



Gold-catalyzed cycloisomerization of [3]-cumulenols



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ABSTRACT

The gold-catalyzed cycloisomerization of tetrasubstituted [3]-cumulenols has been investigated. Overall, two main pathways are followed. In the presence of gold(III) catalysts, a dehydration process prevails giving diastereomerically pure dienyne while gold(I) catalysts favor the cycloisomerization to provide trisubstituted furan derivatives.

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Introduction

[n]-Cumulenes are fascinating molecules [1]. Their extreme level of unsaturation bodes well for intriguing reactivities, especially in the presence of metallic species [2]. Nevertheless, the game can be played only when the starting cumulene is readily available and stable enough to be further engaged. Tetrasubstituted [3]-cumulenols meet these criteria and when armed with a side hydroxy function, the corresponding 2,3,4-trien-1-ol systems become interesting substrates to examine for electrophilic gold catalysis [3]. Assuming a preliminary electrophilic activation of the π -system of the cumulene network, intramolecular nucleophilic attack from the pendant hydroxy function is anticipated and should deliver an oxygen unsaturated heterocycle presumably of furan type (eq. (1), Scheme 1) [4]. Gold catalysis has provided several versatile routes to furanic systems, most of them relying on a key C–O bond formation from different type of unsaturated precursors bearing an alcohol or a ketone function [5]. Furan moieties are widespread in natural products with relevant biological properties such as kolloide A [6] and (–)-deoxypukalide [7]. They are also found in numerous drugs, for instance the anti-ulcer drug ranitidine or the

anti-bacterial furazolidone and have proven to be valuable synthons for further elaboration [8].

Closest to our approach is the report by Y. Liu who has recently examined the gold-catalyzed cycloisomerization of [3]-cumulenones, obtained from diyne precursors, to provide furan derivatives (eq. (2), Scheme 1) [2g]. The same report also described the Brønsted catalyzed dehydration of the arylcumulenols to give the corresponding dienyne in good yields (eq. (3), Scheme 1). It should also be mentioned that T. Skrydstrup developed a gold(I)-catalyzed double hydration of diyne substrates delivering 2,5-symmetrically substituted furans [9]. In this context, our objective was to devise an access to trisubstituted furan derivatives directly from [3]-cumulenols. This implied to find the proper gold-based catalytic system which would be compatible with the hydroxy function of the cumulenol system and not trigger a dehydrative process. Indeed, this could be quite challenging since gold(III) salts have for instance been shown to catalyze the nucleophilic substitution of propargylic alcohols [10]. Moreover, we wanted to broaden the scope of the substituents on the final furanic products which implied to engage diversely substituted cumulenols.

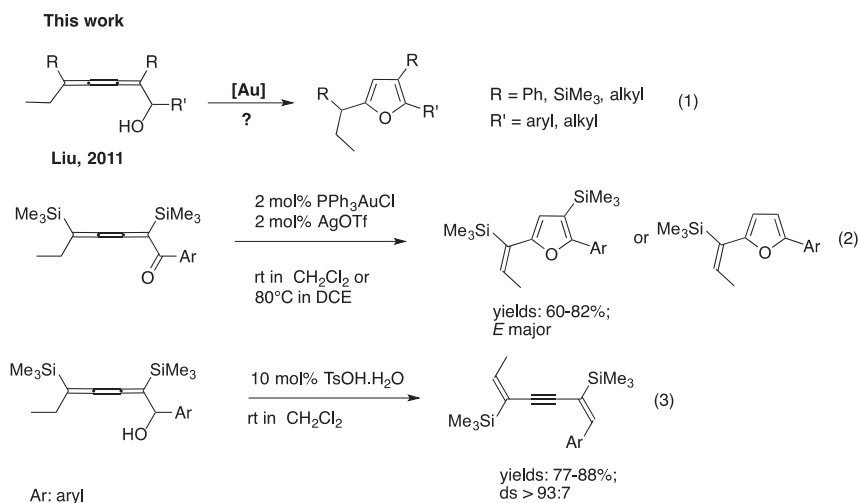
Results and discussion

Synthesis of precursors

For that purpose, we relied on the synthesis of [3]-cumulenols also documented by Y. Liu [11], who developed a zirconium-

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Scheme 1. Context of the [3]-cumulenol gold-catalyzed cycloisomerization.

mediated coupling of 1,3-butadiynes with aldehydes. In this work, we used bis-trimethylsilyl, bis-phenyl and bis-*n*-hexyl diynes as butadiynyl substrates combined with cyclohexylaldehyde and various aryl aldehydes as electrophilic partners. The expected representative [3]-cumulenols were produced satisfactorily as judged from the examination of the ^1H NMR spectra of the crude products (Scheme 2). Nevertheless, we faced some difficulties at the purification stage in some cases. Chromatography of some substrates, even with neutralized silica gel, leads to dehydration products **3** accompanied by decomposition products. We thus devised a one pot sequence consisting of the synthesis of the precursor **1** followed by a rapid filtration over silica gel neutralized by sodium carbonate. The resulting product showed sufficient purity to be engaged in the cycloisomerization step with gold catalysis.

Preliminary catalyst screening

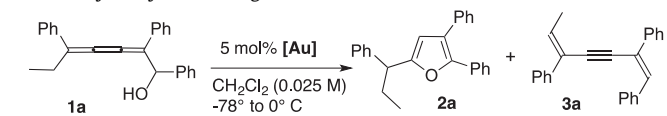
Our preliminary catalyst screening was achieved with substrate **1a** (Table 1) and provided useful trends. Not surprisingly, the more electrophilic and oxophilic gold(III) salts [10,12,13] favored the dehydration product **3a** (entries 2–3). Same result was obtained with the oxophilic AgOTf (entry 1) [14]. In sharp contrast, gold(I) salt AuCl (entry 6) allowed to retrieve the expected carbophilic activation favoring the exclusive formation of **2a**. In the same line, a complete selectivity was also observed with cationic gold(I) complexes (entries 7–9). Interestingly, a better yield was observed with

a triflate counter ion compared to a hexafluoroantimonate (entry 7 vs. 8) which would be consistent with the fact that a triflate anion has already been claimed as an efficient proton shuttle [15]. To pursue our study, we selected AuBr₃ to provide dienyne **3a** and the AuClPPh₃-AgOTf mixture as a privileged catalytic system since it provided the best yield of **2a** in the shortest reaction time.

Dehydration process

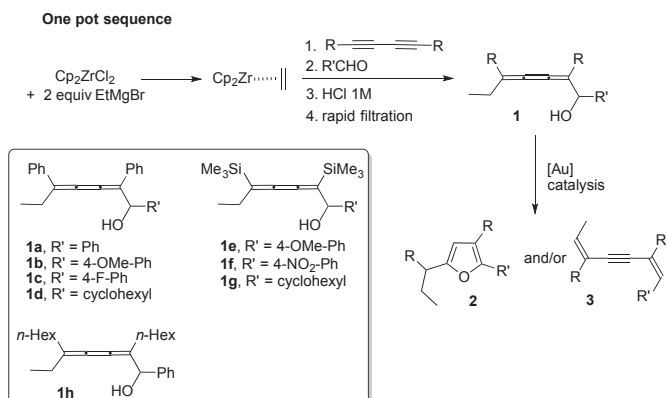
It appeared interesting to examine the possibility to develop a versatile access to dienyne products **3**. For that purpose, we submitted various cumulenols to gold(III) catalysis (Table 2). As expected, bis-aryl cumulenol derivatives provided exclusively the dehydration products **3** in moderate to fair yields. Not surprisingly, para-fluoro substituted precursor (**1c**, entry 3) resulted in a poorer reaction. In contrast, bis-TMS precursors gave inseparable mixtures of products **2** and **3**, featuring a significant influence of the R' substituent (entries 5 vs. 6). Partial desilylation on **2f** or total one on **2g** was observed which can be ascribed to the presence of protic sources originating from the dehydration process. The more-electron donating cyclohexyl resulted indeed in a logical higher yield of dienyne **3g**. All dienyne **3** were isolated as single diastereomers [16]. Their structures were assigned by analogy with the one of **3b** which was secured by X-ray crystallography (Fig. 1) [17].

Table 1
Preliminary catalytic screening.



Entry	Catalyst	Conversion	Yield ^a	2:3 ratio
1	AgOTf	100% after 18 h	51%	0:100
2	AuBr ₃	100% after 18 h	59%	0:100
3	AuCl ₃	100% after 18 h	46%	20:80
4	AuCN	None after 24 h	—	—
5	AuClPPh ₃	None after 24 h	—	—
6	AuCl	100% after 56 h	53%	100:0
7	AuClPPh ₃ +AgOTf	100% after 10 h	59%	100:0
8	AuClPPh ₃ +AgSbF ₆	33% after 18 h	27%	100:0
9	[JohnPhosAu(NCMe)]SbF ₆	100% after 42 h	47%	100:0

^a Overall yield from butadiyne precursor; sequence run on a 1 mmol scale.



Scheme 2. One pot sequence: [3]-cumulenol synthesis - gold-catalyzed step.

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