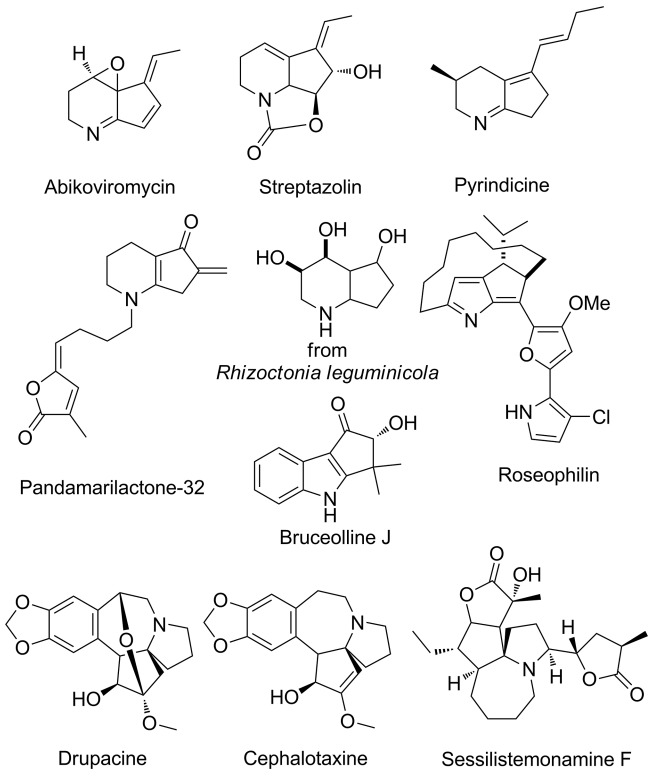


Figure 1. Natural compounds containing a cyclopenta-fused N-heterocyclic ring.

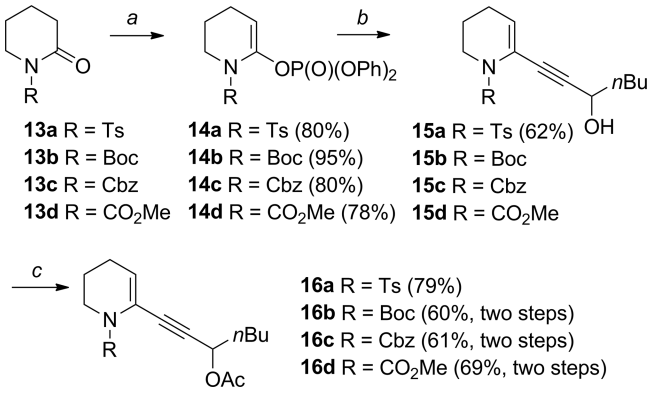
To accomplish this, however, a few issues have to be dealt with. First, because of the likely contribution of the N atom in stabilizing positively charged intermediates, whether and how the presence of the heteroatom influences the rate and the regiochemical outcome of the reaction had to be assessed. In our previous studies on the Brønsted acid-catalyzed Nazarov reaction of masked and classical dienones,[7] deprotonation of the oxyallyl cation exclusively led to compounds of type **12** having the more substituted double bond and not to even traces of its regioisomer **10**, in strong contrast with the outcome of the gold-catalyzed reaction of the corresponding carbacyclic systems (Scheme 1). Moreover, the choice of the N protecting group is not of secondary importance, as its involvement in gold-catalyzed rearrangement of closely related *N*-Boc enynes has been shown,[8] thus posing a concern about a possible competition in the nucleophilic attack to the activated triple bond. Because the cyclization leading to intermediate **8** involves a vinylgold species, a further question arises about the conservation of the high torquoselectivity we have previously observed in Brønsted acid-catalyzed Nazarov reactions, which led to *cis* disubstituted cyclopenta-fused *N*-heterocycles.[7a,7b,7d,7g] and which we have exploited for the formal enantioselective synthesis of roseophilin.[10f] Finally, to establish this approach as a reliable synthetic strategy for cyclopenta-annulated N-heterocycles, the scope of the reaction had to be assessed on the alkyne chain R^1 and the heterocycle ring size and substituents. In this paper we demonstrate that the tandem gold(I)-catalyzed propargylic rearrangement/Nazarov reaction of propargylic esters **7** is a useful strategy for the synthesis of annulated N-heterocycles but, also, that the picture for this process is much more complex than that previously reported for non-heterocyclic systems, with a whole series of elements [N-protecting group, heterocycle ring size, gold(I) counterion, etc.] all influencing reaction rate and selectivity (regio- and stereoselectivity) in one way or another. To assist us in the comprehension of the experimental results, the energies and structures of the intermediates and transition states involved in this process were determined by a computational study, the results of which are well in accordance with the experimental data and which we present in this paper.

Results and Discussion

Evaluating the Reactivity of Model Compounds

We have recently shown that *N*-Boc-protected enynes closely related to **7** (but lacking the acetyloxy group) are excellent substrates for a gold(I)-catalyzed oxyauration involving the *N*-Boc carbonyl oxygen which eventually affords exocyclic vinylogous amides.[8a] Thus, in order to avoid any possible interference by a *N*-alkoxycarbonyl group, we decided to find the best reaction conditions for the sequential [3,3]-rearrangement/Nazarov cyclization with compound **16a**, bearing a *N*-Tosyl protecting group. The synthesis of this model compound (Scheme 2) was carried by converting the *N*-Ts-substituted δ-valerolactam **13a** into the corresponding enol phosphate **14a** which was immediately subjected to Sonogashira coupling[11] with 1-heptyn-3-ol to give alcohol **15a** in 62% after chromatography. This was eventually treated with acetic anhydride to provide acetate **16a** in 79% yield.[12]

To find the best catalyst, we first screened a series of silver and copper salts as sources of the non-coordinating anion with 3 mol-% of Ph_3PAuCl in CH_2Cl_2 at room temperature (Table 1).[13] The reactions were monitored by TLC and, after consumption of **16a**, they were left whilst stirring (usually 16 h at room temperature) to allow hydrolysis (if occurred) of the acetate intermediate(s) to the final Nazarov product(s). With all screened catalysts, compound **16a** was a competent substrate. However, the expected acetate **17a**[14] was always obtained in mixture with cyclopentenone **20a**,



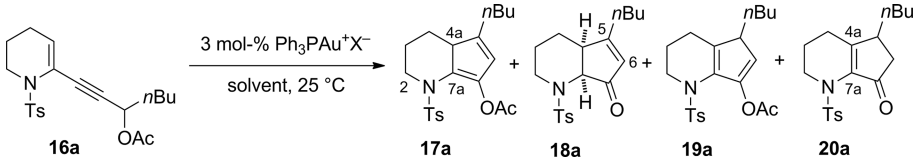
Scheme 2. [a] KHMDS, –78 °C, 1.5 h; then $(PhO)_2POCl$, –78 °C, 1 h. [b] heptyn-3-ol, 15 mol-% CuI, 6 mol-% $(Ph_3P)_2PdCl_2$, $CHCl_3$/Et_3N, 1:2, 55 °C, 5–7 h. [c] Ac_2O, Et_3N, DMAP, DCM, 0 °C to room temp., 1–7 h.

possessing the more substituted double bond in 4a–7a position and possibly deriving from the hydrolysis in situ of its acetate precursor **19a**. Intriguingly, we never isolated this acetate.[14] With AgOTf[15] (entry 1) complete conversion was observed in less than 1.5 hours, whereas hydrolysis occurred only partially in 16 hours, providing acetate **17a** in 51% yield and cyclopentenone **20a** in 35% yield after chromatography. Trying to increase the relative amount of acetate **17a**, the reaction was carried out in different solvents (THF, 1,4-dioxane, acetonitrile, dichloroethane). The best result was achieved in toluene which provided pure acetate **17a** in 61% yield and **20a** in 18% yield after chromatography. Decreasing the reaction temperature to 0 °C the ratio between **17a** and **20a** was further improved (4:1), but the yield of **17a** was not changed much (60%) as degradation took place during the reaction.

In sharp contrast with the results obtained by using AgOTf and even more with those reported for the corresponding carbacyclic systems **1** (Scheme 1),[5a,5b] with all of the other silver salts the major product was always cyclopentenone **20a** (entries 4–6) accompanied by lower amounts of acetate **17a** and only traces (less than 5%) of cyclopentenone **18a**. The best silver salt was $AgSbF_6$ (entry 6) as the reaction provided cyclopentenone **20a** in 70% yield after chromatography together with some residual acetate **17a** (14%). Again contrarily to expectations, the reaction was much slower when using "wet" CH_2Cl_2.[5a] In this case, only after 5 h the conversion was complete.[16] Instead, the concurrent hydrolysis of acetate **19a** was faster to provide **20a** again as the major product but in a lower ratio with residual acetate **17a** (55% and 30% respectively after chromatography) than in commercial CH_2Cl_2. Similarly, a lower ratio between **20a** and **17a** was obtained when the reaction was carried out with $AgSbF_6$ in chloroform (entry 10).

To demonstrate that the formation of ketone **20a** occurs via hydrolysis in situ of acetate intermediate **19a**, we set up one experiment in $CDCl_3$ and monitored the progress of the reaction by ^1H NMR spectroscopy (Figure 2). Aliquots of the reaction mixture were filtered through a Celite layer and diluted after 0.5, 1 and 2.5 h from the addition of the

Table 1. Sequential gold(I)-catalyzed rearrangement/Nazarov reaction of acetate **16a**.[a]



Entry	Catalyst[b]	Conditions[c]	Time [h][d,e]	Yield[f] 17a	18a	19a	20a
1	$Ph_3PAuCl/AgOTf$	CH_2Cl_2	1.5	51	–[g]	–	35
2		toluene	1	61	–	–	18
3		toluene, 0 °C	5	60	–	–	15
4	$Ph_3PAuCl/AgBF_4$	CH_2Cl_2	3	18	5	–	62
5	$Ph_3PAuCl/AgNTf_2$·ACN	CH_2Cl_2	6	18	5	–	50
6	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	2.5	14	3	–	70
7		wet CH_2Cl_2	5 (0)	30	–	–	55
8		dry CH_2Cl_2	5[i] (0)	18[h]	–	22[h]	19[h]
9	$Ph_3PAuSbF_6$[j]	CH_2Cl_2	3	18	–	–	64
10	$Ph_3PAuCl/AgSbF_6$	$CHCl_3$	2 (0.5)	30	–	–	60
11	$Ph_3PAuCl/Cu(OTf)_2$	CH_2Cl_2	6[k]	–	19	–	29
12		CH_2Cl_2, reflux	0.7 (3)	–	58[h]	–	42[h]
13	AgOTf	CH_2Cl_2	3	–	–	–	< 5[h]
14	$AgSbF_6$	CH_2Cl_2	3	–	–	–	< 5[h]
15	$Cu(OTf)_2$	CH_2Cl_2	16 (0)	–	–	–	–

[a] Reactions were carried out on 0.1–0.15 mmol scale, at 25 °C and left standing whilst stirring 16 h after consumption of the starting material. An aqueous work-up was carried out to recover the products from the reaction mixture. [b] Catalysts were prepared by adding the silver salt to a 0.004 M solution of the gold(I) chloride in the reaction solvent. [c] Solvents were not dried before use unless otherwise indicated. [d] Time to reach complete conversion of the starting material. [e] In brackets, time left for hydrolysis. [f] Yield after chromatography unless otherwise indicated. [g] Not detected by ^1H NMR analysis of the crude reaction mixture. [h] By ^1H NMR analysis of the crude reaction mixture. [i] The reaction stopped at a 70% conversion. [j] The reaction was carried out with 6 mol-% of catalyst and after filtration of AgCl. [k] The conversion was not complete and degradation of the starting material occurred.

catalyst. After 30 min, ^{1}H NMR analysis actually showed three new sets of signals, of which one for cyclopentenone **20a** and two for the two acetates (**17a** and **19a**). As we could anticipate from our previous results, the ratio between intermediates **19a** and **17a** decreased during the reaction concurrently to a relative increase of **20a**. At the end of the reaction, only the signals of **20a** and acetate **17a** were present in the spectrum.

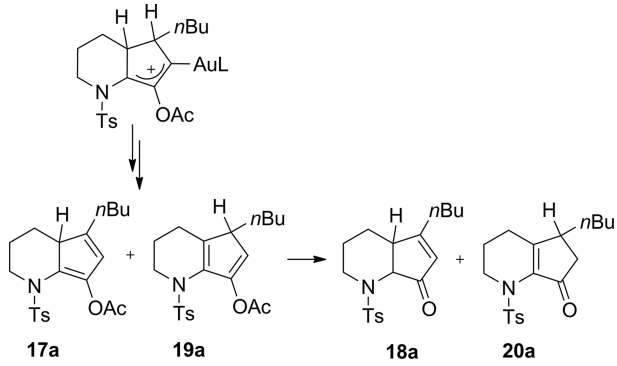
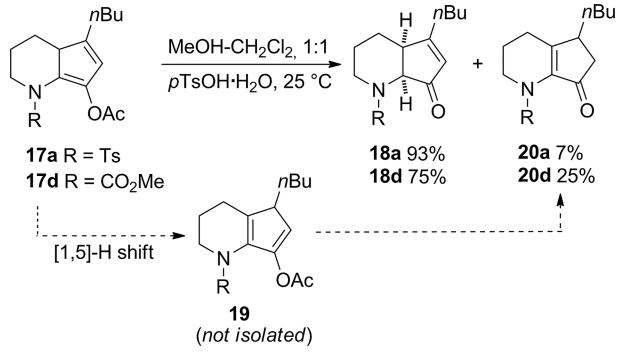


Figure 2. Monitoring by ^{1}H NMR of the reaction of **16a** in $CDCl_3$.

Having in mind to prevent hydrolysis of the acetate intermediates and to isolate **19a** we also carried out one experiment in anhydrous CH_2Cl_2 (entry 8) but the reaction was slower and, after 5 h, only reached an approximately 50% conversion into the acetates (roughly in a 1:1 ratio between **17a** and **19a**) by ^{1}H NMR analysis of the crude reaction mixture.[17] Degradation of enynyl acetate **16a** occurred to a great extent under these conditions, though, and we observed the formation also of a small amount of final product **20a** (19% by ^{1}H NMR of the crude reaction mixture) probably due to the presence of adventitious water.[18]

Given the role that silver can have in gold-catalyzed reaction,[19] we carried out an experiment with a catalyst obtained after filtration through a Celite layer (entry 9), in order to exclude AgCl from the reaction medium. Since decomposition of the catalyst during such an operation has been reported[20] we opted for a larger amount of initial catalyst (6 mol-%). We were glad to see that the reaction occurred as usual, thus demonstrating that the silver halide does not affect neither the reaction rate nor the selectivity.[21] On the other hand, AgOTf alone (entry 13) as well as $AgSbF_6$ (entry 14) did catalyze the reaction, albeit to a very low extent (less than 5% conversion after 3 h).[22]

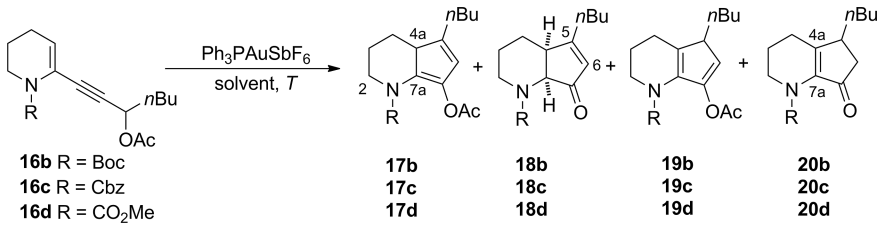
Finally, when the reaction was carried out using $Cu(OTf)_2$ to generate the active gold(I) catalyst (entry 11),[23] both isomers **18a** and **20a** were obtained in a 1.5:1 ratio and 48% yield (degradation of the starting material was observed under these conditions). Repeating the reaction in refluxing dichloromethane, consumption of the starting material was complete in 40 min and hydrolysis in 3 h, providing again a mixture of the two isomers in a 1:1.4 ratio. It is interesting to note here that only with $Cu(OTf)_2$ we observe hydrolysis of acetate **17a**. Unlike AgOTf, copper triflate remains in solution and due to its Lewis acid character it can accelerate the hydrolysis of the acetates. Also, with triflate as a counterion from both AgOTf and $Cu(OTf)_2$, there is an appreciable increase of the relative amount of either acetate **17a** or its product of hydrolysis **18a**. A [1,5]-H shift in **19a** to form **17a** triggered by triflic acid (as $H_3O^+TfO^-$) generated in situ can be excluded because by acidic treatment we instead observe some conversion of **17a** into **19a**. In fact, when acetate **17a** was dissolved in dichloromethane/MeOH and treated with a catalytic amount of monohydrate *p*TsOH (Scheme 3), it slowly (16 h) provided the corresponding *cis* fused (see later) cyclopentenone **18a** as the main product and in a 13:1 ratio with **20a**, the formation of which could be accounted for by an acid catalyzed [1,5]-H shift in **17a**.[24] On the contrary, attempts at basic hydrolysis (K_2CO_3 in MeOH) led to decomposition of the starting material.[25] Similarly, we observed decomposition of cyclopentenone **18a** when we tried to convert it into its isomer **20a** upon treatment with bases.[26]



Scheme 3. Hydrolysis of acetates **17a** and **17d**.

The best reaction conditions (3 mol-% $Ph_3PAuCl/AgSbF_6$, in DCM at room temperature) found for enyne **16a** were then extended to the corresponding substrates protected as *N*-Boc (**16b**), *N*-Cbz (**16c**) and *N*-CO_2Me (**16d**), all prepared in good overall yield as described for **16a** starting from the corresponding protected lactams (Scheme 2). Given our previous results on the gold-catalyzed oxyauration of simple *N*-Boc protected enynes,[8a] we anticipated a possible interaction of the carbamate carbonyl group with the activated triple bond before the acetate rearrangement and so we were not surprised by the much lower reactivity of substrates **16b–d**. The reaction of *N*-Boc derivative **16b** (Table 2, entries 1–3) only provided degradation products plus a minor amount of the oxyauration product (about 20%) when the reaction was carried out in toluene.[27] The formation of this byproduct, in particular, is consistent with our hypothesis of a carbamate carbonyl group competing for the activated triple bond (see later for DFT calculation on this issue). Better results, but only with 8 mol-% of catalyst, were obtained with *N*-Cbz derivative **16c** (entry 5) which provided cyclopentenone **20c** (61% yield after chromatography) as the sole product. In this case, both consumption of the starting material and hydrolysis were complete after 3 h in refluxing DCM. Also in this case, some degradation of the starting material occurred, albeit in a much lower extent than with *N*-Boc compound **16b**. Similarly, with the *N*-CO_2Me protected compound the

Table 2. Sequential gold(I)-catalyzed rearrangement/Nazarov reaction of acetates **16b–d**.[a,b]



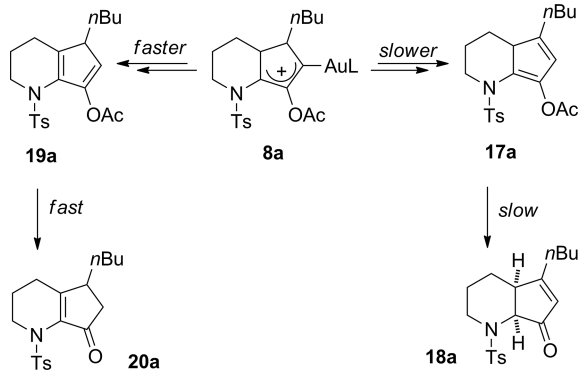
Entry	Substrate	Conditions[c]	Time [h][d]	Yield[e]			
				17	**18**	**19**	**20**
1	**16b**	CH_2Cl_2, 25 °C	16[f]	–[g]	–	–	–
2		toluene, 25 °C to reflux	3[f]	–	–	–	–
3		acetone, 25 °C to reflux	3[f]	–	–	–	–
4[h]	**16c**	CH_2Cl_2, 25 °C	20[j]	–	–	–	48
5[h,i]		CH_2Cl_2, reflux	3	–	–	–	61
6	**16d**	CH_2Cl_2, 25 °C	2	–	–	–	–
7		CH_2Cl_2, reflux	2[k]	14	–	–	64
8		toluene, reflux	1.5[k]	11	–	–	50
9		THF, reflux	1.5[k]	15	–	–	45

[a] Reactions carried out on 0.15–0.2 mmol, with 5 mol-% of catalyst unless otherwise indicated. [b] Catalysts were prepared by adding the silver salt to a 0.004 M solution of the gold(I) chloride in the reaction solvent. [c] Solvents were not dried before use unless otherwise indicated. [d] Time to reach complete conversion of the starting material. [e] Yield after chromatography unless otherwise indicated. [f] Complete degradation of the starting material occurred. [g] Not detected by ^{1}H NMR analysis of the crude reaction mixture. [h] Reaction carried out with 8 mol-% of catalyst. [i] Reaction carried out on a 0.075 mmol scale. [j] Degradation occurred to a certain extent. [k] Then left standing for 16 h at room temperature.

reaction did not take place if not by heating in refluxing dichloromethane (entry 7) with 5 mol-% of catalyst. Again, Nazarov compound **20d** with the double bond at 4a-7a position was the major product after chromatography (64%) and in this case we isolated also a smaller amount of acetate **17d** (14%).[28] Similarly to acetate **17a**, when we subjected acetate **17d** to hydrolysis in DCM/MeOH (1:1) and in the presence of catalytic amount of monohydrate *p*TsOH (Scheme 3), its quantitative conversion into the corresponding Nazarov product **18d** was slow (16 h) and this was obtained in a 4:1 mixture with its isomer **20d**.

Mechanistic Considerations and DFT Calculations

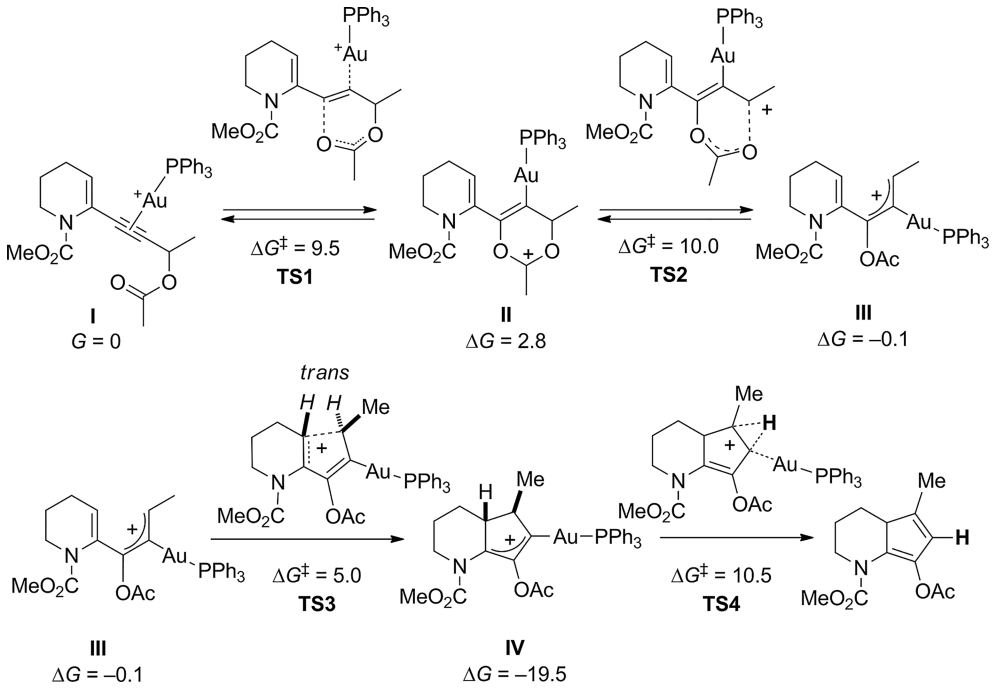
The fact that we could in most cases isolate acetates **17a** and **17d** and never their isomers (**19a** and **19d**) from the crude reaction mixtures of the gold-catalyzed reactions, together with the observation that acetates **17** are very slowly converted into the corresponding cyclopentenones when subjected to hydrolytic conditions (Scheme 3), suggests that acetates **17**, after their formation in the protodeauration step involving oxyallyl cation **8** (Scheme 4), only slowly hydrolyze under the conditions of the gold-catalyzed reaction. Instead, isomers **19** are quickly converted into the corresponding cyclopentenones **20** and so we never isolated them (see the NMR study above, Figure 2). Since cyclopentenone **20** is the major or only product in the reactions carried out in DCM when using $AgSbF_6$ as the anion source we can hypothesize that, under these conditions, formation of acetate **19** from oxyallyl cation **8** is faster than formation of its isomer **17** and that then a fast hydrolysis of **19** under the reaction conditions occurs. It is interesting to compare here this result with those reported by Zhang et al. on the corresponding carbacyclic systems **1** (Scheme 1), in which the formation of a unique cyclopentenone (**6**) with the less substituted double bond was observed.[5a]



Scheme 4. The two competing pathways to **18a** and **20a**.

In order to understand this process in more detail, and help identifying the structures and energies of the critical steps of the mechanism, we studied the potential reaction coordinates computationally. The structures were located using the B3LYP[29] density functional theory method as implemented in the Gaussian suite of programs.[30]

For the sake of simplicity, two model complexes were considered for the computational studies, that is **I** (Scheme 5), which contains the smallest substituent (methyl) in the propargylic position and a *N*-CO_2Me moiety; and the corresponding one with the *N*-tosyl group. In the former case, the methyl carbamate is conformationally simpler than the tosylate group, and would allow us to



Scheme 5. Top: acetate rearrangement in the initial steps of the mechanism. Bottom: cyclization step from **III** and protodeauration step.

mimic also compound **16d** and related carbamates **16b**–**c**. The alkynyl–gold(I) cationic complex **I** (Scheme 5) was thus considered as the starting point of the mechanism (G = 0 kcal/mol), and all reported energies in the following discussion are relative to it. The energy values correspond to ΔG Gibbs Free energies, computed at B3LYP/6-31G** level (LANL2DZ[31] for gold atom). The overall discussion is based on model **I**. The results with the corresponding *N*-tosyl derivative are very similar and reinforce the conclusions.

Initially, the coordination of the gold atom to the triple bond induces a rapid two step acetate rearrangement to form the pre-Nazarov cyclization complex **III** (Scheme 5). The attack of the acetate carbonyl oxygen of **I** to the gold-activated alkyne leads to the formation of a cyclic intermediate **II**, and the subsequent C–O bond breaking event renders an allylic cation (**III**), stabilized by the presence of the gold atom.[32] Noteworthy, the computed energies indicate that **I** and **III** are isoenergetic (0.1 kcal/mol difference), and that the activation energies of both steps are fairly low, ca. 10 kcal/mol, meaning that in the absence of further evolution, **I** and **III** would be in an almost 1:1 equilibrium. However, complex **III** evolves through an easy cyclization to **IV**, a process that presents a very low barrier of 5.1 kcal/mol (**TS3**, Scheme 5). In accordance to the conrotatory nature of the Nazarov reaction under thermal conditions, the reaction is predicted to be diastereoselective, with formation of the C–C bond that presents the two H atoms in a *trans* relationship. The alternative diastereoisomeric transition state, in which the two H are *cis* to each other is 3.9 kcal/mol higher in energy, and thus, not operative. The low activation barriers can explain the fast rate of a reaction that is completed at room temperature in less than two hours. Although not shown in the Scheme the results with the *N*-tosyl derivative are comparable, showing activation energies of 11.4 and 10.9 kcal/mol for the two step acetate rearrangement processes, a reaction energy of +0.7 kcal/mol in the formation of **III**, and a low activation barrier for the Nazarov cyclization (4.0 kcal/mol).

At this point, we attempted to explain the diene formation through a single-step intramolecular hydride shift with concomitant C–Au bond breaking. In fact, the corresponding transition structure **TS4** was located (Scheme 5), but its accompanying activation energy (30 kcal/mol from **IV** to **TS4**) is too high to be feasible under the experimental reaction conditions.[33] Therefore, an external base is needed for the deprotonation, and it is important to highlight that several possible candidates exist in the reaction media, like the gold counterion in the gold(I) salt or the anion forming the silver or copper salt. Even some water molecules present in the reaction media could play a significant role and, in fact, the intervention of water molecules in the deprotonation/protodeauration steps has been suggested for the tandem process involving enynyl acetates **1** (Scheme 1) in "wet" CH_2Cl_2.[5b,34] We were particularly interested in the proton abstraction step since, based on our experimental findings, the regioselectivity of the reaction, which was not an issue with enynyl acetates **1**, seems to be determined with our substrates just at this stage. We have in fact shown (vide supra) that once the final diene-acetates **VI** and **VIII** (models for acetates **19** and **17**, respectively, Figure 3) are formed, there are not evident signs of significant equilibration between them during the reaction. So, as a plausible approximation, and without knowing the exact nature of the molecule responsible for the abstraction, to demonstrate that this is actually the regiodetermining stage, we decided to

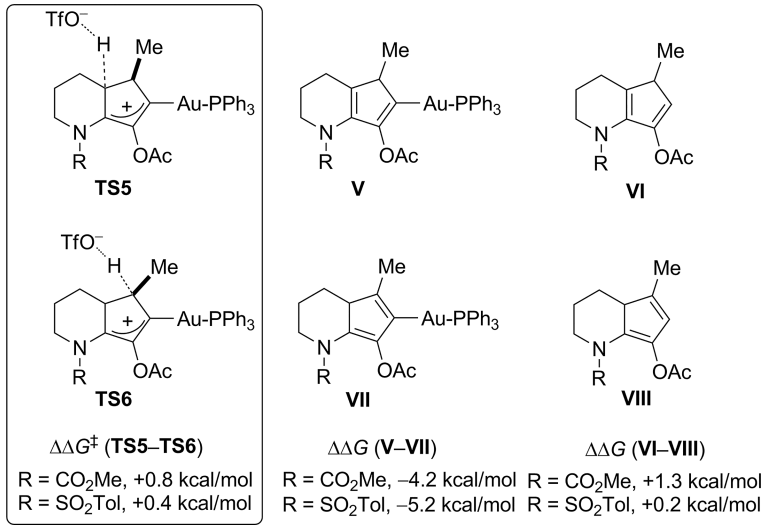
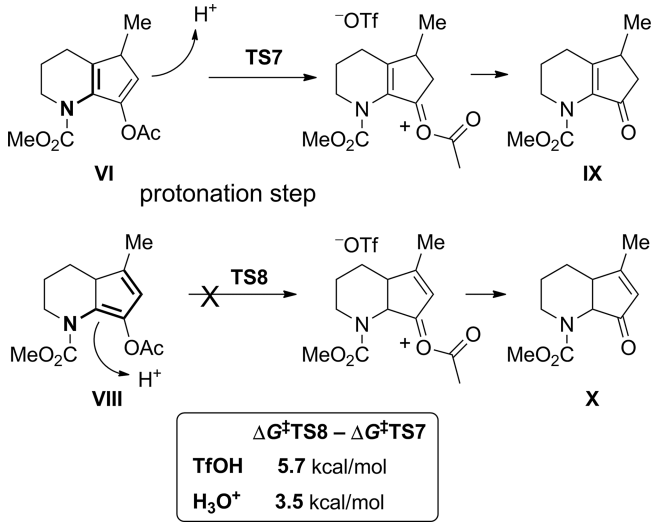


Figure 3. Transition states **TS5** and **TS6** in the presence of triflate anion and compounds formed thereafter.

compute the deprotonation step by using the triflate anion as the base (Figure 3 and Figure S2 in Supporting Information).[35]

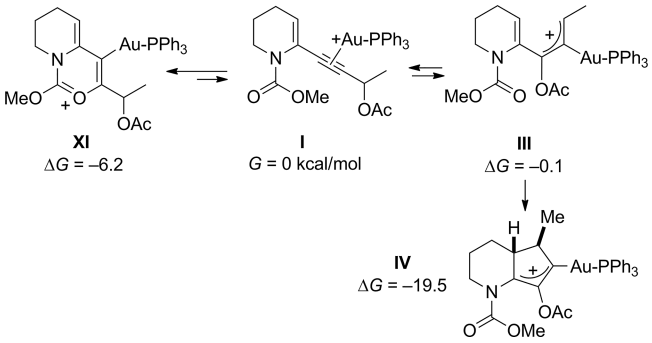
Our computational results indicate that the triflate mediated hydrogen abstraction is, in fact, not highly regioselective, the difference between **TS5** and **TS6** being of only 0.8 kcal/mol in favor of the formation of **VII** isomer (en route to **17**). In the case of the *N*-tosyl group, the difference is 0.4 kcal/mol (favoring **TS6**). The experimental data (Table 1) show a regioselectivity that ranges from 4:1 (**17a** over **20a**, entry 3), when using AgOTf as the source of the non-coordinating anion, to 1:5 (**20a** over **17a**, entry 6), when instead using $AgSbF_6$, which computationally accounts for a difference of less than 1 kcal/mol in each sense. As we will show later, with different types of substrates the regioselectivity we observed when using $AgSbF_6$ was instead complete in favour of ketones derived from hydrolysis of acetate **VI** (i.e. **19**).

After the formation of **VI**- and **VIII**-type dienes (Figure 3), the most logical process would follow via hydrolysis to the final products (Scheme 6). There is a final interesting question at this point, regarding the very different experimental hydrolysis rates of the two diene types, **17** and **19**. Once again, as the exact nature of the protonating species is unknown, we chose triflic acid and H_3O^+ as simple models to study computationally this issue, and the transition states for the hydrogen transfer were located. Noteworthy, the protonation of **VI** (model of diene **19**) is predicted to be three or four orders of magnitude faster than the corresponding protonation of **VIII** (model of **17**), as derived from a 3.5 kcal/mol (H_3O^+) or 5.7 kcal/mol (TfOH) energy difference in favor of the former. These data easily explain why non-hydrolyzed **17** and hydrolyzed **20** are the final products of the reaction. The result can be understood in light of the dienamine structure of compound **17** (**VIII**), and the donor character of the nitrogen atom, which can induce a stabilization of that structure making it less prone to hydrolysis.



Scheme 6. Hydrolysis of diene-acetates **VI** and **VIII** in the presence of a model acid (TfOH or H_3O^+).

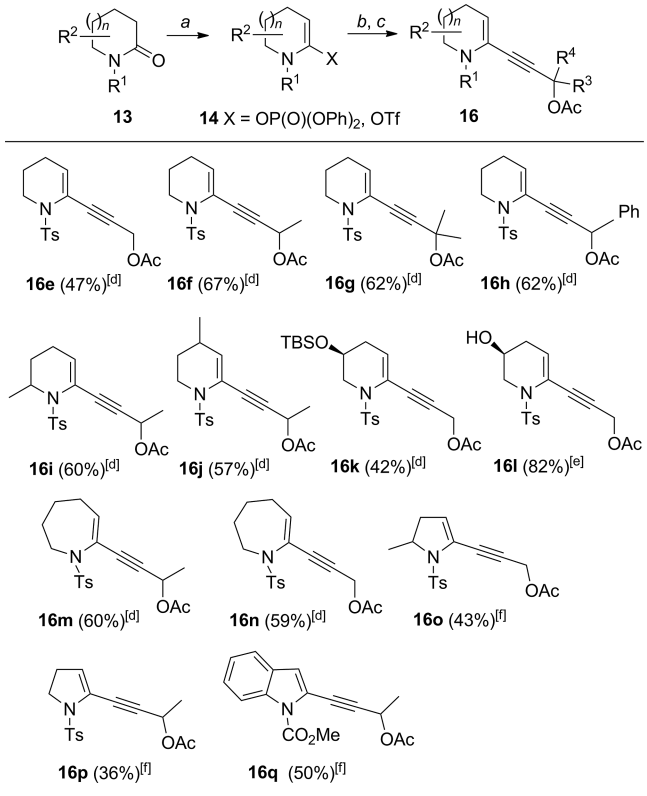
Concerning the lower reaction rates of *N*-alkoxycarbonyl protected substrates **16b**–**d**, as we have hypothesized, DFT calculations predict the formation of a non-productive cyclized intermediate (from carbonyl oxygen attack), which is more stable than the starting material, thus sequestering the gold catalyst for a while and reducing the reaction rate (Scheme 7). The starting compound **I** can proceed through acetate rearrangement to form **III** or through cyclization with the methyl ester to form **XI**. The three complexes **XI**, **I**, and **III** are in equilibrium, which is shifted towards the non-productive, but low in energy (–6.1 kcal/mol) side complex **XI**. Only the irreversible Nazarov cyclization from **III** to **IV** is finally able to displace this equilibrium towards the formation of the bicyclic adducts. Thus, **XI** is partially sequestering the gold catalyst and decreasing the reaction rate.



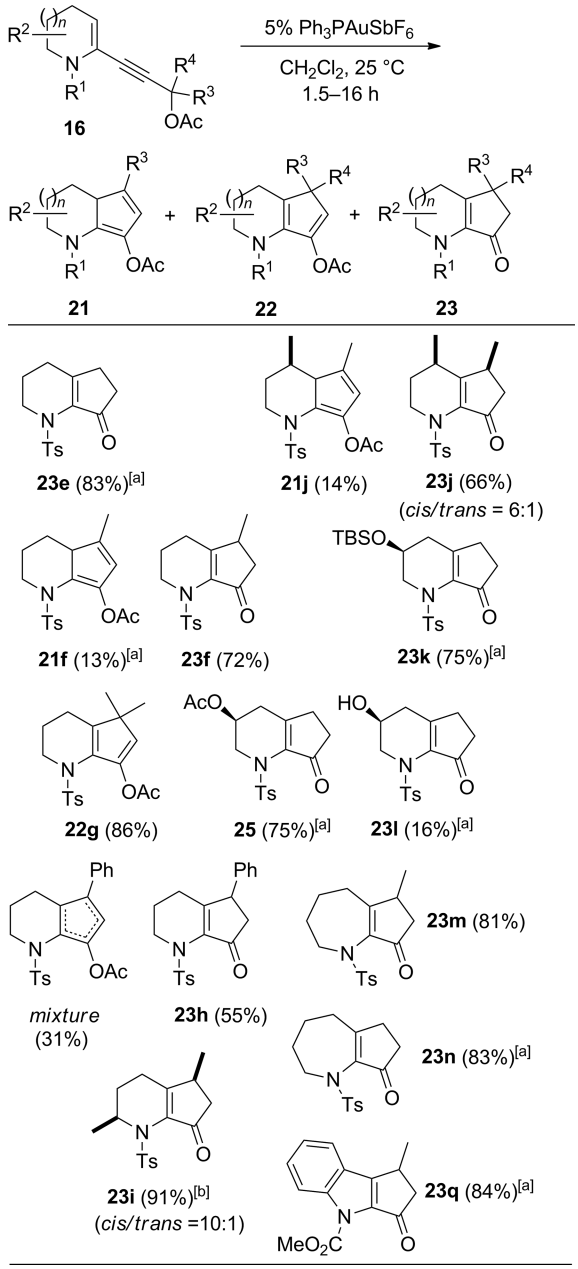
Scheme 7. DFT predicted formation of the non-productive **XI** intermediate.

The Torquoselectivity

To evaluate the torquoselectivity[36] in the ring closure we synthesized model compounds **16i** and **16j** (Scheme 8) from the corresponding lactams,[37] which should provide Nazarov compounds with defined stereochemistry we had already prepared in the past.[7a] The reaction of enyne **16i** was first carried out in DCM at room temperature in the presence of 5 mol-% of $Ph_3PAuSbF_6$ as the catalyst and provided, quite interestingly, only cyclopentenone **23i** in 78% yield after chromatography (Scheme 9) with no traces of the acetate **21i**.



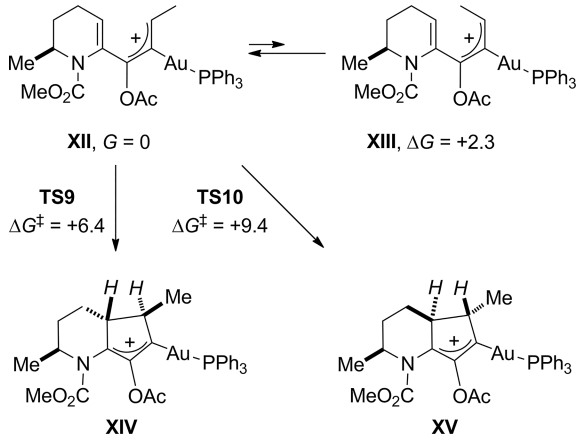
Scheme 8. *Reagents and conditions:* [a] KHMDS, –78 °C, 1.5 h; then $(PhO)_2POCl$ or $PhNTf_2$, –78 °C, 1 h. [b] alkynol, 15 mol-% CuI, 6 mol-% $(Ph_3P)_2PdCl_2$, $CHCl_3/Et_3N$, 1:2, 55 °C, 5–7 h. [c] Ac_2O, Et_3N, DMAP, DCM, 0 °C to room temp., 1–7 h. [d] Yield over two steps. [e] Prepared from **16k**. [f] Yield over three steps.



Scheme 9. [a] Reaction carried out under reflux. [b] 83% yield, pure *cis* after chromatography. Reaction carried out with $(c\text{-Hex})_3PAuSbF_6$.

^{1}H NMR analysis of **23i** revealed that a 6:1 mixture of diastereomers was present, with the *cis* compound being predominant. As the pre-Nazarov complex is a vinylgold species, a few ligands with different properties were screened to evaluate their possible role in the ring closure selectivity. Best results were obtained with the electron-rich ligand $(c\text{-hex})_3P$ (10:1 *cis*/*trans* ratio, separable mixture, 91% yield) whereas with electron-poor [$(p\text{CF}_3\text{C}_6\text{H}_4)_3P$] and NHC-carbene ligands [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene], not only the selectivity did not ameliorate but the reaction provided a mixture of cyclopentenones, acetates and degradation products. Moreover, the reaction with 5 mol-% $(c\text{-hex})_3PAuSbF_6$ was much cleaner than with

Ph_3P.[38] These results are consistent with our previous observations on the torquoselectivity in the Nazarov reaction,[7a,7b,7d,7g] although the *cis* selectivity was in those cases complete.[7a] For stereoelectronic reasons, the ring closure occurs in a way to form the new bond on the opposite side of the axially oriented 6-Me group.[7d,7g] The bases for the lower torquoselectivity in the gold-catalyzed process are not easy to understand, and could be either kinetic (i.e. both clockwise and counterclockwise ring closures could take place at different rate in the putative intermediate **XII**, Scheme 10) or related to the geometry of the oxyallyl cation before ring closure. In the latter case a counterclockwise ring closure of the isomer **XIII** would lead to the *trans* compound. However, DFT calculations revealed that the preference for **XII** is clear, with a difference over **XIII** of 2.3 kcal/mol because of steric reasons.[3g] Thus the major *cis* dimethyl diastereoisomer (**XIV**) is formed by a counterclockwise conrotatory ring closure of **XII**, with a low activation energy of 6.4 kcal/mol (**TS9**), whereas its *trans* diastereomer **XV** is formed by conrotatory clockwise ring closure from **XII** (**TS10**, 9.4 kcal/mol). Because of the predominance of intermediate **XII** it is likely that the alternative pathway from **XIII** is never operative.[39]



Scheme 10. DFT study on the torquoselectivity of the ring closure.

The torquoselectivity with 4-methyl substitute enyne **16j** was in line (6:1) with that observed for **16i**, as this substrate provided a separable 6:1 mixture of *cis* (major) and *trans* (minor) compounds **23j** (66% after chromatography) when using $Ph_3PAuSbF_6$ as the catalyst, together with some acetate **21j** (14% after chromatography). In this case, the use of other ligands did not improve the torquoselectivity and, moreover, caused the formation of a complex mixture of all acetates and cyclopentenone isomers.

Assessing the Scope of the Reaction

To assess the scope of the reaction, a series of enynyl acetates (Scheme 8) was prepared by varying the substituents on the alkyne moiety and on the piperidine ring as well as the heterocycle. All acetates **16** were prepared in good yield over two or three steps from lactam-derived enol phosphates **14**, with the exception of pyrrolidin-2-one derivatives **16o** and **16p**, and enyne **16q**, which were obtained from the corresponding lactam-derived enol triflates.[7a,7b,40,41] The results are shown in Scheme 9.

The number of alkyl groups at 3′ position seems to affect the reaction outcome and reactivity. Unsubstituted acetate **16e** reacted slower at room temperature and it required higher temperature (refluxing DCM) to be completely converted into **23e** (83%) only. This could be due to a slower rearrangement of the propargyl acetate moiety as a positive charge develops on a primary C atom (C3′) in the transition state. Interestingly, no traces of acetate **21e** (or the corresponding ketone) were found in the crude reaction mixture, meaning that proton abstraction is much more favored if occurs at the more substituted position to generate the most substituted double bond. The calculated energy difference between the two competing transition state is 1.2 kcal/mol (as usually using triflate as the base) which corresponds to a 7:1 selectivity (Figure 4).

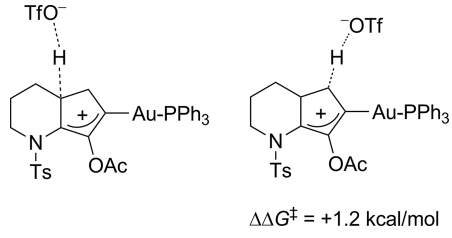
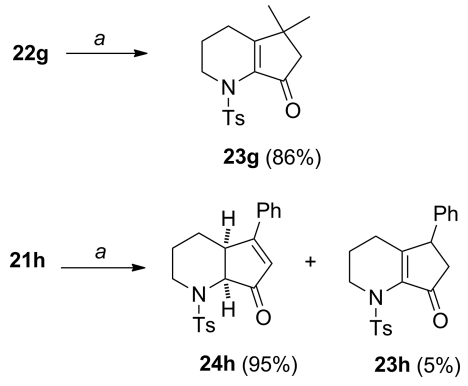


Figure 4. DFT study on the competing proton abstraction pathway in the reaction of **16e**.

The results obtained with 3′-methyl-substituted **16f** were in line with those for our model compound **16a** whereas, curiously, dimethyl-substituted acetate **16g** provided acetate **22g** (86%) only, which did not hydrolyze spontaneously. This was later done by treatment with *p*TsOH (Scheme 11) which furnished Nazarov compound **23g** in 86% yield. With the 3′-phenyl-substituted enyne **16h** the reaction provided expected cyclopentenone **23h** in 55% after chromatography. Acetate **21h**, formed during the reaction in mixture with **23h** in ca. 1:1 ratio, during the purification underwent [1,5]-H shift giving a complex mixture of few acetate isomeric products. A small amount of pure **21h** was treated with *p*TsOH (Scheme 11), and it was converted into a mixture of **24h** (95%) and **23h**. With compound **24h** it was possible to demonstrate by ^{1}H NMR studies the *cis* fusion of the rings (in analogy to the corresponding carbacyclic systems)[5a] and the structure of most populated conformer. 7a-H is a doublet with a low coupling constant (6.8 Hz) with 4a-H indicating its equatorial orientation, further confirmed by the lack of any NOE of 7a-H with 2-H_{ax} and 4-H_{ax}. Consequently, 4a-H is axially oriented. Similarly, in compound **18a** (Scheme 3) 7a-H is a doublet with a low coupling constant (6.9 Hz) with 4a-H confirming the *cis* fusion also for this compound. Hydroxy-substituted piperidine derivatives, both protected (**16k**) and unprotected (**16l**) on the OH group, were compatible with the reaction conditions. However, while **16k** provided cyclopentenone **23k** as the sole products in 75% yield after chromatography, substrate **16l** furnished the acetylated derivatives **25** as the

major compound (75%), accompanied by a minor amount of the corresponding alcohol **23l** (16%). Clearly, the free OH group acts a nucleophile by trapping the acyl cation which is released in the final step of the process (Scheme 6).



Scheme 11. [a] pTsOH (cat.), DCM-MeOH, 1:1, room temp., 16 h.

Also seven-membered rings as in **16m** and **16n** were compatible as these substrates provided, after complete hydrolysis of the corresponding acetate intermediates, Nazarov compounds **23m** (81%) and **23n** (83%) only and in excellent yield after chromatography. As in the case of **16e**, the reaction of **16n** required refluxing conditions, too. In both cases, disappearance of the starting material was faster than with the corresponding six-membered heterocycles and no traces of acetate isomers were detected by ^{1}H NMR analysis the crude reaction mixture. Not unexpectedly,[7a] the ring closure of five-membered derivatives **16o** and **16p** did not occur both at room temperature and in refluxing CH_2Cl_2, but we only recovered residual starting material with a certain amount of unidentified degradation compounds. The reaction of **16p** was also carried out in refluxing toluene, but to no avail. We have already reported the greater difficulty in the ring closure to give a 5–5 fused system, presumably due to ring strain in the intermediate azabicyclo[3.3.0]octenyl cation.[7a] On the other hands, we were very glad to observe that propargyl acetate **16q** containing a *N*-CO_2Me-protected indole nucleus reacted smoothly in refluxing CH_2Cl_2, to provide the corresponding cyclopenta-fused aromatic system **23q** in 84% yield after 1.5 h, thus paving a new way for the synthesis of natural compounds containing the cyclopenta[*b*]indole nucleus.

Conclusions

In this paper we have demonstrated that the tandem gold(I)-catalyzed rearrangement/Nazarov reaction of propargylic ester derivatives is a useful strategy for the synthesis, in just four steps, of cyclopenta-fused N-heterocyclic structures present in many natural compounds. First, readily available lactams are converted into the corresponding enol phosphates and triflates and coupled to propargyl alcohols under Sonogashira conditions. After acetylation, the gold-catalyzed rearrangement of the enynyl acetates readily (and best) occurs when using hexafluoroantimonate as the non-coordinating anion. This generates a divinyl cation which undergoes a 4π electrocyclization forming the target annulated N-heterocyclic compound in good to excellent yield. This process has been studied in details both experimentally and computationally, and the influence of the reaction conditions and the structure of the substrates on the reaction rate, regio- and stereoselectivity have been evaluated. The main features can be summarized as follows: (a) compared to the tandem process of carbacyclic enynyl acetates, the presence of the N atom clearly favors the nearly exclusive formation of the Nazarov product having the most substituted double bond, i.e. at the 4a-7a position. This is true with most catalysts we used, although its isomer (i.e. with the double bond at the 5–6 position) was the major product when triflate was the gold(I) counterion. (b) In contrast to similar cases in literature, suitably prepared "wet" dichloromethane seems to be not necessary to have a complete hydrolysis of the acetate intermediates. However the presence of some water in the solvent seems in any case essential for the process to occur properly, as in dry CH_2Cl_2 the conversion into the Nazarov product mixture was much lower. Under the best conditions (with $Ph_3PAuSbF_6$) the hydrolysis of only one of the two regioisomeric acetates occurs, leading to the 4a-7a unsaturated compound. (c) All N-protecting groups are compatible with the propargyl acetate rearrangement, with exception of the *N*-Boc group, and with the *N*-Ts being the best. The other *N*-alkoxycarbonyl groups somehow interfere, though, and heating is necessary to achieve complete conversion. (d) With piperidine rings substituted at 4 or 6 position, moderate to high torquoselectivity in the ring closure in favor of the *cis* diastereomers is observed when the propargyl moiety bears a substituent at C3′. This is in accordance to the results previously reported by us for the classical Nazarov reaction, meaning that the gold atom on the divinyl cation has a little effect on the stereoelectronically preferred conrotation mode. (e) The scope of the reaction ranges from six to seven-membered N-heterocyclic rings and various substituents at C3′ on the propargyl moiety, but is not extended to pyrroline derivatives which proved unsuitable for this approach. Instead, an indole containing enynyl acetate reacted smoothly to provide the cyclopenta[*b*]indole nucleus. Because of the combination of easily accessible propargyl alcohols and readily available lactams in the assemblage of the substrates required for the tandem process, this methodology is surely suited for the preparation of natural and biologically active compounds possessing a cyclopenta-annulated N-heterocyclic nucleus.

Experimental Section

General: Anhydrous solvents were prepared according to the standard techniques. Commercially available reagents were used without further purification. Chromatographic separations were per-

formed under pressure on silica gel 60 (Merck, 70–230 mesh) by using flash column techniques; R_f values refer to TLC carried out on 0.25 mm silica gel plates with the same eluent as indicated for column chromatography. ^{1}H NMR spectra were recorded at 200 or 400 MHz and ^{13}C NMR spectra at 100.4 MHz, both in $CDCl_3$ solution. Mass spectra were carried out by direct inlet of a 10 ppm solution in CH_3OH on an Ion Trap LC/MS system with electrospray ionization (ESI) interface in the positive ion mode.

Diphenyl 1-(4-Tolylsulfonyl)-1,4,5,6-tetrahydropyridin-2-yl Phosphate (14a): A 0.5 M solution of KHMDS (8.9 mL, 4.44 mmol) in toluene was diluted in anhydrous THF (28 mL) and cooled to –78 °C. A solution of N-tosyl δ-valerolactam **13a** (900 mg, 3.55 mmol) in anhydrous THF (14 mL) was added dropwise. The resulting mixture was stirred for 1.5 h at –78 °C and then diphenylchlorophosphate (0.92 mL, 4.44 mmol) was slowly added and the stirring continued below –70 °C for 1 h. The mixture was first warmed to 0 °C and then quenched with aqueous 10% NaOH (88 mL). The product was extracted with Et_2O (4× 40 mL); the combined organic extracts were washed with 10% NaOH (40 mL) and dried with anhydrous K_2CO_3 for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (*n*-hexane/EtOAc, 2:1 + 1% Et_3N; R_f = 0.29) and product **14a** was obtained (1.38 g, 80%) as a colorless oil. Phosphate **14a** was stored at 4 °C as 0.1 M solution in the eluent containing 1% Et_3N until use. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.2 Hz, 2 H, Ts), 7.35–7.17 (m, 12 H, Ts and Ph), 5.25 (dd, J = 6.6, 3.8 Hz, 1 H, 3-H), 3.66–3.64 (m, 2 H, 6-H), 2.37 (s, 3 H, CH_3 Ts), 2.08–2.03 (m, 2 H, 4-H), 1.56–1.51 (m, 2 H, 5-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 150.4 (s, C2), 143.8 (s, Ts), 139.6 (s, 2 C, Ph), 137.0 (s, Ts), 129.7 (d, 4 C, Ph), 129.6 (d, 2 C, Ts), 127.6 (d, 2 C, Ts), 125.5 (d, 2 C, Ph), 120.4 (d, 4 C, Ph), 100.5 (d, C3), 47.5 (t, C6), 21.5 (q, *C*H$_3$ Ts), 21.3 (t, C4), 20.9 (t, C5) ppm. MS (ESI): *m*/*z* (%) = 993 (100) [2M + Na]$^+$, 508 (13.1) [M + Na]$^+$, 486 (8) [M + 1]$^+$.

1-[1-(4-Tolylsulfonyl)-1,4,5,6-tetrahydropyridin-2-ylethynyl]pentyl Acetate (16a): Phosphate **14a** (1.16 g, 2.4 mmol) was dissolved in an anhydrous 2:1 Et_3N/$CHCl_3$ mixture (14 mL), and (±)-heptyn-3-ol (0.32 mL, 2.4 mmol), CuI (46 mg, 0.24 mmol) and $(Ph_3P)_2PdCl_2$ (84 mg, 0.12 mmol) were added under nitrogen atmosphere. The reaction mixture was heated at 55 °C (external) for 3 h and then a second portion of (±)-heptyn-3-ol (0.16 mL, 1.2 mmol), CuI (23 mg, 0.12 mmol) and $(Ph_3P)_2PdCl_2$ (17 mg, 0.024 mmol) was added. Heating was continued at 55 °C for 3 h. The mixture was cooled to room temperature and water (36 mL) was added. The product was extracted with Et_2O (3× 36 mL) and the combined organic extracts were dried with anhydrous K_2CO_3 for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (*n*-hexane/Et_2O, 2:1 + 1% Et_3N; R_f = 0.30) affording enynyl alcohol **15a** as a pale yellow oil (515 mg, 62%). **15a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.2 Hz, 2 H, Ts), 7.30 (d, J = 8.2 Hz, 2 H, Ts), 5.63 (t, J = 4.3 Hz, 1 H, 3-H), 4.43 (t, J = 6.6 Hz, 1 H, 1′-H), 3.68–3.65 (m, 2 H, 6-H), 2.42 (s, 3 H, CH_3 Ts), 2.06 (td, J = 6.6, 4.3 Hz, 3 H, 4-H and O*H*), 1.76–1.59 (m, 4 H, 5-H and 2′-H), 1.47–1.23 (m, 4 H, 3′-H and 4′-H), 0.91 (t, J = 7.2 Hz, 3 H, 5′-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 143.5 (s, Ts), 137.3 (s, Ts), 129.5 (d, 2 C, Ts), 127.4 (d, 2 C, Ts), 123.6 (d, C3), 120.4 (s, C2), 90.9 (s, C2a), 80.9 (s, C2b), 62.8 (d, C1′), 46.0 (t, C6), 37.2 (t, C2′), 27.2 (t, C5), 23.2 (t, C4), 22.4 (t, C3′), 22.3 (q, *C*H$_3$ Ts), 21.5 (t, C4′), 13.9 (q, C5′) ppm. MS (ESI): *m*/*z* (%) = 717 (100) [2M + Na]$^+$, 348 (14) [M + 1]$^+$. A solution of enynyl alcohol **15a** (515 mg, 1.48 mmol), DMAP (37 mg, 0.30 mmol) and Et_3N (0.57 mL, 4.44 mmol) in DCM (6 mL) was cooled (ice bath) and Ac_2O (0.28 mL, 3 mmol) was added. The reaction mixture was stirred at room temperature and monitored by TLC. When the conversion was complete, a satd solution of $NaHCO_3$ (15 mL) was added and the product extracted with DCM (3× 15 mL). The combined organic extracts were dried with anhydrous K_2CO_3 for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (*n*-hexane/EtOAc, 8:1 + 1% Et_3N; R_f = 0.21) affording pure **16a** as a pale yellow oil (455 mg, 79%). This was stored at 4 °C as 0.1 M solution in the eluent containing 1% Et_3N until use. **16a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.2 Hz, 2 H, Ts), 7.29 (d, J = 8.2 Hz, 2 H, Ts), 5.65 (t, J = 4.2 Hz, 1 H, 3-H), 5.45 (t, J = 6.6 Hz, 1 H, 1′-H), 3.64–3.62 (m, 2 H, 6-H), 2.42 (s, 3 H, CH_3 Ts), 2.08 (s, 3 H, CH_3 Ac), 2.06–2.03 (m, 2 H, 4-H), 1.72–1.74 (m, 2 H, 5-H), 1.65–1.59 (m, 2 H, 2′-H), 1.44–1.31 (m, 4 H, 3′-H and 4′-H), 0.90 (t, J = 7.2 Hz, 3 H, 5′-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 170.0 (s, *C*O), 143.4 (s, Ts), 137.2 (s, Ts), 129.5 (d, 2 C, Ts), 127.5 (d, 2 C, Ts), 124.4 (d, C3), 120.2 (s, C2), 97.2 (s, C2b), 81.1 (s, C2a), 64.4 (d, C1′), 46.0 (t, C6), 34.2 (t, C2′), 27.0 (t, C3′), 23.2 (t, C4), 22.2 (t, C4′), 21.5 (q, *C*H$_3$ Ts), 21.0 (q, *C*H$_3$ Ac), 21.0 (t, C5), 13.9 (q, C5′) ppm. MS (ESI): *m*/*z* (%) = 801 (100) [2M + Na]$^+$, 412 (13) [M + Na]$^+$.

5-Butyl-1-(4-tolylsulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (20a): Precatalyst Ph_3PAuCl (2.2 mg, 4.5 μmol, 3 mol-%) was dissolved in DCM (1.2 mL) and $AgSbF_6$ (1.5 mg, 4.5 μmol, 3 mol-%) was added. The formed suspension was left to stir at room temperature under nitrogen atmosphere. After 20 min a solution of enynyl acetate **16a** (59 mg, 0.15 mmol) in DCM (1.9 mL) was added and reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After complete consumption of the enynyl acetate (2.5 h) the reaction mixture was left to stir at room temperature overnight (16 h). Water (4 mL) was added and the product extracted with DCM (3× 4 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated. Chromatography (*n*-hexane/EtOAc, 6:1) afforded pure ketone **20a** (R_f = 0.17; 37 mg, 70%) as a yellow oil and acetate **17a** (R_f = 0.24; 8 mg, 14%) as an orange oil.

20a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.2 Hz, 2 H, Ts), 7.29 (d, J = 8.2 Hz, 2 H, Ts), 3.50–3.36 (m, 2 H, 2-H), 2.72–2.68 (bm, 1 H, 5-H), 2.60 (dd, J = 18.2, 6.4 Hz, 1 H, 6-H), 2.47 (dt, J = 19.9, 6.8 Hz, 1 H, 4-H), 2.41 (s, 3 H, CH_3 Ts), 2.28 (dt, J = 19.9, 6.4 Hz, 1 H, 4-H′), 2.13 (dd, J = 18.2, 2.2 Hz, 1 H, 6-H′), 2.01–1.99 (m, 2 H, 3-H), 1.76–1.71 (m, 1 H, 1′-H), 1.43–1.21 (m, 5 H, 1′-H′, 2′-H and 3′-H), 0.90 (t, J = 7.0 Hz, 3 H, 4′-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 200.1 (s, C7), 162.6 (s, C7a), 143.6 (s, Ts), 138.2 (s, C4a), 137.5 (s, Ts), 129.5 (d, 2 C, Ts), 127.9 (d, 2 C, Ts), 46.2 (t, C2), 40.1 (t, C6), 39.3 (d, C5), 32.9 (t, C1′), 29.0 (t, C2′), 24.1 (t, C4), 22.9 (t, C3′), 21.9 (t, C3), 21.7 (q, CH_3 Ts), 14.1 (q, C4′) ppm. MS (ESI): *m*/*z* (%) = 717 (100) [2M + Na]$^+$, 370 (12) [M + Na]$^+$. $C_{19}H_{25}NO_3S$ (347.47): calcd. C 65.68, H 7.25, N 4.03; found C 65.36, H 7.43, N 4.07.

17a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.0 Hz, 2 H, Ts), 7.25 (d, J = 8.0 Hz, 2 H, Ts), 6.03 (br. s, 1 H, 6-H), 4.16–4.09 (m, 1 H, 2-H), 3.05 (td, J = 13.6, 2.8 Hz, 1 H, 2-H′), 2.41 (s, 3 H, CH_3 Ts), 2.21–2.03 (m, 7 H, CH_3 Ac, 4-H, 4a-H and 1′-H), 1.64–1.56 (m, 1 H, 3-H), 1.48–1.23 (m, 5 H, 3-H′, 2′-H and 3′-H), 1.04 (qd, J = 12.8, 3.6 Hz, 1 H, 4-H′), 0.88 (t, J = 7.2 Hz, 4′-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 168.5 (s, *C*O), 150.3 (s, C7), 143.6 (s, Ts), 137.4 (s, Ts), 129.5 (d, 2 C, Ts), 127.4 (d, 2 C, Ts), 123.7 (s, C7a), 122.9 (d, C6), 49.5 (t, C2), 45.5 (d, C4a), 30.7 (t, C2′), 29.7 (s, C5), 28.4 (t, C4), 28.1 (t, C1′), 25.0 (t, C3), 22.4 (t, C3′), 21.5 (q, *C*H$_3$ Ts), 20.7 (q, *C*H$_3$ Ac), 13.9 (q, C4′) ppm. MS

(ESI): *m*/*z* (%) = 801 (100) $[2M + Na]^+$, 390 (12) $[M + Na]^+$. $C_{21}H_{27}NO_4S$ (389.51): calcd. C 64.75, H 6.99, N 3.06; found C 64.82, H 7.08, N 3.04.

Acknowledgments

Financial support from the University of Florence is acknowledged. M. P. and B. F. thank the European Commission for a Marie Curie fellowship (FP7-PEOPLE-2012-ITN, project ECHONET "Expanding capability in Heterocyclic Organic Synthesis", project number 316379). Ente Cassa di Risparmio di Firenze is acknowledged for granting a 400 MHz NMR instrument. SGI/IZO-SGIker (UPV-EHU) is acknowledged for allocation of computational resources. Mr. Emanuele Chiti is acknowledged for carrying out some experiments. Dr. Maurizio Passaponti is acknowledged for technical assistance.

[1] For a recent and excellent review see: D. J. Aitken, H. Eijsberg, A. Frongia, J. Ollivier, P. P. Piras, *Synthesis* **2014**, *46*, 1–24.

[2] For the most recent reviews, see: a) D. R. Wenz, J. R. de Alaniz, *Eur. J. Org. Chem.* **2015**, 23–37; b) M. A. Tius, *Chem. Soc. Rev.* **2014**, *43*, 2979–3002; c) M. J. Di Grandi, *Org. Biomol. Chem.* **2014**, *12*, 5331–5345; d) W. T. Spencer, T. Vaidya, A. J. Frontier, *Eur. J. Org. Chem.* **2013**, 3621–3633; e) T. Vaidya, R. Eisenberg, A. J. Frontier, *ChemCatChem* **2011**, *3*, 1531–1548. For an older but excellent review on the Nazarov reaction covering the past decade, see: f) A. J. Frontier, C. Collison, *Tetrahedron* **2005**, *61*, 7577–7606.

[3] For homogeneous Au^I-catalyzed processes involving a Nazarov reaction see: a) M. Hoffmann, J.-M. Weibel, P. de Frémont, P. Pale, A. Blanc, *Org. Lett.* **2014**, *16*, 908–911; b) W. Rao, M. J. Koh, D. Li, H. Hirao, P. W. H. Chan, *J. Am. Chem. Soc.* **2013**, *135*, 7926–7932; c) E. Álvarez, D. Miguel, P. García-García, M. A. Fernández-Rodríguez, F. Rodríguez, R. Sanz, *Synthesis* **2012**, *44*, 1874–1884; d) R. Sanz, D. Miguel, M. Gohain, P. García-García, M. A. Fernández-Rodríguez, A. González-Pérez, O. Nieto-Faza, Á. R. de Lera, F. Rodríguez, *Chem. Eur. J.* **2010**, *16*, 9818–9828; e) C. H. Oh, S. Karmakar, *J. Org. Chem.* **2009**, *74*, 370–374; f) S. E. An, J. Jeong, B. Baskar, J. Lee, J. Seo, Y. H. Rhee, *Chem. Eur. J.* **2009**, *15*, 11837–11841; g) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006; h) S. Suárez-Pantiga, E. Rubio, C. Alvarez-Rúa, J. M. González, *Org. Lett.* **2009**, *11*, 13–16; i) G. Y. Lin, C. W. Li, S. H. Hung, R. S. Liu, *Org. Lett.* **2008**, *10*, 5059–5062; j) J. H. Lee, F. D. Toste, *Angew. Chem.* **2007**, *119*, 930–932; k) J. H. Lee, F. D. Toste, *Angew. Chem. Int. Ed.* **2007**, *46*, 912–914; *Angew. Chem.* **2007**, *119*, 930; l) G.-Y. Lin, C.-Y. Yang, R.-S. Liu, *J. Org. Chem.* **2007**, *72*, 6753–6757; m) G. Lemière, V. Gandon, K. Cariou, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *Org. Lett.* **2007**, *9*, 2207–2209; n) G. Y. Lin, C. Y. Yang, R. S. Liu, *J. Org. Chem.* **2007**, *72*, 6753–6757; o) Z.-X. Ma, S. He, W. Song, R. P. Hsung, *Org. Lett.* **2002**, *14*, 5736–5739. For homogeneous Au^I-catalyzed iso-Nazarov reactions, see: p) C. C. Lin, T. M. Teng, C. C. Tsai, H. Y. Liao, R. S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16417–16423; q) C. C. Lin, T. M. Teng, A. Odedra, R. S. Liu, *J. Am. Chem. Soc.* **2007**, *129*, 3798–3798.

[4] For homogeneous Au^{III}-catalyzed Nazarov reactions, see: a) T. Vaidya, R. Cheng, P. N. Carlsen, A. J. Frontier, R. Eisenberg, *Org. Lett.* **2014**, *16*, 800–803; b) M. E. Krafft, D. V. Vidhani, J. W. Cran, M. Manoharan, *Chem. Commun.* **2011**, *47*, 6707–6709; c) S. Karmakar, A. Kim, C. H. Oh, *Synthesis* **2009**, 194–198; d) T. Jin, Y. Yamamoto, *Org. Lett.* **2008**, *10*, 3137–3139, see also ref.[3a]

[5] a) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443; b) F. Q. Shi, X. Li, Y. Xia, L. Zhang, Z. X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 15503–15512, see also ref.[3g,3m]

[6] The metal-catalyzed rearrangement of 3-acyloxy-1,4-enynes, called the Rautenstrauch rearrangement, occurs instead via initial 1,2-shift of the carboxylate and is another excellent way to prepare cyclopenta-fused systems. For a very recent example, see: a) W. Zi, H. Wu, F. D. Toste, *J. Am. Chem. Soc.* DOI: 10.1021/jacs.5b00613; see also: b) O. N. Faza, C. S. López, R. Álvarez, Á. R. de Lera, *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437; c) V. Rautenstrauch, *J. Org. Chem.* **1984**, *49*, 950–952; d) X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803; e) K. Kato, T. Kobayashi, T. Fujimami, S. Motodate, T. Kusakabe, T. Mochida, H. Akita, *Synlett* **2008**, 1081–1085; f) P. A. Caruana, A. J. Frontier, *Tetrahedron* **2007**, *63*, 10646–10656; g) Y. Nakanishi, K. Miki, K. Ohe, *Tetrahedron* **2007**, *63*, 12138–12148; h) D. Nakagawa, M. Miyashita, K. Tanino, *Tetrahedron Lett.* **2010**, *51*, 2771–2773, see also ref.[4c]

[7] a) E. G. Occhiato, C. Prandi, A. Ferrali, A. Guarna, P. Venturello, *J. Org. Chem.* **2003**, *68*, 9728–9741; b) C. Prandi, A. Ferrali, A. Guarna, P. Venturello, E. G. Occhiato, *J. Org. Chem.* **2004**, *69*, 7705–7709; c) C. Prandi, A. Deagostino, P. Venturello, E. G. Occhiato, *Org. Lett.* **2005**, *7*, 4345–4348; d) A. Cavalli, M. Masetti, M. Recanatini, C. Prandi, A. Guarna, E. G. Occhiato, *Chem. Eur. J.* **2006**, *12*, 2836–2845; e) P. Larini, A. Guarna, E. G. Occhiato, *Org. Lett.* **2006**, *8*, 781–784; f) L. Bartali, P. Larini, A. Guarna, E. G. Occhiato, *Synthesis* **2007**, 1733–1737; g) A. Cavalli, A. Pacetti, M. Recanatini, C. Prandi, D. Scarpi, E. G. Occhiato, *Chem. Eur. J.* **2008**, *14*, 9292–9304.

[8] a) A. Oppedisano, C. Prandi, P. Venturello, A. Deagostino, G. Goti, D. Scarpi, E. G. Occhiato, *J. Org. Chem.* **2013**, *78*, 11007–11016; b) E.-S. Lee, H.-S. Yeom, J.-H. Hwang, S. Shin, *Eur. J. Org. Chem.* **2007**, 3503–3507; c) A. Buzas, F. Gagosz, *Synlett* **2006**, 2727–2730.

[9] The [1]pyrindine system that is formed is contained in a few natural compounds. For example, for streptazolin, streptazon C, and streptazon A, isolated from *Streptomyces viridochromogenes*, *S. luteogriseus*, and FORM5, Strain A1, see: a) H. Drautz, H. Zähner, E. Kupfer, W. Keller-Schierlein, *Helv. Chim. Acta* **1981**, *64*, 1752–1768; b) S. Grabley, H. Kluge, H.-U. Hoppe, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 664–665; *Angew. Chem.* **1987**, *99*, 692; c) S. Grabley, P. Hammann, H. Kluge, J. Wink, P. Kricke, A. Zeeck, *J. Antibiot.* **1991**, *44*, 797–800; d) C. Puder, P. Krastel, A. Zeeck, *J. Nat. Prod.* **2000**, *63*, 1258–1260; e) C. Puder, S. Loya, A. Hizi, A. Zeeck, *J. Nat. Prod.* **2001**, *64*, 42–45. For the synthesis of streptazolin and related natural products, see: f) B. M. Trost, C. K. Chung, A. B. Pinkerton, *Angew. Chem. Int. Ed.* **2004**, *43*, 4327–4329; *Angew. Chem.* **2004**, *116*, 4427, and references cited therein. For pyrindicin, isolated from *Streptomyces sp.* SCC 2313, see: g) S. Omura, H. Tanaka, J. Awaya, Y. Narimatsu, Y. Konda, T. Hata, *Agric. Biol. Chem.* **1974**, *38*, 899–906. For abikoviromycin, isolated from *S. abikoensis*, see: h) A. I. Gurevich, M. N. Kolosov, V. G. Korobko, V. V. Onoprienko, *Tetrahedron Lett.* **1968**, *9*, 2209–2212. For 1-pyrindine alkaloids from *Rhizoctonia leguminicola*, see: i) F. P. Guengerich, S. J. Di Mari, H. P. Broquist, *J. Am. Chem. Soc.* **1973**, *95*, 2055–2056. For pandamarilactone-32 and analogues from *Pandanus amaryllifolius*, see: j) M. G. Nonatoa, M. J. Garson, R. J. W. Truscott, J. A. Carver, *Phytochemistry* **1993**, *34*, 1159–1163. For proline-specific Maillard compounds, see: k) C.-W. Chen, G. Lu, C.-T. Ho, *J. Agric. Food Chem.* **1997**, *45*, 2996–2999. For decahydrocyclopenta[*b*]-azepines, for example Drupacine, isolated from *Cephalotaxus harringtonia*, see: l) R. G. Powell, R. V. Madrigal, C. R. Smith Jr., K. L. Mikolajczak, *J. Org. Chem.* **1974**, *39*, 676–679. Sessilistemonamine F, from *Stichoneuron caudatum*, see: m) R. A. Ramli, W. Lie, S. G. Pyne, *J. Nat. Prod.* **2014**, *77*, 894–901. For cyclopenta-fused pyrroline rings, for rexample roseophilin, isolated from *S. griseoviridis*, see: n) A. Fürstner, *Angew. Chem. Int. Ed.* **2003**, *42*, 3582–3603; *Angew. Chem.* **2003**, *115*,

3706. A plethora of natural, cyclopentannulated indole alkaloids exist; for example Bruceolline J, isolated from *Brucea mollis*, see: o) H. Chen, J. Bai, Z.-F. Fang, S.-S. Yu, S.-G. Ma, S. Xu, Y. Li, J. Qu, J.-H. Ren, L. Li, Y.-K. Si, X.-G. Chen, *J. Nat. Prod.* **2011**, *74*, 2438–2445.

[10] Cephalotaxine synthesis: a) S. H. Kim, J. K. Cha, *Synthesis* **2000**, 2113–2116. For formal and total syntheses of roseophilin by the Nazarov reaction, see: b) D. J. Kerr, L. B. Flynn, *Org. Lett.* **2012**, *14*, 1740–1743; c) C. Song, H. Liu, M. Hong, Y. Liu, F. Jia, L. Sun, Z. Pan, J. Chang, *J. Org. Chem.* **2012**, *77*, 704–706; d) M. Hong, H. Liu, L. Sun, F. Jia, Y. Liu, Q. Jiang, C. Song, *Synlett* **2011**, 2995–2996; e) A. Y. Bitar, A. J. Frontier, *Org. Lett.* **2009**, *11*, 49–52; f) E. G. Occhiato, C. Prandi, A. Ferrali, A. Guarna, *J. Org. Chem.* **2005**, *70*, 4542–4545; g) P. E. Harrington, M. A. Tius, *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514.

[11] We used the procedure reported by us in ref.[8a] for simple alkynes.

[12] As with simpler enynes,[8a] compounds **16** decompose when neat, but they can be stored for months in solution of the chromatographic eluant containing 1% Et_3N. Because of their instability when neat, we cannot provide elemental analysis for these compounds.

[13] This was the best solvent for the corresponding carbacyclic substrates, see ref.[5a]

[14] Monitoring the reaction by TLC we observed the formation of only one spot which corresponded to both acetates. Acetate **17a** and **19a** are easily distinguished by ^1H NMR as in **17a** the bridgehead proton 4a-H can be identified at 2.21–2.30 ppm and the olefinic 6-H proton resonates at δ = 6.03 ppm as a singlet. In **19a** this proton is more shielded and resonates at δ = 5.88 ppm as a doublet (with a very low coupling constant) because of the coupling with 5-H (which is a multiplet at 2.98–2.92 ppm).

[15] The $Ph_3PAuOTf$ catalyst was the best in the oxyauration of the triple bond in *N*-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines, see ref.[8a]

[16] Degradation of the active gold(I) catalyst has been report to increase with the relative amount of water in organic solvents. M. Kumar, J. Jasinski, G. B. Hammond, B. Xu, *Chem. Eur. J.* **2014**, *20*, 3113–3119.

[17] No aqueous work up, only filtration through Celite.

[18] Adventitious water was also responsible for the hydrolysis of acetate **4** in carbacyclic systems (Scheme 1), see ref.[5a]

[19] D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019.

[20] M. Kumar, G. B. Hammond, B. Xu, *Org. Lett.* **2014**, *16*, 3452–3455.

[21] An opposite result has been recently reported for the [3,3]-rearrangement of propargyl ester derivatives, see: L.-J. Wang, H.-T. Zhu, A.-Q. Wang, Y.-F. Qiu, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2014**, *79*, 204–212.

[22] For the silver-catalyzed [3,3]-rearrangement of propargyl esters see: *Silver in Organic Chemistry* (Ed.: M. Harmata), John Wiley & Sons, **2010**, p. 402.

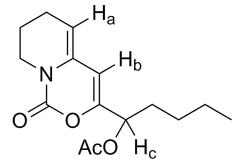
[23] A. Guérinot, W. Fang, M. Sircoglou, C. Bour, S. Bezzenine-Lafollée, V. Gandon, *Angew. Chem. Int. Ed.* **2013**, *52*, 5848–5852; *Angew. Chem.* **2013**, *125*, 5960.

[24] In the hydrolysis of **17a** with 1% TfOH the shift was more pronounced as we obtained a mixture of **18a** and **20a** in 2:1 ratio.

[25] This degradation could be due to the acidity of the bridgehead proton in acetates **17**. Deprotonation at that position leads to an aromatic cyclopentadienyl anion and from this, probably, to various unidentified byproducts during work-up.

[26] Two experiments were performed in MeOH with 0.8 equiv. of MeONa and with 2 equiv. of DBU in THF. Isomerization has been instead successfully performed with the corresponding carbacyclic systems (see ref.[5a]) and it has been reported for five-membered N-heterocycles. See: M. M. Domostoj, E. Irwing, F. Scheimann, K. J. Hale, *Org. Lett.* **2004**, *6*, 2615–2618.

[27] The cyclic urethane intermediate was not isolated. Diagnostic signals are the triplet at δ = 4.71 ppm and the singlet at δ = 5.56 ppm assigned to protons H_a and H_b, respectively. Proton H_c resonates at δ = 5.15 ppm as a triplet:



[28] In this particular case, monitoring the reaction by TLC revealed the formation of two spots corresponding to the two acetate isomers and only one of this disappeared to form a more polar spot corresponding to Nazarov product **20d**.

[29] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; c) W. Kohn, A. D. Becke, R. G. Parr, *J. Phys. Chem.* **1996**, *100*, 12974–12980.

[30] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, revision D.01, Gaussian, Inc., Wallingford CT, **2013**.

[31] a) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270–283; b) W. R. Wadt, P. J. Hay, *J. Chem. Phys.* **1985**, *82*, 284–298; c) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299–310.

[32] This species could also be considered as a gold-carbene, although it should be more adequately described as a gold-stabilized carbocation, see: a) A. Fürstner, L. Morency, *Angew. Chem. Int. Ed.* **2008**, *47*, 5030–5033; *Angew. Chem.* **2008**, *120*, 5108. See also ref.[3g] and references cited therein.

[33] Interestingly, this [1,2]-H shift process has been postulated to be the rate-limiting step in the tandem [3,3]-rearrangement/Nazarov reaction of simpler enynyl acetates in the gas phase.[5b]

[34] Interestingly, when the reaction of **16a** was carried out in anhydrous DCM, we observed a significant decrease in the conversion rate of the substrate into any of the acetate intermediates accompanied by the formation of degradation products.

[35] The results for the water assisted process are shown in the Supporting Information, and the conclusions are in total agreement with the ones withdrawn from Figure 3. With water as a base, the process leading to **VII** is favoured by 0.6 kcal/mol.

[36] For the most recent studies on the torquoselectivity in Nazarov reactions, see: a) T. D. R. Morgan, L. M. LeBlanc, G. H. Ardagh, R. J. Boyd, D. J. Burnell, *J. Org. Chem.* **2015**, *80*, 1042–1051; b) B. L. Flynn, N. Manchala, E. H. Krenske, *J. Am. Chem. Soc.* **2013**, *135*, 9156–9163, and references cited therein, see also ref.[2b]

[37] See Supporting Information for the preparation of all lactams.

[38] We noticed that the solution maintains its initial orange colour (whereas it turns blackish when Ph_3P is used as the ligand), which is probably accounted for by a greater stability of the

cationic gold complex. The same ligand was tested with model compound **16a** but the regioisomeric ratio did not change compared to Ph_3P ligand.
[39] Clearly our calculations overestimate the kinetic preference for **XIV** (by 3 kcal/mol), which is not experimentally so high.
[40] T. Luker, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1997**, *62*, 8131–8140.
[41] X.-H. Xu, X. Wang, G.-K. Liu, E. Tokunaga, N. Shibata, *Org. Lett.* **2012**, *14*, 2544–2547.

Received: April 10, 2015
Published Online: May 15, 2015

