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# Contrasted effect of CO on the metal-catalyzed cycloisomerization of O-tethered enynes derived from monoterpenes

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The CO-bubbling effect in cycloisomerization reactions of enynes derived from monoterpenes has been studied using  $PtCl_2$ ,  $[Rh_2Cl_2(CO)_4]$  and  $AuCl_3$  as catalytic systems. All the precursors are efficient catalysts for the cycloisomerization of O-tethered enynes. The reaction proceeds through *exo-dig* and *endo-dig* pathways, which are consistent with the exclusive coordination of the alkyne triple bond to the metal center. The CO ligand not only increases the reaction rates but also induces significant variations in the two reaction pathways. Notably, this effect is also strongly dependent on the nature of the starting enyne. Copyright © 2011 John Wiley & Sons, Ltd.

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#### Introduction

Functionalized cyclic compounds are very important because they are often part of the basic skeleton of biological active products and transition metal-catalyzed cycloisomerization of enynes represents an important synthetic tool depending on both the nature of the starting material and the metal catalyst.<sup>[1]</sup>

We gained experience in modifying natural terpenes through palladium-catalyzed carbonylation reactions, including cyclocarbonylations.<sup>[2]</sup> In the course of proceeding further in this work, structural modifications on these pure monoterpenes were then carried out. Starting from monoterpenes bearing an alcohol function, a terminal alkyne moiety was introduced, leading to the corresponding O-tethered enynes. We reported the cycloisomerization of cyclic and acyclic 1,6- or 1,7-enynes into polycyclic derivatives containing an inner cyclopropane ring, or 1,3- or 1,4diene moieties, depending on the studied enyne structure.[3-5] More particularly, we examined the reactivity of the enynes 1, 2 and 3 derived from perillyl alcohol, isopulegol and nerol, respectively, in the presence of rhodium, platinum and gold catalysts. In this communication, we report the first observations we have made on contrasted selectivities observed when the reaction is performed under a CO atmosphere, in addition to kinetic effects as recently observed.<sup>[6-8]</sup> Indeed, Fürstner et al.<sup>[7]</sup> reported the cycloisomerization of enynes catalyzed by PtCl<sub>2</sub>, with an acceleration of the reaction rate, but not on the selectivity of the products, due to the presence of CO. A similar rate increase was reported by Chatani et al. and Shibata et al.<sup>[6,8]</sup> for the cycloisomerization of 1,6-envnes and nitrogen-tethered 1,6-envnes catalyzed by iridium or ruthenium complexes under CO.

#### Experimental

Enynes, prepared according to the previously reported procedure,<sup>[3]</sup> and  $PtCl_2$ ,  $AuCl_3$  or  $[Rh_2Cl_2(CO)_4]$  (0.025 molar equivalent)

in toluene (0.1 Msolution) were stirred at 80 °C, under CO bubbling. Progress of the reaction was followed by gas chromatography (GC). After each experiment, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (eluent: pentane–ethyl acetate, 200:1). Selectivity was calculated from the ratio of the corresponding peak surfaces in GC.

GC apparatus was a PerkinElmer GC Clarus FID, equipped with a Stabilawax-DA capillary column (30 m, 0.25 mm i.d., 0.25  $\mu$ m, Restek), with helium as carrier gas, oven temperature 80 °C, hold 2 min to 200 °C at 20 °C/min, hold 7 min.

### **Results and Discussion**

As previously identified in our studies,<sup>[3–5]</sup> the cycloisomerization of O-tethered enynes **1–3** provides the cyclopropanes **1a**, **2a** and **3a**, the 1,3-dienes **1b**, **2b** and **3 d**, whereas the 1,4-dienes **3b** and **3c** are only obtained starting from nerol, as shown in Fig. 1. Here, we recall the structures of these cyclic products and compare the reaction rates and selectivities obtained with PtCl<sub>2</sub>,  $[Rh_2(\mu-Cl)_2$ (CO)<sub>4</sub>], and AuCl<sub>3</sub> when an atmosphere of CO is maintained in the reaction medium.

In order to accelerate these reactions, requiring usually 2 h for total conversion, we introduced one atmosphere of CO, as previously reported by other research groups.<sup>[6–8]</sup> In addition to the kinetic effects, we were interested to observe a CO effect which

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Figure 1. Cycloisomerization of O-tethered enynes derived from monoterpenes 1–3: (a) enyne derived from perillyl alcohol 1; (b) enyne derived from isopulegol 2; (c) enyne derived from nerol 3.

could be significant for the selectivity of the three cycloisomerization reactions.

All the reactions were performed in toluene at 80 °C, starting from PtCl<sub>2</sub>, [Rh<sub>2</sub>( $\mu$ -Cl)<sub>2</sub>(CO)<sub>4</sub>], and AuCl<sub>3</sub>. Tables 1–3 show the results obtained at various reaction times in the presence or absence of CO. Small amounts (close to the detection limits) of other products were detected by chromatography, but these can be disregarded by comparison with the product yields shown in the tables.

We did not observe any CO incorporation into the products. Shibata *et al.* made the same observation with no carbonylative

product detected during their study of a cationic iridiumcatalyzed cycloisomerization of 1,6-enynes bridged by nitrogen under a CO atmosphere.<sup>[8b]</sup> Incorporation of CO would result from the oxidative coupling of the alkyne and alkene moieties, followed by the migratory CO insertion. Such a reaction can occur with platinum and rhodium catalysts but not with gold ones.<sup>[9]</sup> Thus, in the present study, only the triple bond coordinates the Pt, Rh or Au metal center and follows the carbenoid mechanism we previously proposed.<sup>[4,5]</sup>

<b>Table 1.</b> Cycloisomerization results obtained with the enyne derived from perillyl alcohol							
Entry	Catalyst	Reaction time (min)	P <sub>CO</sub>	Conv. (%)	Selectivity in <b>1a</b> (%)	Selectivity in <b>1b</b> (%)	
1 F	PtCl <sub>2</sub>	5	_	98	57	34	
2		5	1 atm	80	54	32	
3		30	1 atm	98	47	36	
4 [	$[Rh_2Cl_2(CO)_4]$	5	—	12	54	46	
5		120	—	43	68	32	
6		5	1 atm	12	81	—	
7		120	1 atm	94	81	8	
8 A	AuCl <sub>3</sub>	5	—	5	100	—	
9		120	—	10	100	—	
10		5	1 atm	12	100	—	
11		120	1 atm	37	100	—	

<b>Table 2.</b> Cycloisomerization results obtained with the enyne derived from isopulegol								
Entry	v Catalyst	Reaction time (min)	P <sub>CO</sub>	Conv. (%)	Selectivity in <b>2a</b> (%)	Selectivity in <b>2b</b> (%)		
12	PtCl <sub>2</sub>	5	_	6	n.d.	n.d.		
13		120	_	88	18	72		
14		5	1 atm	19	9	81		
15		120	1 atm	97	4	84		
16	$[Rh_2Cl_2(CO)_4]$	5	_	5	n.d.	n.d.		
17		120	_	15	13	37		
18		5	1 atm	3	n.d.	n.d.		
19		120	1 atm	60	15	68		
20	AuCl <sub>3</sub>	5	—	2	n.d.	n.d.		
21		120	_	6	n.d.	n.d.		
22		5	1 atm	12	15	50		
23		120	1 atm	18	18	61		
n.d., not determined, due to the low conversion rate.								

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		Reaction time (min)	P <sub>CO</sub>	Conv. (%)	Selectivity in <b>3a</b> (%)	Selectivity in <b>3b</b> (%)	Selectivity in <b>3c</b> (%)	Selectivity in <b>3 d</b> (%)
24 Pt	PtCl <sub>2</sub>	5	_	6	n.d.	n.d.	n.d.	n.d.
25		120	_	99	13	57	3	14
26		5	1 atm	21	7	6	—	59
27		120	1 atm	99	6	2	0	70
28 [R	Rh <sub>2</sub> Cl <sub>2</sub> (CO) <sub>4</sub> ]	5	_	32	26	60	6	3
29		120	_	77	23	48	14	16
30		5	1 atm	32	13	59	14	3
31		120	1 atm	99	16	68	4	3
32 A	AuCl₃	5	_	5	n.d.	n.d.	n.d.	n.d.
33		120	_	13	14	9	14	16
34		5	1 atm	16	26	10	23	10
35		120	1 atm	73	39	13	16	9

#### Cycloisomerization of Enyne Derived from Perillyl Alcohol

The most significant results obtained are listed in Table 1. In all cases, the main product is the cyclopropane derivative **1a**.  $AuCl_3$  exclusively provides **1a** whether or not CO is present. The reaction remains relatively slow, although an acceleration effect is observed when one CO atmosphere is maintained; for instance, after a reaction time of 5 min the yield increases from 5% to 12% (entries 8 and 10) and after 2 h from 10% to 37% (entries 10 and 11). The present reaction follows the *endo-dig* pathway shown in Scheme 1, with stabilization of the zwitterionic intermediate **1a**'. The electrophilic character of the metal is enhanced by the presence of CO to coordinate the alkyne moiety.

The effect of CO is more dramatic in the case of  $[Rh_2Cl_2(CO)_4]$ rhodium catalyst since the conversion is around twice as fast with CO and strongly favors compound **1a** (entries 5 and 7). This uncommon cyclopropane product in the rhodium-mediated cycloisomerization of an enyne provides, after 2 h, a 94% conversion, 81% of **1a** and only 7% of the 1,3-diene **1b** (entry 7). Formation of this latter product can result from either the oxidative coupling or the 5 *exo-dig* mechanism generating the carbenoid intermediate **1b**' (Scheme 2). In the absence of any detected carbonylated product, we favor the carbenoid mechanism.

Concerning PtCl<sub>2</sub>, we did not observe an acceleration of the reaction rate like that described by Fürstner.<sup>[7]</sup> On the contrary, there was a slight decrease of the rate (entries 1 and 2).The selectivities are similar. The production of **1a** and **1b** can obey both *endo-* and *exo-dig* mechanisms described in Schemes 1 and 2, with cyclopropane being the main product obtained.

#### Cycloisomerization of Enyne Derived from Isopulegol

The same *endo-* and *exo-dig* mechanisms described above occur to produce compounds **2a** and **2b**. The main results are displayed in Table 2. With the three catalysts, the 1,3-diene **2b** is favored, such selectivity presumably being due to the occurrence of the bicyclo six-membered instead of the tricyclic compound **2a** containing a seven-membered structure. Moreover, the alkyne and the alkene functions of the enyne are in an *anti* configuration. Thus the *exo-dig* pathway is favored essentially for this steric reason. An almost total conversion can be reached with PtCl<sub>2</sub> (entry 15), while the rhodium and gold catalysts afford lower conversions (entries 19 and 23). In each case, the presence of CO increases the reaction rate and the formation of **2b**.

#### **Cycloisomerization of Enyne Derived from Nerol**

In the case of nerol, the CO effect on the kinetics and selectivity of the reaction is more pronounced. The most significant results are shown in Table 3. As we previously observed,<sup>[5]</sup> the reaction allows four products to be formed: one cyclopropane **3a**, two 1,4-dienes **3b,c**, and one 1,3-diene **3 d**.

Selectivity is dramatically modified in the presence of  $PtCl_2$  under one atmosphere of CO (entries 26 and 27). Indeed, for 99% conversion, the major product is **3b**, with 57% selectivity (entry 25), whereas the same reaction under one atmosphere of CO leads to the major formation of **3 d** with 70% selectivity, the selectivity in **3b** being reduced to 2% (entry 27). The selectivity in **3a** is reduced from 13% to 6%, and that of **3c** from 3% to 0%. Thus coordination



Scheme 1. Cycloisomerization of enyne 1 involving the endo-dig pathway, according to Bruneau.<sup>[10]</sup>



Scheme 2. Cycloisomerization of enyne 1 involving the *exo-dig* pathway, according to Bruneau.<sup>[10]</sup>

of CO to platinum significantly favors the *endo-dig* pathway corresponding to the nucleophilic attack of the C=C double bond on the terminal carbon atom of the alkyne, leading to the carbenoid intermediate  $\mathbf{3}''$  (Scheme 3). The full mechanism for the formation of  $\mathbf{3} \mathbf{d}$  (and also of  $\mathbf{3c}$ ) is detailed in Chatani *et al.*<sup>[6]</sup>

This selectivity is oriented toward the product **3a** in the case of AuCl<sub>3</sub>, which arises from the same intermediate  $\mathbf{3}''$  shown in Scheme 3. As observed for the two enynes derived from isopule-gol and perillyl alcohol, the conversion remains incomplete after 2 h of reaction even if a significant acceleration effect results from

the presence of CO. Notably, the second intermediate resulting from the *exo-dig* pathway is still formed, leading to significant quantities of the two isomers **3b** and **3c** (entry 35).

When using  $[Rh_2Cl_2(CO)_4]$ , product **3b** is the major isomer obtained, with 68% selectivity (entry 33). As mentioned before, **3b** derives from intermediate **3'** (Scheme 3). Presumably, in the presence of CO, the  $[RhCl(CO)_2]$  entity, by cleavage of the chlorobridges, is preserved; coordination of the alkyne function occurs to produce a square planar species, which is attacked by the close double bond.



# Conclusion

The three Rh(I), Pt(II) and Au(III) d<sup>8</sup> precursors, whose the electrophilic character increases from Rh to Au and is still enhanced under one atmosphere of CO, are efficient catalysts for the cycloi-somerization of O-tethered enynes. In the present case, the reaction proceeds by *exo-dig* and *endo-dig* pathways, consistent with the exclusive coordination of the alkyne triple bond to the metal center. As the CO ligand possesses a  $\pi$ -acceptor character it provides significant flexibility for the coordination of the alkyne and increases the electrophilicity of the triple bond. The CO ligand not only increases the reaction pathways. This effect appears strongly dependent on the nature of the starting enyne. It is particularly the case of the enyne derived from nerol, whereas for the two other enynes derived from perillyl alcohol or isopulegol the CO effect is only pronounced in the reaction rate.

In order to have more information concerning the mechanism and the species involved, we expect to perform infrared studies on the catalytic conditions of the reaction. The aim concerns also the possibility to anticipate somewhat the reactivity of similar enynes and eventually the effects of substituents in order to modulate the selectivity according to the coordination sphere of the metal complex.

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