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Rh- and Pt-catalyzed cycloisomerization of enynes derived from terpenes

Philippe Costes, Jochen Weckesser, Odile Dechy-Cabaret*, Martine Urrutigoïty, and Philippe Kalck

The Rh-catalyzed cycloisomerization of new terpenoid derivatives featuring an O-tethered enyne unexpectedly leads to polycyclic derivatives containing an inner cyclopropane ring or a diene moiety, depending on the structure of the enyne, as observed in the $PtCl_2$-catalyzed processes.

Keywords: terpenes; enyne cycloisomerization; rhodium; platinum; homogeneous catalysis

Introduction

Terpenes and terpenoids represent a large class of natural compounds with noticeable organoleptic properties.[1] Chemical modification through selective metal-mediated reactions opens the way to create novel compounds potentially bearing unprecedented biological activities. We gained experience in modifying natural terpenes through palladium-mediated cyclocarbonylation to selectively prepare lactones and ketones.[2] To proceed further in this work we envisioned adding a reactive moiety on the initial terpenoid to enlarge the variety of structures accessible through a metal-catalyzed reaction. Monoterpenic allylamines were thus prepared to give direct access to lactams through cyclocarbonylation.[3] As the very rich chemistry of enynes has made possible the preparation of a variety of carbocycles depending on both the nature of the enyne and the metal catalyst,[4] we then turned our attention to the addition of an alkyne moiety on an unsaturated terpenoid and investigated the functionalization of the resulting enynes. O-tethered enynes were easily prepared from monoterpenic alcohols through an O-alkylation[5] and here we report our preliminary results on the study of their reactivity in Rh-catalyzed cycloisomerization.

Results and Discussion

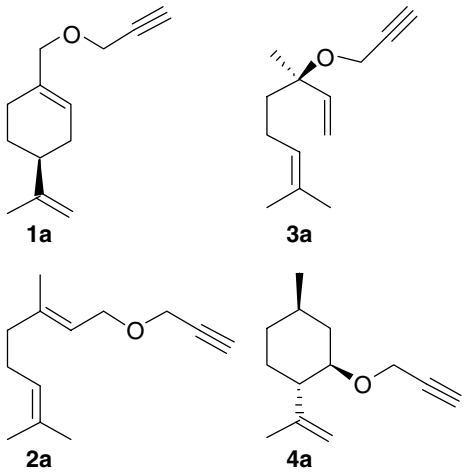
Enynes derived from terpenoids have already been prepared in two steps from saturated terpenoids bearing a carbonyl functionality:[6] in that work both the alkyne and the alkene moieties were introduced to the natural terpenoid. In order to achieve the preparation of the enynes in only one step, we chose natural terpenoids bearing an alkene moiety in their structure. An alcohol functionality was also required in the structure for the anchoring of the alkyne moiety through an O-alkylation with a bromo-alkyne. O-tethered enynes were thus prepared[5] in one step starting from (−)-perillyl alcohol **1**, geraniol **2**, (−)-linalool **3** and (−)-isopulegol **4**. Treatment of the natural terpenoid bearing an alcohol function by NaH in THF gave the corresponding alcoolate. Addition of propargyl bromide in THF led to the corresponding enynes **1a**–**4a** with a terminal alkyne in 84, 84, 26 and 75% yields, respectively (Scheme 1). All the enynes were isolated in good yields except for **3a** prepared from the tertiary alcohol linalool. Enynes **1a**–**3a** are 1,6-enynes while isopulegol leads to the 1,7-enyne **4a**. However, as a second double bond is already present in the natural terpenoids **1**–**3**, there is also the possibility for the enynes **1a** and **2a** to react as 1,10-enynes and for **3a** to react as a 1,8-enyne.

Firstly, we explored the cyclocarbonylation of **1a** into a tricyclic cyclopentenone through the so-called Pauson–Khand reaction.[7a] However we observed no conversion of the starting enyne in the dicobaltoctacarbonyl mediated cyclization, even in stoichiometric conditions[7b] [1 molar equiv. of $Co_2(CO)_8$, 10 molar equiv. of TMANO]. As rhodium-based catalysts have been reported to promote Pauson–Khand type cyclization of O-tethered enynes,[8] we introduced $[RhCl(CO)_2]_2$ in catalytic amounts in a toluene solution of enyne **1a** and the reaction mixture was stirred at 80 °C under one atm of CO. Total conversion was obtained in 2 h and the chromatogram showed two products, the major product being formed in two diastereoisomeric forms (entry 1, Table 1) and the minor one in a single form. Surprisingly, the MS of the major product showed a molecular peak at *m/z* 190, which is consistent with the absence of carbonyl group, while 2D-NMR experiments clearly indicated the presence of an inner cyclopropane ring and established the tricyclic structure **1b** (Scheme 2). The MS of the minor product also showed a molecular peak at *m/z* 190 and NMR analyses allowed us to propose the dienic structure **1c**. An 87% selectivity in cyclopropane **1b** vs diene **1c** was obtained, calculated from the ratio of the corresponding peak surfaces in the GC analysis. The configuration of each diastereoisomer of **1b** could not be elucidated since all attempts of chromatographic separation of the diastereoisomeric mixture failed. Notably, even under high CO pressure (up to 90 bar), no carbonylated products were obtained.

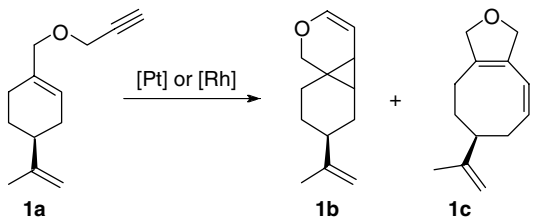
Although this type of cyclization of allyl propargyl ethers into 3-oxabicyclo[4.1.0]hept-4-ene has never been reported for Rh-based catalysts, this is a well-known transformation of heteroatom-

* *Correspondence to: Odile Dechy-Cabaret, Laboratoire de Chimie de Coordination du CNRS, UPR 8241, composante ENSIACET-INP, 118 route de Narbonne, 31077 Toulouse Cedex 4, France. E-mail: Odile.DechyCabaret@ensiacet.fr*

Laboratoire de Chimie de Coordination du CNRS, UPR 8241, composante ENSIACET-INP, 118 route de Narbonne, 31077 Toulouse Cedex 4, France



Scheme 1. Structure of the O-tethered enynes **1a**–**4a** derived from (−)-perillyl alcohol **1**, geraniol **2**, (−)-linalool **3**, and (−)-isopulegol **4**.



Scheme 2. Cycloisomerization of enyne **1a** derived from perillyl alcohol.

tethered 1,6-enynes mediated by platinum precursors.[9] The tricyclic product **1b** was similarly obtained by carrying out cycloisomerization of enyne **1a** in presence of $PtCl_2$. In a similar way as for the Rh-mediated process a toluene solution of **1a** was treated with 2.5% molar $PtCl_2$ at 80 °C for 2 h: total conversion was obtained and the chromatogram showed two products, the same as in the Rh-mediated process, however with a much lower selectivity in cyclopropane **1b** (Table 1, entry 2). Interestingly, kinetic studies on the Pt-mediated process showed that total conversion was obtained in only 5 min (Table 1, entry 3), but still with a low selectivity in cyclopropane **1b** (50% in 5 min and 49% in 120 min) compared with the selectivity achieved in the Rh-mediated process [98% in 5 min (Table 1, entry 4) and 87% in 120 min].

Faced with this unprecedented Rh-mediated cycloisomerization, we tried to explore the influence of the reaction conditions. The main results of our studies are reported in Table 1. The Rh-mediated formation of the cyclopropane **1b** proved to be decelerated in the absence of CO (entry 5) and also highly decelerated when toluene was replaced by THF, a coordinating solvent (entries 6–7). In contrast, no significant influence of the presence of CO and of the nature of the solvent were observed in the Pt-mediated reaction (data not shown). Presumably these two metal-mediated processes follow different reaction pathways. In all cases selectivity in cyclopropane **1b** was far better with Rh-catalysts (87–98% compared with around 50% with Pt-catalyst). The diastereoisomeric excess remains low in all experiments (only 9–14%) and does not seem to be influenced by the various tested parameters.

To have more insight into the mechanism, we prepared the deuterated enyne **1a**–$\mathbf{d_1}$ labeled with deuterium at the terminal alkyne by nBuLi deprotonation followed by D_2O quenching.[10] Notably, both the Rh- and the Pt-catalyzed reactions of **1a**–$\mathbf{d_1}$ afforded the corresponding tricyclic product **1b**–$\mathbf{d_1}$ (Scheme 3). As depicted in Scheme 3, this result is consistent with a carbenoid mechanism for both metals as generally invoked for Pt-mediated cycloisomerization of heteroatom-tethered enyne[11] and excludes a Rh-vinylidene pathway (dashed arrows), as previously reported for the Rh-catalyzed cycloisomerization of enynes into 1,3-dienes,[12] although further experiments are needed to confirm it.

To further study this Rh-catalyzed cycloisomerization, the optimized procedure described in entry 1, Table 1 was then applied to the geraniol-derived enyne **2a**, leading to the bicyclic product **2b** as a single diastereoisomer (Scheme 3). This proves that the Rh-catalyzed cycloisomerization proceeds stereospecifically, translating the configuration of the reacting alkene into the stereochemistry of the emerging cyclopropane unit; unfortunately the exact relative configuration of the diastereoisomer **2b** could not be elucidated by NMR. As observed for the enyne **1a**, no cyclopropanation of the second double bond in **2a** was observed, showing that the cyclization of the conceivable 10-membered ring does not compete with the formation of the bicyclo[4.1.0] skeleton.

The course of the Rh-catalyzed cycloisomerization was completely different for the isopulegol-derived 1,7-enyne **4a**, which was converted into the diene **4c** as in the Pt-mediated reaction[5] instead of the expected cyclopropane and for the linalool-derived

Table 1. Rh- and Pt-catalyzed cycloisomerization of enyne **1a**

Entry	Catalyst	Solvent	P_{CO}	Reaction time (min)	Conversion[a]	Selectivity[b] of **1b**	d.e.[c]
1	$[RhCl(CO)_2]_2$	Toluene	1 atm	120	98	87	11
2	$PtCl_2$	Toluene	0	120	100	49	9
3	$PtCl_2$	Toluene	0	5	100	48	12
4	$[RhCl(CO)_2]_2$	Toluene	1 atm	5	13	98	10
5	$[RhCl(CO)_2]_2$	Toluene	0	120	70	96	11
6	$[RhCl(CO)_2]_2$	THF	0	120	7	98	14
7	$[RhCl(CO)_2]_2$	THF	1 atm	120	35	98	10

Experimental conditions: substrate = 1.5 mmol, catalytic precursor 2.5% mol, solvent = 15 ml, T = 80 °C
[a] Determined through GC analysis using decane as internal standard
[b] Determined through GC analysis.
[c] Diastereoisomeric excess, determined through GC analysis

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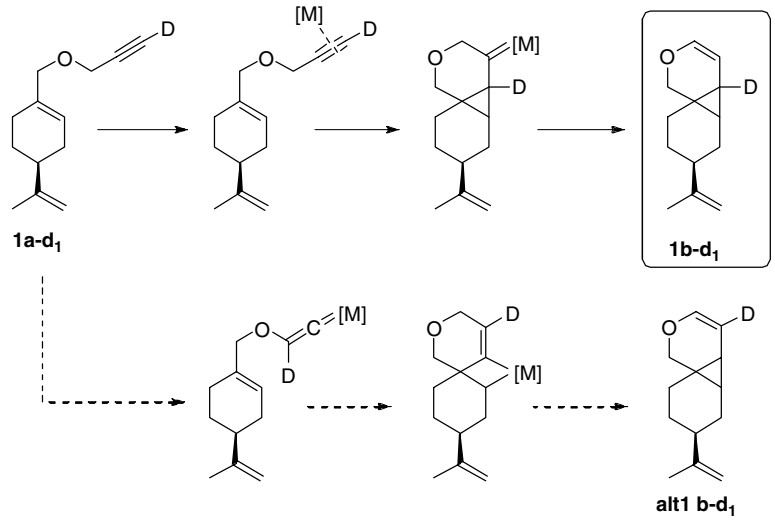
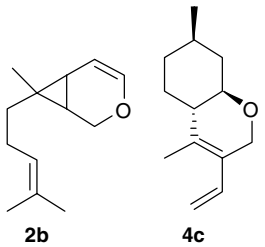


Scheme 3. Carbenoid-mechanism (continuous arrows) vs vinylidene-mechanism (dashed arrows) on the deuterated enyne **1a–d$_1$**.



Scheme 4. Cycloisomerization products from enynes **2a** and **4a**.

enyne **3a**, which was totally recovered after 2 h of reaction. These specific reactivities indicate that the process is strongly dependant on the substrate structure; more particularly the length of the enyne tether, the substitution of the double bond and the presence of substituants in the α-position of the triple bond seem to influence the course of the reaction.

Conclusions

In summary, we have reported a new selective Rh-mediated cyclopropanation which constitutes a straightforward access to highly valuable bicyclic or tricyclic derivatives incorporating either an inner cyclopropane moiety or a diene moiety depending on the enyne structure. Further studies on this process are being launched to provide insights into the reaction mechanism, which seems similar to the previously described Pt-mediated pathway, and to identify the key structural features that govern the enyne reactivity in this process.

Experimental

^{1}H NMR spectra were recorded at ambient temperature using Bruker AV500 and TMS was used as an internal standard. Chemical shift values (δ) are given in ppm relative to TMS ($\delta = 0.00$). ^{13}C NMR spectra were recorded at 125.8 MHz with the same instrument and internal standard.

The general procedure for the Rh- or Pt-catalyzed cycloisomerization reaction is as follows. The enyne and $Rh_2Cl_2(CO)_4$ or $PtCl_2$ (0.025 molar equivalent) in freshly distillated toluene (0.1 M solution) were stirred at 80 °C under CO bubbling or without. At the end of the reaction, the solvent was evaporated under vacuum and the dark brown residue was purified by flash chromatography on silica gel (eluent pentane–ethylacetate, 200 : 1).

Spectral data for **1b**[5] *and* **1b–d$_1$** *(significant data are in bold)*

^{1}H-NMR (500 MHz, $CDCl_3$): diastereoisomers a and b mixture. **1b**: 0.2–2.3 (12Ha + 12Hb), 3.47 (*d*, 1Ha, ^2J = 10.2 Hz), 3.57 (*d*, 1Hb, ^2J = 10.2 Hz), 3.91 (*d*, 1Ha, ^2J = 10.2 Hz), 3.94 (*d*, 1Hb, ^2J = 10.2 Hz), 4.65–4.68 (*m*, 2Hb, ^2J = 15 Hz), 4.71–4.74 (*m*, 2Ha, ^2J = 15 Hz), **5.27 (*dd*, 1Ha, ^3J = 5.6 Hz, ^3J = 5.6 Hz), 5.30 (*dd*, 1Hb, ^3J = 5.6 Hz, ^3J = 5.6 Hz),** 6.10 (*d*, 1Hb, ^3J = 5 Hz), 6.11 (*d*, 1Ha, ^3J = 5 Hz). **1b–d$_1$**: 0.2–2.3 (11Ha + 11Hb), 3.48 (*d*, 1Ha, ^2J = 10.2 Hz), 3.57 (*d*, 1Hb, ^2J = 10.2 Hz), 3.92 (*d*, 1Ha, ^2J = 10.2 Hz), 3.92 (*d*, 1Hb, ^2J = 10.2 Hz), 4.64–4.68 (*m*, 2Hb, ^2J = 14.3 Hz), 4.71–4.74 (*m*, 2Ha, ^2J = 14.2 Hz), **5.27 (*d*, 1Ha, ^3J = 5.7 Hz), 5.29 (*d*, 1Hb, ^3J = 5.8 Hz),** 6.10 (*d*, 1Hb, ^3J = 5.8 Hz), 6.10 (*d*, 1Ha, ^3J = 5.7 Hz).

Spectral data for **1c**

^{1}H-NMR (500 MHz, $CDCl_3$): 1.78 (*s*, 3H), 1.92 (*m*, 2H), 2.05 (*m*, 1H), 2.14 (*m*, 2H), 2.24 (*m*, 1H), 2.42 (*dd*, 1H, ^3J = 8.3 Hz, ^4J = 4.5 Hz), 4.58 (*m*, 4H), 4.76 (*m*, 2H), 5.68 (*ddd*, 1H, ^3J = 10.8 Hz, ^3J = 10.9 Hz, ^3J = 10.8 Hz), 5.84 (*d*, 1H, ^3J = 10.8 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$): 20.7 (CH_3), 22.6 (CH_2), 30.7 (CH_2), 32.8 (CH_2), 45.6 (CH), 79.3 (CH_2), 80.5 (CH_2), 108.8 (CH_2), 122.3 (CH), 130.9 (CH), 141.2 (C), 149.4 (C), 150.7 (C).

Spectral data for **2b**

^{1}H-NMR (500 MHz, $CDCl_3$): 1.02 (*s*, 3H), 1.03 (*m*, 1H), 1.07 (*m*, 1H), 1.29–1.32 (*m*, 2H), 1.63 (*s*, 3H), 1.79 (*s*, 3H), 2.08 (*m*, 2H), 4.01 (*dd*, 1H, ^2J = 11.5 Hz, J = 1.5 Hz), 4.08 (*dd*, 1H, ^2J = 11.5 Hz, J = 4.7 Hz), 4.95 (*dd*, 1H, J = 5.1 Hz, ^3J = 6.2 Hz), 5.11 (*tm*, 1H, ^3J = 7.1 Hz), 6.26 (*d*, 1H, ^3J = 6.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): 11.7 (CH_3), 16.4 (CH), 17.6 (CH_3), 23.1 (CH), 25.5 (CH_2), 25.7 (CH_3), 28.7 (C), 41.5 (CH_2), 61.0 (CH_2), 99.8 (CH), 124.4 (CH), 131.3 (C), 141.1 (CH).

Spectral data for **4c**[5]

^{1}H-NMR (500 MHz, $CDCl_3$): 0.98 (*d*, 3H, $J = 6.6$ Hz), 0.96–1.02 (*m*, 2H), 1.11 (*d*, 1H, $^2J = 11.9$ Hz), 1.55 (*m*, 1H), 1.76 (*m*, 1H), 1.78 (*d*, 3H, $J = 1.7$ Hz), 1.90–1.94 (*m*, 1H), 1.97 (*ddt*, 1H, $J = 1.8$ Hz, $J = 3.7$ Hz, $^2J = 11.9$ Hz), 2.07–2.10 (*m*, 1H), 3.13 (*ddd,* 1H, $J = 3.7$ Hz, $J = 9.5$ Hz, $J = 11.4$ Hz), 4.35 (*td*, 1H, $J = 2.2$ Hz, $^2J = 14.9$ Hz), 4.45 (*d*, 1H, $^2J = 14.9$ Hz), 4.97 (*d*, 1H, $J = 17.6$ Hz), 4.99 (*d*, 1H, $J = 11.0$ Hz), 6.70 (*ddd*, 1H, $J = 0.6$ Hz, $J = 11.0$ Hz, $J = 17.6$ Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): 14.3 (CH_3), 22.2 (CH_3), 27.2 (CH_2), 34.5 (CH_2), 40.1 (CH), 41.6 (CH_2), 44.4 (CH), 66.5 (CH_2), 78.4 (CH), 111.0 (CH_2), 127.2 (C), 131.8 (CH), 134.3 (C).

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