DOI: 10.1002/cctc.201200484

Ring Expansions Within the Gold-Catalyzed Cycloisomerization of *O*-Tethered 1,6-Enynes. Application to the Synthesis of Natural-Product-like Macrocycles

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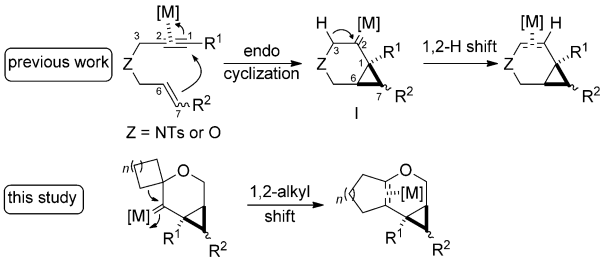
Cycloisomerization reactions of enynes by using electrophilic late-transition-metal salts have attracted intensive research effort since the pioneering works of Trost et al. almost 30 years ago.[1,2] In this field, a lot of metal complexes have been identified to efficiently catalyze cycloisomerizations of enynes, featuring also skeletal rearrangements, the most commonly used of which are undoubtedly platinum and gold salts.[3] Indeed, since the discovery in the early 2000s that stable cationic complexes of gold(I) could efficiently promote these latter processes at room temperature,[4] many research groups have added their own contributions to this topic.[5] Thus, new reaction pathways, as well as new synthetic applications, have bloomed in the literature,[6] at the same time illustrating both the versatility of this process and its high "substrate dependence". Herein, as a continuation of our previous work on enynes,[7] we report some results that we have gathered during our exploration of the reactivity of oxygen-tethered 1,6-enynes under gold catalysis, accompanied by a practical two-steps synthetic procedure that allows the transformation of the cyclization compounds into macrolactones.

It is commonly accepted that the cycloisomerization of enynes by using carbophilic Lewis acids is initiated by the activation of the alkyne partner.[8] Depletion of the electronic density of the triple bond triggers a nucleophilic attack from the neighboring alkene, which can follow an *endo* or *exo* mode of cyclization. Whereas 1,5-enynes react exclusively through the *endo* route,[7b–c,9] 1,6-enynes offer various cycloisomerization patterns. The cyclization mode is essentially dictated by stereoelectronic factors that bias the reactivity of an enyne substrate toward one pathway or the other. For example, heteroatom-tethered 1,6-enynes will prefer an *endo* cyclization pathway, thereby leading to bicylo[4.1.0]heptene skeletons, through key transition-metal-stabilized cation **I**[10] (which can also be seen as a carbene[11]). This latter structure then undergoes a 1,2-hydride shift from the 3 position, thereby allowing the release of the cyclized compound (Scheme 1, top).

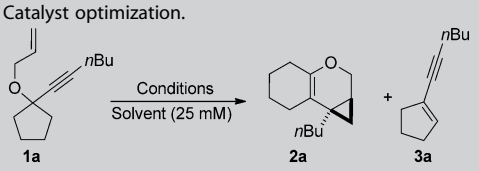


Scheme 1. Mechanisms for the ring expansion.

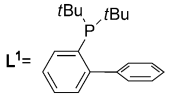
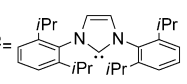
We wondered if the introduction of a strained ring at the unsubstituted 3 position could give rise to ring expansion by classic Wagner–Meerwein transposition onto the transition-metal-stabilized carbocation that originates from the cyclization pathway (Scheme 1, bottom). Gold has been shown to effect ring expansions in various reactions.[12] Several examples have been reported in the context of enyne cycloisomerizations,[9b,13] some of which have led to useful synthetic applications.[14] Thus, we synthesized model compound **1a** and assessed the activity of various catalysts to test our hypothesis (Table 1).

Platinum(II)–chloride and platinum(IV)–chloride salts were completely inactive, even after prolonged heating (Table 1, en-

Table 1. Catalyst optimization.



Entry	Catalyst	Loading [mol%]	*T* [°C]	Solvent	*t* [h]	Product	Yield [%]
1	$PtCl_2$	5	reflux	toluene	15	**1a**	
2	$PtCl_4$	5	80	toluene	5	**1a**	
3	AuCl	2	RT	CH_2Cl_2	27	**1a**	
4[a]	$AuCl_3$	2	RT	CH_2Cl_2	27	**3a**	33
5	$[Ph_3PAuCl]/AgSbF_6$	2	RT	CH_2Cl_2	0.5	**2a**	50
6	$[Ph_3PAuCl]/AgNTf_2$	2	RT	CH_2Cl_2	0.5	**2a**	49
7	$[(tBu)_3PAuCl]/AgSbF_6$	2	RT	CH_2Cl_2	1.5	**2a**	75
8	$[L^1Au(MeCN)]SbF_6$[b]	2	RT	CH_2Cl_2	1.5	**2a**	84
9	$[L^2AuCl]/AgSbF_6$[b]	2	RT	CH_2Cl_2	1.5	**2a**	85
10	$[(IrCp^*Cl_2)_2]$	5	reflux	DCE		**1a**	

[a] Compound **3a** was obtained with the starting material. [b] L^1=  L^2= 

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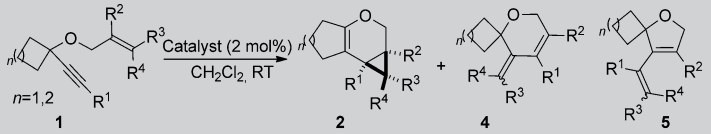
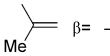
Supporting information (full experimental details and spectra) for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201200484.

tries 1 and 2). Gold(I)–chloride and gold(III)–chloride salts also did not furnish any cyclized compounds (Table 1, entries 3 and 4); $AuCl_3$ gave consequent amounts of elimination product **3a**. When we switched to cationic gold(I) catalysts, we were pleased to obtain the desired compound (**2a**). The PPh_3 ligand led to moderate yields, independent of the counteranion (Table 1, entries 5 and 6). However, the use of the bulky donor ligand $P(t\text{Bu})_3$ improved the yield to 75% (Table 1, entry 7). Thus, we decided to try cationic gold(I) catalysts with hindered, strongly donating ligands and we found that phosphine **L**[1] (Table 1, entry 8) or NHC **L**[2] (Table 1, entry 9) were ideal ligands for this cycloisomerization reaction: the desired compound was isolated in 84% and 85% yield, respectively. We also investigated the activity of an Ir^{III} dimer complex that has been recently shown to be active in some enyne-cycloisomerization processes,[15] but, even after prolonged heating in 1,2-dichloroethane (DCE), the starting material was fully recovered (Table 1, entry 10).

Table 2. Gold-catalyzed reactions of *O*-tethered 1,6-enynes **1b**–**1p**.



Entry	Substrate		Catalyst[a]	*t* [h]	Product(s)	Yield [%]
1	**1b**	$R^1=R^2=H$	**A**	1	**2b**, **4b**	65, 18
2	**1c**	$R^1=Ph$, $R^2=H$	**B**	14	**2c**	76
2	**1d**	$R^1=Ph$, $R^2=Me$	**B**	1.25	**2d**	>98
4	**1e**	$R^1=i\text{Pr}$, $R^2=H$	**B**	14	**2e**	55
5	**1f**	$R^1=\alpha$,[e] $R^2=H$	**B**	1.5	**2f**	62
6	**1g**	$R^1=CO_2Et$, $R^2=H$	**B**	1	**4g**, **5g**	97 (8:2)[b]
7	**1h**	$R^2=R^3=R^4=H$	**B**	2	**2h**	82
8	**1i**	$R^2=R^4=H$, $R^3=Ph$	**B**	2	**2i**	81
9	**1j**	$R^2=Me$, $R^3=R^4=H$	**B**	18	**2j**	37
10	**1k**	$R^2=H$, $R^3=R^4=Me$	**B**	2	**2k**	12[c]
11	**1l**	$R^1=\beta$,[e] $R^2=H$	**A**	4	**2l**	81
12	**1m**	$R^1=n\text{Bu}$, $R^2=H$	**A**	17	**2m**	70
13	**1n**	$R^1=n\text{Bu}$, $R^2=Me$	**A**	6	**2n**	85
14	**1o**	$R^1=Ph$, $R^2=H$	**A**	17	**2o**	15
15	**1p**		[d]	48	**2p**	52

[a] **A** = [**L**[1]Au(MeCN)]SbF_6, **B** = [**L**[2]AuCl]/$AgSbF_6$. [b] Inseparable mixture. [c] Formation of the corresponding allene was observed. [d] [(2,4-*t*BuPhO)$_3$PAuCl/$AgSbF_6$] was used as the catalyst. [e] α=  β= 

With these optimized conditions in hand (Table 1, entries 8 and 9), we examined the scope and limitations of the ring-expansion reaction (Table 2). First, we started our study with five-membered-ring precursors. The treatment of enyne **1b** with catalyst **A** afforded a mixture of the expected ring-expansion product (**2b**) in 65% yield, as well as compound **4b**, which originated from a 5-*exo*-dig process, in 18% yield.[5] The selectivity and yield of the reaction were improved by the introduction of a phenyl group onto the terminal alkyne by using catalyst **B**. Only ring-expansion product **2c** was obtained in 76% yield (Table 2, entry 2). When the double bond was substituted by a methyl group, compound **2d** was obtained in quantitative yield (Table 2, entry 3). Substitution of the alkyne by isopropyl or vinyl groups in the presence of catalyst **B** led to the ring-expansion compounds in similarly moderate yields (Table 2, entries 4 and 5). When ester-substituted compound **1g** was submitted to the same catalytic system, an inseparable mixture of products **4g** and **5g** was obtained in a good yield (97%, 80:20 ratio). Acetylenic–cyclopropyl-substituted substrates **1h**–**1j** afforded very good yields of the expected ring-expansion products (Table 2, entries 7 and 8). The expected stereochemistry of compound **2i** was confirmed by X-ray diffraction (Figure 1). In contrast, when the double bond was substituted by a Me group at the R^2 position, a low yield of product **2j** (37%) was obtained (Table 2, entry 9). Moreover, when a prenyl group was present (Table 2, entries 10), a very low yield of the ring-expansion product was obtained. Indeed, in the ^1H NMR spectrum of the crude product, we noticed the presence of an aldehyde signal, as well as large amounts of a volatile allenic compound, which was confirmed by ^{13}C NMR spectroscopy with a signal at $\delta = 200$ ppm. In this case, a competitive 1,5-hydride shift onto the activated triple bond occurred, as reported by Gagosz and co-workers[16] and ourselves.[7e]

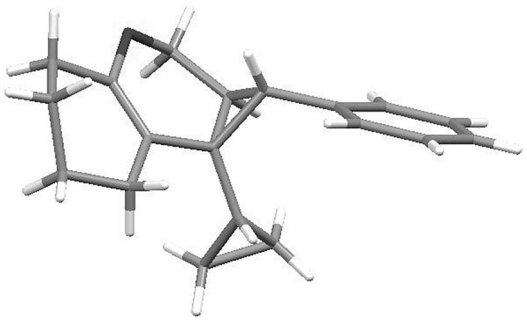
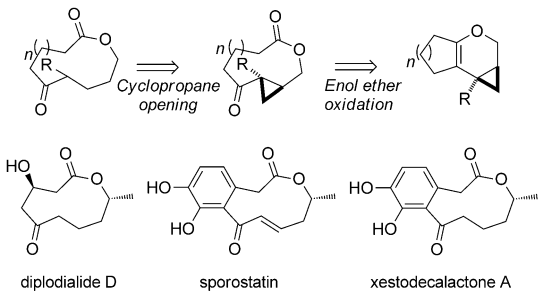


Figure 1. X-ray crystal structure of compound **2i** (CCDC-887772).

Next, we switched our attention to four-membered-ring derivatives. Substrates **1l**–**1n** led to ring-expansion products **2l**–**2n** in good yields with catalyst **B** (Table 2, entries 11–13). In the case of compound **1o**, a very low yield (15%) was obtained (Table 2, entry 14). Indeed, this product seemed to be more unstable than its homologue (**2c**; Table 2, entry 2) and decomposed in a few hours as a solution in $CDCl_3$.

Finally, compound **1p**, bearing an acetate group on the cyclobutane moiety, was reacted with catalysts **A** and **B** but only the corresponding allene was isolated in quantitative yield in each case. To avoid this undesired reactivity, we used the more-electrophilic catalyst [(2,4-*t*BuPhO)$_3$PAuCl/AgSbF$_6$], which was reported by Gagosz and co-workers to be inefficient at promoting 1,5-hydride shifts.[16] Thus, the desired ring-expansion product (**2p**) was obtained in 52% yield (Table 2, entry 15), albeit with a non-negligible amount of allene byproduct.

Next, we were interested in developing a two-step synthetic sequence for the synthesis of medium-sized-ringed lactones from products **2**,[7d] first by oxidation of the enol–ether function and then by opening of the cyclopropane moiety. Such a synthetic sequence could provide access to macrocyclic skeletons that are reminiscent of natural products (Scheme 2).[17]

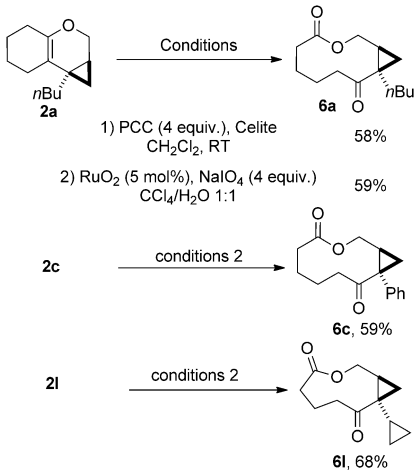


Scheme 2. Strategy for the synthesis of macrolactones.

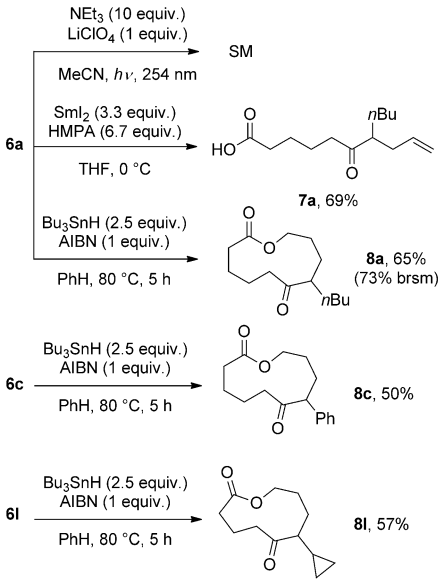
First, the oxidative cleavage of enol-ether **2a** was performed in fair yield (about 60%) by using either pyridinium chlorochromate (PCC) or Ru complexes in combination with $NaIO_4$, thereby giving macrolactone **6a** (Scheme 3). By using Ru-complex conditions, we were able to obtain macrolactones **6c** and **6l** in 59% and 68% yield, respectively.

To promote the cyclopropane-opening step, we naturally considered homolytic methods, given the fact that a ketone was present at the α position of this strained moiety (Scheme 4).

Because photochemical conditions[18] were completely inefficient, we submitted compound **6a** to a 2:1 SmI_2/hexamethylphosphoramide (HMPA) mixture[19] and obtained carboxylic acid **7a**. Although the cyclopropane was clearly opened, compound **7a** was not the expected product and presumably arose from a reduction of the secondary radical generated after cyclopropane opening, thereby leading to the elimination of the carboxylate group. We expected that this undesired step could be avoided if a hydrogen donor was present in the reaction mixture. Thus, we switched to Bu_3SnH/azobisisobutyronitrile (AIBN)[20] and successfully obtained the desired macrocycle **8a** in 65% yield, albeit with incomplete conversion of the starting material (Scheme 4). Then, we extended this synthetic sequence to cyclized compounds **6c** and **6l** and we obtained their expected corresponding deca- and undeca-5-ketolactones (**8c** and **8l**) in moderate yields (50 and 57%, respectively; Scheme 4).



Scheme 3. Oxidative cleavage of enol ether **2**.



Scheme 4. Synthesis of various macrolactones.

In conclusion, we have reported the gold-catalyzed cycloisomerization of *O*-tethered 1,6-enynes, which featured a small-sized ring expansion. Thus, we obtained fused tricyclic compounds that contained a substituted dihydropyrane moiety. In this study, we found that bulky donor ligands on the cationic gold(I) center were necessary to efficiently promote this cycloisomerization process. Skeletal reorganization with no ring expansion can become competitive and can completely prevail when hydrogen or electron-withdrawing groups are placed at the acetylenic position. Finally, we have developed a two-step

synthetic sequence that allows the conversion of these cyclized compounds into valuable macrocycles that are reminiscent of natural products; we are currently working on the application of this sequence to the synthesis of natural products.

Acknowledgements

The authors thank the UPMC, the CNRS, ANR Blan 0302 "Allenes" (postdoctoral grant to Y.H.), the MRES (PhD grants to A.S. and G.L.), the IUF (L.F. and M.M.), and FR2769 for technical support.

Keywords: cycloisomerization · enynes · gold · radical reactions · ring expansion

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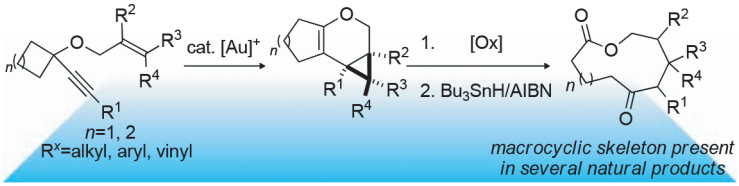
Received: July 18, 2012
Published online on ■■ ■■, 0000



Goldenyne: *O*-tethered 1,6-enynes that contain a strained ring at the 3 position can cycloisomerize upon cationic gold(I) catalysis through a ring-expansion process. A two-step sequence allows the transformation of the cyclized compounds into ketomacrolactones, which are reminiscent of natural products.

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Ring Expansions Within the Gold-Catalyzed Cycloisomerization of *O*-Tethered 1,6-Enynes. Application to the Synthesis of Natural-Product-like Macrocycles

