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Gold- vs. Platinum-Catalyzed Polycyclizations by *O*-Acyl Migration. Solvent-Free Reactions

Xavier Moreau,[a] Jean-Philippe Goddard,[a] Matthieu Bernard,[a] Gilles Lemière,[a] Juan Manuel López-Romero,[a] Emily Mainetti,[a] Nicolas Marion,[a] Virginie Mouriès,[a] Serge Thorimbert,[a] Louis Fensterbank,[a,]* and Max Malacria[a,]*

[a] Université Pierre et Marie Curie-Paris 6, Laboratoire de Chimie Organique (UMR CNRS 7611), Institut de Chimie Moléculaire (FR 2769), case 229, 4 place Jussieu, 75252 Paris cedex 05, France
Fax: (+33)-(0)1-4427-7360; e-mail: louis.fensterbank@upmc.fr or max.malacria@upmc.fr

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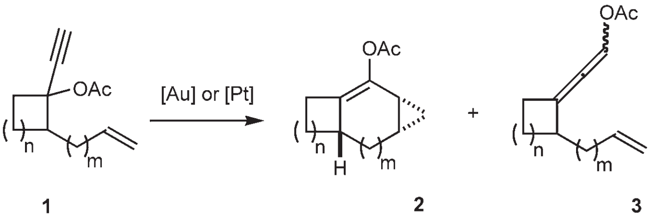
Abstract: Polycyclic derivatives incorporating a cyclopropyl group have been efficiently synthesized from propargyl acetates using platinum(II), gold(I) and gold(III) catalysis. These reactions which are also viable for the preparation of medium-sized rings, proceed with a complete diastereocontrol and can also be run in neat conditions.

Keywords: cyclopropanes; enynes; gold; platinum; solvent-free reactions

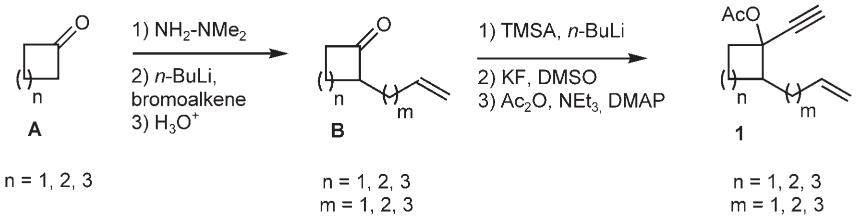


Scheme 1. General reaction.

For two decades now, enyne cycloisomerization reactions have witnessed intense developments.[1] An interesting variant has emerged with the use of highly electrophilic metal species,[2] such as $PtCl_2$ as well as gold(I) or (III) salts,[3] which have allowed various transformations. Importantly, charged intermediates are generally involved in these processes so that heteroatomic functions can be involved. For instance, we[4] and others[5] have shown that different acyl groups at the propargylic position of an enyne can migrate in a 1,2-fashion with concomitant intramolecular cyclopropanation onto the ene part of the substrate. This transformation has lent itself to versatile applications such as natural product synthesis[6] as well as the formation of medium-sized rings.[4a] In this perspective, we report the general cycloisomerization reaction of monocyclic propargylic enyne acetates **1** leading to the formation of tricyclic compounds **2** with various ring combinations (Scheme 1), according to the n and m parameters. The comparison between Pt(II), Au(I) and Au(III) catalysis is also underlined.

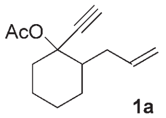
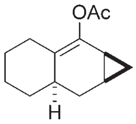
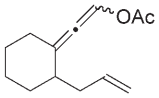
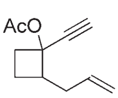
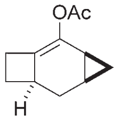
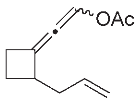
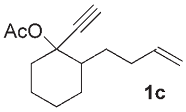
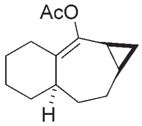
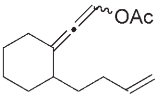
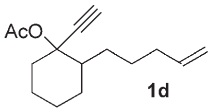
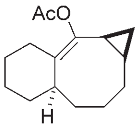
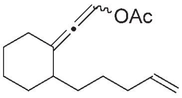
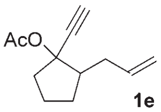
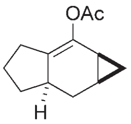
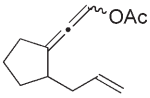
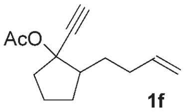
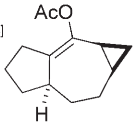
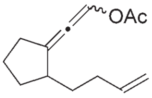
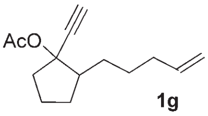
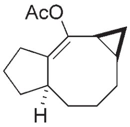
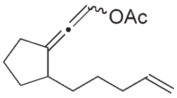
Precursors **1** were readily prepared from the corresponding cyclic ketones **A** in a five-step sequence. Alkylation of ketones **A** was achieved through hydrazone enolates by using successively *N*,*N*-dimethylhydrazine, *n*-BuLi, an alkyl bromide and final hydrolysis.[7] The corresponding ketones **B** were alkylated by the TMS-protected lithium acetylide and subsequent desilylation and acylation provided enyne **1** in good overall yields (21 to 52%) as a mixture of diastereoisomers (Scheme 2).[8]

We initially focused on allylic (m = 1) precursors **1** that should give birth to a central 6-membered ring on polycycles **2**. Gratifyingly, we could validate our design with cyclohexyl substrate **1a** which afforded tricyclic compound **2a** in 88% yield under platinum catalysis (Table 1, entry 1). No other product such as an Alder-ene or metathesis-like substance was observed in this reaction. Cyclobutyl precursor **1b** proved to be also very reactive and afforded highly strained product **2b** in high yield with $PtCl_2$ while Au(III) and Au(I) gave lower yields (63% and 61%, respectively, entry 2). Minor amounts (<10%) of α,β-unsaturated aldehyde possibly originating from adventitious hydrolysis of allenyl esters **3b** were also observed.[9] Contrary to our initial fear, switching to a central 7-membered ring did not cause any difficulty since a quantitative yield of **2c** was obtained with $PtCl_2$. Gold catalysis was not as efficient, and allenyl ester **3c** was formed in around 30% yield (entry 3). Extension to the cyclooctene series provided valuable information. When the reaction of **1d** wasrun with



Scheme 2. Synthesis of precursors.

Table 1. Cycloisomerizations catalyzed by Pt(II), Au(I) and Au(III).

Entry	Enyne **1**		Catalyst[a]	Products **2** and **3** and Yield			
1		**1a**	$PtCl_2$	**2a**, 88%		**3a**, 0%	
2		**1b**	$PtCl_2$ $AuCl_3$ Au(I)	**2b**, 89% 63% 61%		**3b**, 0% 28% 31%	
3		**1c**	$PtCl_2$ $AuCl_3$ Au(I)	**2c**, 98% 55% 61%		**3c**, 0% 32% 32%	
4		**1d**	$PtCl_2$[b] $AuCl_3$ Au(I)	**2d**, 50% 16% 11%		**3d**, 32% 68% 51%	
5		**1e**	$PtCl_2$ $AuCl_3$ Au(I)	**2e**, 98% 96% 58%		**3e**, 0% 0% 11%	
6		**1f**	$PtCl_2$ $AuCl_3$	**2f**, 82%[c] 94%		**3f**, 0% 0%	
7		**1g**	$PtCl_2$[b] $AuCl_3$ Au(I)	**2g**, 66% 92% 53%		**3g**, 24% 0% 25%	

[a] Au(I) refers to PPh_3AuSbF_6 generated *in situ* from an equimolar mixture of $AgSbF_6$ and $AuClPPh_3$. Reactions were run at 80 °C in toluene with $PtCl_2$ (5 mol%) for 2 h and at room temperature in CH_2Cl_2 with gold catalysts (2 mol%) for 5–10 min.

[b] Reactions with $PtCl_2$ were run at room temperature for 24–48 h.

[c] A minor diastereomer (<5%) was observed.

$PtCl_2$ at 80 °C, a complex mixture was obtained among which products **2d** and **3d** could be observed. Running the reactions at room temperature optimized the yields of **2d**. A similar trend was observed with 5-membered ring precursor **1g**. Interestingly, gold catalysis gave mixed results and a net supremacy of plati-

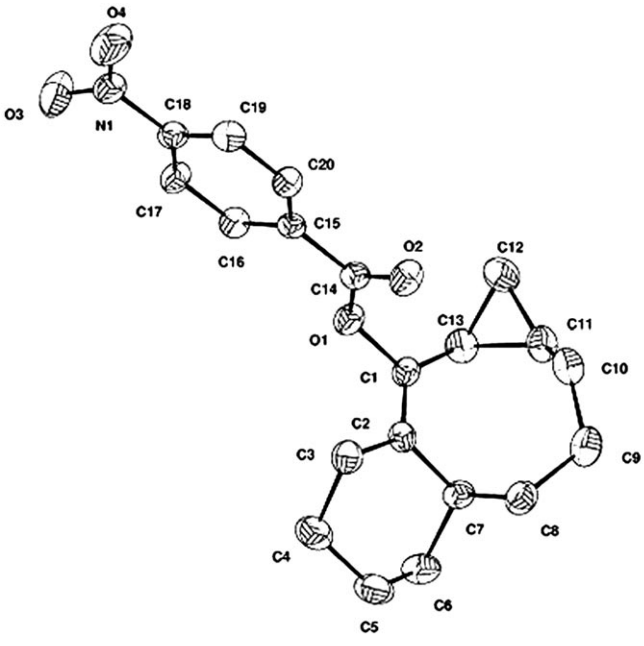
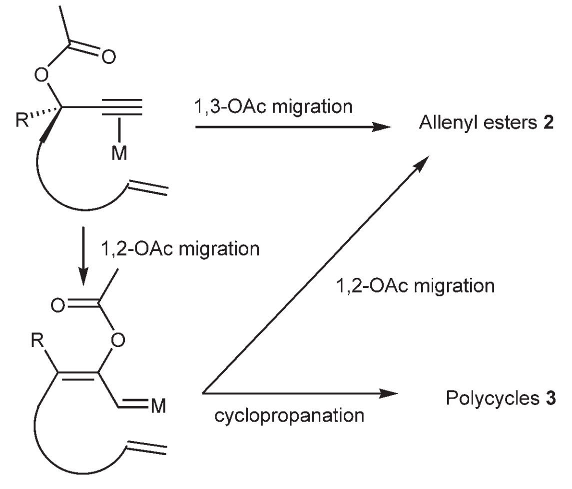


Figure 1. X-ray view of **2dPNB**.

num *vs.* gold was observed in the case of the 6-membered ring template **1d**. In contrast, a very high yield of **2g** could be reached with Au(III) (entry 7). Good yields and highly diastereoselective reactions were also obtained with other 5-membered ring precursors **1e** and **1f** (entries 5 and 6).

It is worthy of note that all tricyclic compounds **2** have been isolated as single diastereoisomers whose relative stereochemistry was deduced from NOE measurements.[10] Further confirmation was obtained with a X-ray structure determination[11] of the paranitrobenzoate derivative (**2dPNB**) of **2d** (Figure 1) obtained in 62% yield upon $PtCl_2$ catalysis at room temperature, accompanied by 14% of the corresponding allene. In contrast, two diastereoisomers of allenyl esters **3** have been generally isolated in a ratio close to 1:1. A mechanism rationale for these transformations is under scrutinity, notably their diastereoselection. According to the proposed mechanism for the intermolecular version of the reaction,[5j,12] a [2+1] cyclopropanation would take place after [1,2] acetate migration leading to the formation of polycyclic derivatives **2** (Scheme 3). A second [1,2] migration would give the allenyl esters **3**. The latter could alternatively originate from a direct [1,3] migration.

In this report, we focus on synthetic purposes and in order to have a better insight into this reactivity, we examined other precursors **1h–k** of Table 2 using $PtCl_2$ which has proven to be the most versatile catalyst in most of these reactions. Introducing a *gem*-dimethyl group on **1h**, compared to precursor **1c**, resulted in a less effective formation of the tricyclic derivative and some allenyl ester **3h** was also isolated.



Scheme 3. Mechanism proposal for the formation of cyclopropanes **2** and allenyl esters **3**.

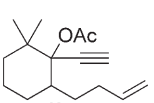
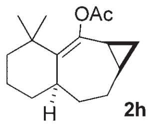
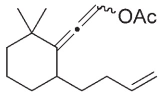
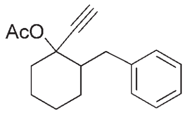
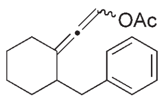
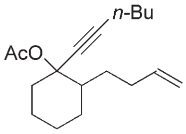
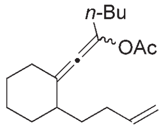
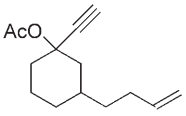
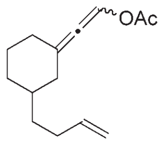
In the case of precursor **1i**, no hydroarylation product was observed,[13] instead allenyl ester **3i** was formed in 68% yield. As previously observed,[4b] the introduction of an alkyl group on the alkyne favors the formation of the allenyl ester **3j**. We also examined the possibility to construct the bicyclo[3.5.1]decane skeleton present in taxoid natural products. Unfortunately, only traces of **2k** were formed upon $PtCl_2$ as well as gold catalysis. Here also, the major product was allenyl ester **3k**.

We were then attracted by the possibility to run these reactions in solvent-free conditions.[14] In addition to the environmental benefits from such an approach,[15] we anticipated that the concentration of the reaction media could significantly influence the ratio of tricyclic products **2** *vs.* allenyl esters **3** notably obtained in the case of gold-catalyzed reactions. Interestingly also, only a few reports describe gold-catalyzed reactions in neat conditions[16] and generally do not compare diluted with solvent free reactions.

We were pleased to find that $PtCl_2$ in neat conditions allowed in most cases the clean conversion of the starting propargylic acetate into the tricyclic product **2** as the sole isolated product. Yields, which are usually high, are often in the same order as the ones obtained in toluene (compare Table 1 and Table 3). Nevertheless, it has to be noted that dimeric and other oligomeric products[17] were formed in the reactions of **1e** and **1f**. Longer reaction times were needed when the reaction was performed at room temperature (20 h *vs.* 2 h).

Having established the possibility of running neat reactions with $PtCl_2$, we turned our attention to gold which gave us mixture of products in solution. Reactions of propargylic acetates with $AuCl_3$ at room temperature were generally very slow and poor conversions were observed. For instance, after 1 h the 5,6,3-

Table 2. Scope and limitations of the cycloisomerization process.

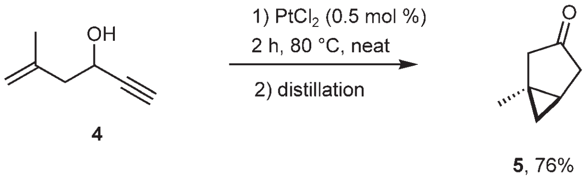
Entry	Enyne **1**	Catalyst[a]	Products **2** and **3** and Yield	
1	 **1h**	$PtCl_2$	 **2h**, 71%	 **3h**, 15%
2	 **1i**	$PtCl_2$		 **3i**, 68%
3	 **1j**	$PtCl_2$		 **3j**, 75%
4	 **1k**	$PtCl_2$		 **3k**, 54%

[a] Reactions were run at 80 °C in toluene.

tricyclic compound **2e** was isolated in 38 % yield as well as 46 % of the starting material (Table 3, entry 2). Increasing the reaction time or the temperature was not productive nor was the addition of more catalyst. Starting from the homoallylic cyclopentane **1f** (Table 3, entry 3), we isolated the 5,7,3-tricyclic enol ester **2f** in 15 % yield after 2 h at room temperature. Dimeric and trimeric[17] products were also observed in this reaction. Using $NaAuCl_4$ as catalyst allowed to isolate **2f** in 53 % yield as well as 9 % of **1f**.

Precursor **1c** gave an interesting example of completely altered reactivity between platinum and gold catalysis (Table 3, entry 5), the former giving **2c** in high yield and the latter with Echavarren gold(I) catalyst[18] only allenyl ester **3c**.

In conclusion, this study shows that the platinum(II)- or the gold(I)- and gold (III)-catalyzed cycloisomerization of propargyl acetates is a versatile process for the expedient and stereoselective preparation of various polycyclic products. Despite their lack of generality, preliminary results in solvent-free conditions are encouraging and strongly suggest that these conditions should always be considered when running this type of reactions. A confirmation of this is given by the efficient and clean transformation of enynol **4** into bicyclic ketone **5** isolated in 76 % yield after distillation (see Scheme 4). This reaction could be run on a 4.5 mmol scale and we could use a particularly low loading of catalyst: only 0.5 mol % was introduced!



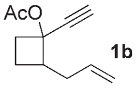
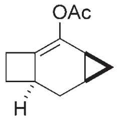
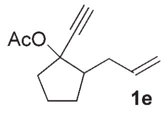
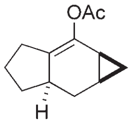
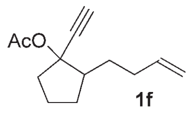
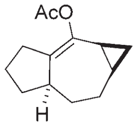
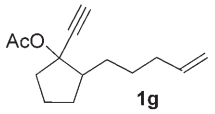
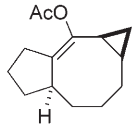
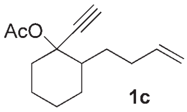
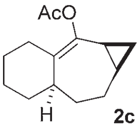
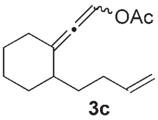
Scheme 4. 1,5-Enynol cycloisomerization in neat conditions.

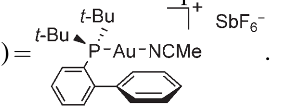
Experimental Section

Typical Procedure for Metal-Catalyzed Reactions

$PtCl_2$ (5.3 mg, 5 mol %), $AuCl_3$ (2.4 mg, 2 mol %) or $AuClPPh_3$ (4 mg, 2 mol %) and $AgSbF_6$ (2.7 mg, 2 mol %) were introduced in a round-bottom flask under an argon atmosphere. Anhydrous toluene or CH_2Cl_2 (16 mL, 0.025 M) was then added. Enyne **1e** (77 mg, 0.4 mmol) was introduced and the reaction mixture was stirred at the appropriate temperature (for 2–3 h at 80 °C with $PtCl_2$, 5–10 min at room temperature with gold catalysts) and was monitored by TLC. After completion, the solution was filtered through a pad of silica and the pad was washed with diethyl ether. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel

Table 3. Cycloisomerizations catalyzed by $PtCl_2$, $AuCl_3$ and Au(I) in neat conditions.

Entry	Enyne	Catalyst (*T* [°C])	Products and Yield
1	 **1b**	$PtCl_2$, 80	 **2b**,74%
2	 **1e**	$PtCl_2$, 80 $AuCl_3$, r.t.	 **2e**, 95% 38% (+ 46% **1e**)
3	 **1f**	$PtCl_2$, 80 $AuCl_3$, r.t. $NaAuCl_4$, r.t.	 **2f**, 45%[a] 15%[b] (+ 29% **1f**) 53% (+ 9% **1f**)
4	 **1g**	$PtCl_2$, 80 $AuCl_3$, r.t.	 **2g**, 63%[b] 46%[b]
5	 **1c**	$PtCl_2$, 80 $AuCl_3$, r.t. Au(I)[c], r.t.	 **2c** 94% 10% 0%  **3c** 0% 86% 89%

[a] Reactions were run at 80 °C in toluene.[a] Oligomeric structures were observed.
[b] Dimeric and trimeric products were isolated.[17]
[c] Au(I) =  .

(petroleum ether/Et_2O, 98/2) to give **2e** as a single diastereoisomer. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.68$ (m, 1H), 2.35 (m, 1H), 2.10 (s, 3H), 2.08 (m, 2H), 1.83 (m, 1H), 1.64 (m, 1H), 1.46 (m, 1H), 1.24 (m, 2H), 0.92–0.78 (m, 3H,), 0.37 (q, $J = 4.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.1$, 141.1, 133.3, 42.6, 34.1, 33.8, 26.8, 25.1, 21.1, 20.9, 13.0, 12.8; IR (neat): $\nu = 2998$, 2930, 1752, 1710, 1451 cm^{-1}; anal. calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.98, H 8.45.

Typical Procedure for Solvent-Free Reaction

To a catalytic amount of $PtCl_2$ (5.3 mg, 5 mol%) or $AuCl_3$ (2.4 mg, 2 mol%) was added enyne **1e** (77 mg, 0.4 mmol) under an argon atmosphere. The reaction mixture was stirred at the appropriate temperature (for 30 min at 80 °C with $PtCl_2$, 5–10 min at room temperature with $AuCl_3$) and monitored by TLC. After completion, the crude mixture was directly purified by flash chromatography on silica gel (petroleum ether/Et_2O, 98/2) to give **2e** as a single diastereoisomer.

Procedure for $PtCl_2$-Catalyzed Enynol Cycloisomerization

To a catalytic amount of $PtCl_2$ (6 mg, 0.5 mol%) was added 5-methyl-hex-5-en-1-yn-3-ol **4** (500 mg, 4.54 mmol). The reaction mixture was stirred 2 h at 80 °C and distilled with a Kugelrohr apparatus (75 °C, 30 mm Hg) to provide **5**;[12a] yield: 380 mg (76%).

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