Homogeneous Catalysis

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Gold-Catalyzed Tandem Cycloisomerization/Cope Rearrangement: An Efficient Access to the Hydroazulenic Motif**

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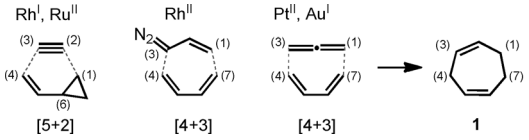
Dedicated to Professor Irina Petrovna Beletskaya

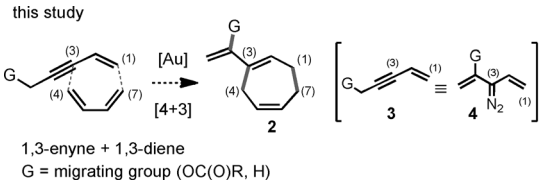
The development of synthetic methods allowing the construction of seven-membered carbocycles is of prime importance in organic synthesis given the large number of biologically relevant natural products featuring this basic unit in their (polycyclic) structure.[1] Among the different methods reported so far, the transition metal catalyzed [5+2] and [4+3] cycloadditions can certainly be considered as the most synthetically valuable.[2,3] They indeed allow a general, convergent, and efficient access to various seven-membered rings, with the possibility to rapidly and considerably increase the structural complexity when performed in an intramolecular manner.

The well-established and probably most powerful strategies to generate the 1,4-cycloheptadienyl unit **1** rely, for instance, on either the rhodium(I)- or ruthenium(II)-catalyzed [5+2] cycloaddition between a vinylcyclopropane and an alkyne,[2a–d] or the rhodium(II)-catalyzed [4+3] cycloaddition between a diene and a vinyldiazo derivative [Eq. (1)].[2e] More recently, electrophilic platimum(II) and gold(I) species have also shown their catalytic potential to produce **1** by a [4+3] cycloaddition between an allene and a diene [Eq. (1)].[2f–i]



(1)

In this context, and following our ongoing interest in the development of synthetically relevant gold-catalyzed transformations,[4] we recently envisaged an alternative strategy to produce the related 2-vinyl-1,4-cycloheptadienyl motif **2** [Eq. (2)]. This would involve a formal gold-catalyzed [4+3] cycloaddition between the 1,3-enyne **3**, possessing a migrating group (G) at the propargylic position, and a 1,3-diene [Eq. (2)].[5,6] The enyne **3** would advantageously replace in this case the less convenient diazo moiety **4**, which is required for the previously developed rhodium-catalyzed [4+3] cycloaddition.[2e] The potential conversion of a trienyne of type **5** into the tetrahydroazulene **8** [Eq. (3)] would represent a reasonable model reaction to study the viability of our strategy. In this complex transformation, which corresponds to an intramolecular version of our approach, **5** would first be cycloisomerized into the divinylcyclopropane **7**[7] (via the gold carbene intermediate **6**) which should then evolve into **8** through a Cope rearrangement.[8,9] This designed tandem reaction would interestingly give rise to a bicyclic motif found in the structure of numerous natural products and would further underscore the potential of gold catalysis for the rapid generation of structural complexity from linear substrates.[10]



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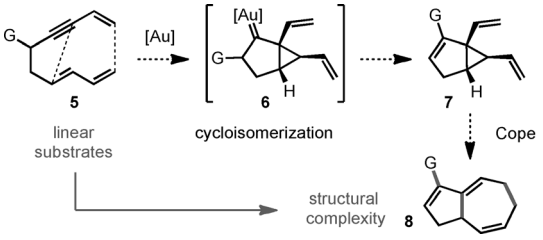

(3)

We started our investigations by studying the reactivity of model the substrate **9a** (Scheme 1). The choice of an acetoxy moiety as the migrating group (G) at the propargylic position C5 was made on the basis of the known migratory aptitude of acyloxy groups in gold-catalyzed cycloisomerizations (**9a**→**10**→**11**).[11] An isopropyl and a methyl group were introduced at C6 and C7, respectively, so that the tandem cycloisomerization/Cope rearrangement (**9a**→**11**→**12a**) would lead to the formation of the valuable bicyclic compound **12a**, which possesses the basic structure found in a series of natural products having interesting biological activities (Scheme 1). The use of **9a** as a model substrate raises, however, two issues: 1) the adverse competitive formation of **14** by a tandem [3,3] rearrangement/Nazarov reaction (**9a**→**13**→**14**);[12] and 2) the degree of stereocontrol in the transformation.

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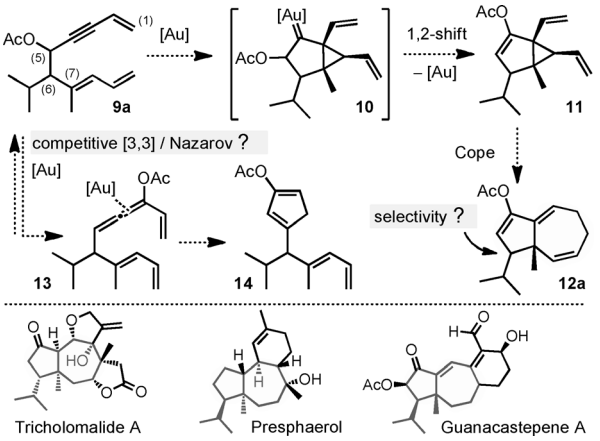
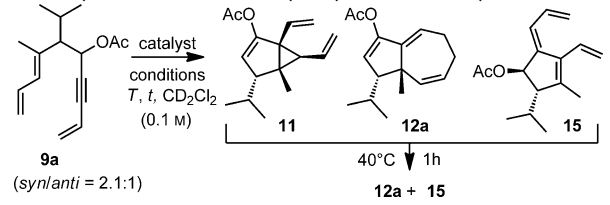


Scheme 1. Designed tandem cycloisomerization/Cope rearrangement with substrate **9a**.

To answer these questions a 2.1:1 *syn*/*anti* mixture of **9a** was first treated with 2 mol% of $[(Ph_3P)Au]NTf_2$[13] in CD_2Cl_2 at 20 °C and the reaction monitored by ^1H NMR spectroscopy (Table 1, entry 1). We were delighted to observe the formation of the desired tetrahydrozulene derivative **12a** along with the postulated intermediate **11** and the *endo*-metathesis-type compound **15**.[14] Notably, no trace of **14** could be detected.[12] It was also noted that **11** was gradually converted into **12a** during the course of the reaction. Once **9a** had been totally consumed (1 h), the reaction mixture was heated to 40 °C to complete the Cope rearrangement of **11**. Under these conditions a 1.4:1 mixture of **12a** and **15** was finally obtained, from which **12a** could be isolated in 50% yield. The transformation proved to be highly stereoselective and **12a** was obtained as a single isomer with a relative *trans* configuration of the Me and *i*Pr groups.[15] We next focused our attention on the optimization of the catalytic conditions and a series of gold(I) catalysts were screened. As seen from the results compiled in Table 1 (entries 1–8), the **12a**/**15** ratio could be dramatically improved, thus reaching a maximum of 16.8:1 when $[(t\text{BuXPhos})Au]NTf_2$ (**16**) was used as the catalyst and the reaction performed at 0 °C (entry 7). The loading of **16** could even be reduced to 1 mol% without noticeable modification of the reaction time and selectivity (entry 8). Under these reaction conditions, an optimal 87% yield of the isolated **12a** could finally be obtained.

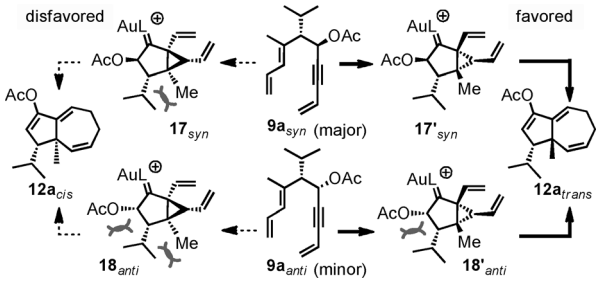
Table 1: Optimization of the catalytic system with trienyne **9a**.



Entry	Catalyst (mol%)	*T* [°C]	*t* [h]	**12a**/**15**[a]	Yield [%][b]
1	$[Ph_3PAu]NTf_2$ (2)	20	1	1.4:1	58 (50)
2	$[(IPr)Au]NTf_2$ (2)	20	1	1.7:1	63
3	[(JohnPhos)Au]NTf_2 (2)	20	0.5	3.3:1	76
4	[(RuPhos)Au]NTf_2 (2)	20	0.5	5.0:1	83
5	[(XPhos)Au]NTf_2 (2)	20	0.5	8.0:1	88
6	[(*t*BuXPhos)Au]NTf_2 (**16**) (2)	20	0.5	11.0:1	92
7	[(*t*BuXPhos)Au]NTf_2 (**16**) (2)	0	3	16.8:1	93
8	[(*t*BuXPhos)Au]NTf_2 (**16**) (1)	0	3	14.1:1	93 (87)

[a] Ratio determined by ^1H NMR analysis of the crude reaction mixture. [b] Yields determined by ^1H NMR spectroscopy. Yields of isolated product given within parentheses. Tf = trifluoromethanesulfonyl, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

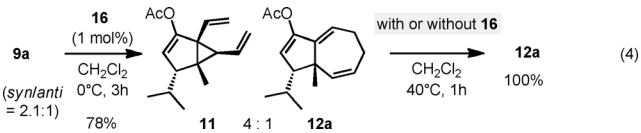
It is particularly interesting to note that while **9a** was used as a mixture of *syn* and *anti* isomers ($\mathbf{9a}_{syn}$ and $\mathbf{9a}_{anti}$; Scheme 2), only a single isomer, $\mathbf{12a}_{trans}$, was obtained. This convergent selectivity can be rationalized by considering the



Scheme 2. Proposal for the selective formation of $\mathbf{12a}_{trans}$.

two pairs of gold carbenoid intermediates, $\mathbf{17}_{syn}$ and $\mathbf{17'}_{syn}$ and $\mathbf{18}_{anti}$ and $\mathbf{18'}_{anti}$, which can potentially be generated from $\mathbf{9a}_{syn}$ and $\mathbf{9a}_{anti}$, respectively (Scheme 2). The unfavorable steric interaction between the Me and *i*Pr groups in $\mathbf{17}_{syn}$ and $\mathbf{18}_{anti}$, is not present in $\mathbf{17'}_{syn}$ and $\mathbf{17'}_{anti}$, and might be the source of the observed high stereoselectivity.

To evaluate the role of the gold catalyst in the Cope rearrangement,[16] the reaction was quenched after **9a** had been completely consumed [Eq. (4)] and the resulting mixture of **11** and **12a** was isolated (78%, **11**/**12a** = 4:1). Heating this mixture in CH_2Cl_2 at 40 °C for 1 hour with or without the gold catalyst **16** led to the complete and clean conversion of **9** into **12a**, thus showing that the gold complex is not involved in the Cope rearrangement.

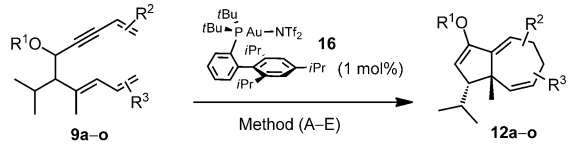


(4)

From a synthetic point of view, the transformation of **9a** into **12a** is remarkable. Not only does it allow the generation of structural complexity from easily accessible linear substrates, but it is also efficient at a low loading of catalyst and is highly selective.

The scope of the reaction was next examined. As seen in Tables 2 and 3, different methods (A–E) were employed to perform the tandem cycloisomerization/Cope rearrangement. The transformation was initiated by reacting the substrate

Table 2: Substrate scope: effects of the migrating group and the substitution on the remote alkenes.



Methods: [a]
A 0°C (CH_2Cl_2), then 40°C (CH_2Cl_2)
B 0°C (CH_2Cl_2), then 60°C ($CHCl_3$)
C 0°C (CH_2Cl_2), then 110°C (toluene)
D 40°C (CH_2Cl_2)
E 40°C (CH_2Cl_2), then 110°C (toluene)

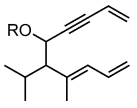
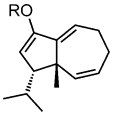
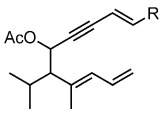
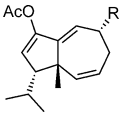
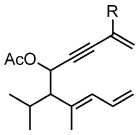
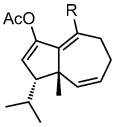
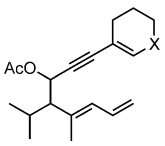
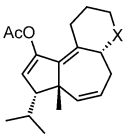
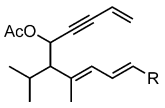
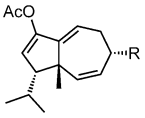
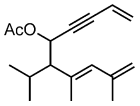
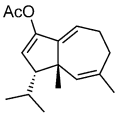
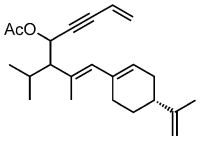
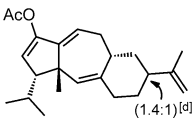
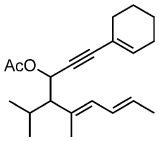
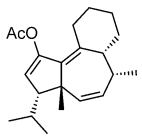
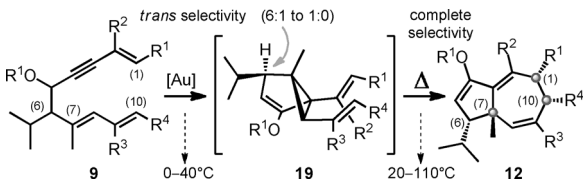
Entry	Substrate	Method (t_1, t_2)	Product, yield
			
1	**9a** (R = Ac)	A (3 h, 1 h)	**12a**, 87% (1:0)
2	**9b** (R = Piv)	A (3 h, 1 h)	**12b**, 80% (>20:1)
3	**9c** (R = Bz)	A (3 h, 1 h)	**12c**, 77% (>20:1)
			
4	**9d** (R = Me; 3:1[d])	A (5 h, 1 h)	**12d**, 99% (1:0)
5	**9e** (R = CH_2OBn; 2.3:1[d])	A (3 h, 1 h)	**12e**, 61% (1:0)
6	**9f** (R = CO_2Me; 2.1:1[d])	D (1 h, –)	**12f**, 92% (>20:1)
			
7	**9g** (R = Me; 2.1:1[d])	C (4 h, 1 h)	**12g**, 53% (>20:1)
8	**9h** (R = CO_2Et; 10:1[d])	E (2 h, 1 h)	**12h**, 95% (6:1)
			
9	**9i** (X = CH_2; 3:1[d])	C (6 h, 8 h)	**12i**, 47% (1:0)
10	**9j** (X = C=O; 3:1[d])	E (12 h, 2 h)	**12j**, 63% (6:1)
			
11	**9k** (R = Me; 2.1:1[d])	B (4 h, 1 h)	**12k**, 80% (1:0)
12	**9l** (R = *n*Bu; 3:1[d])	B (4 h, 1 h)	**12l**, 60% (1:0)
			
13	**9m** (4:1[d])	A (3 h, 1 h)	**12m**, 91% (1:0)
			 (1.4:1)[d]
14	**9n** (2.1:1[d])	C (4 h, 6 h)	**12n**, 81% (1:0)

Table 2: (Continued)

Entry	Substrate	Method (t_1, t_2)	Product, yield
			
15	**9o** (3:1[d])	C (4 h, 24 h)	**12o**, 68% (1:0)

[a] See text. [b] t_1: time required for complete consumption of the substrate. t_2: time required for completing the Cope rearrangement. [c] Yield of isolated product. The *trans*/*cis* ratio, with respect to the *i*Pr, Me relationship, is given within parentheses. [d] The d.r. value was determined by ^{1}H NMR spectroscopy. Bz = benzoyl, Piv = pivaloyl.

with 1 mol% of **16** in CH_2Cl_2 at 0°C or 40°C. Once **9** had been completely consumed (t_1), the Cope rearrangement was then completed (t_2) by heating the resulting mixture at 40°C (CH_2Cl_2), 60°C ($CHCl_3$), or 110°C (toluene) depending upon the substitution pattern of **9**.[17] The transformation proved to be general and a range of tetrahydroazulenic derivatives (**12a–r**) were produced in moderate to excellent yields (Tables 2 and 3). The stereoselectivity of the reaction was high (6:1 to 1:0), despite the fact that the substrates were used as *syn* and *anti* isomeric mixtures. No noticeable difference in terms of yield and selectivity was observed when the migrating AcO group in **9a** was replaced by a PivO or a BzO moiety (Table 2, entries 1–3). Special attention was directed at the reactivity of substrates **9d–o** which possess substituents on the remote alkenyl moieties involved in the Cope rearrangement. As seen from the results (Table 2, entries 4–15), the first cycloisomerization step of the tandem process could generally be performed at 0°C, except when electron-withdrawing groups were present on the alkene moiety attached to the alkyne (Table 2, entries 6, 8, and 10). In these cases, heating to 40°C was required, and caused a slight erosion of the *trans*/*cis* selectivity.[18] Unsurprisingly, the temperature required to achieve the Cope rearrangement proved to be directly linked to the degree of substitution of the alkene: the more substituted the latter, the higher the temperature needed to accomplish the transformation (Table 2, entries 7–10, 14, and 15).[8] It is noteworthy that the substrates **9d–f**,**i–l**,**n**,**o**, with substituents at the terminal position of the external alkenes, led to the stereoselective formation of tetrahydroazulenic derivatives possessing additional stereogenic centers on the newly formed seven-membered ring (Table 2, entries 4–6, 9–12, 14, and 15). The complete stereoselectivity observed may be explained by the boatlike conformation **19** required for the thermal Cope rearrangement to proceed (Scheme 3).[8]



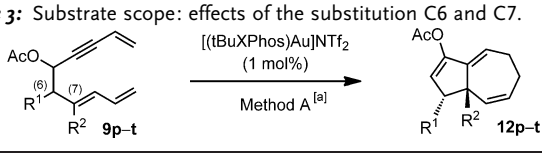
Scheme 3. Selectivity of the Cope rearrangement.

Since the gold(I)-catalyzed cycloisomerization is selective (*i*Pr at C6 and Me at C7, preferentially in a *trans* relationship; **19**, Scheme 3), the configurations of the three stereogenic centers created during the tandem process at C1, C7, and C10 in **12** are in fact dictated solely by that of the *i*Pr group at C6 in **9**. From a synthetic point of view, it is worth drawing attention to the rapidity with which the tricyclic core structure of Presphaerol (Scheme 1) and other related terpenes could be assembled (**12i,j,o;** Table 2, entries 9, 10, and 15).

The experiments summarized in Table 3 relate to the influence of substituents at C6 and C7. When the isopropyl group is replaced by an ethyl substituent, no noticeable difference in reaction time and yield was observed (entry 1). Replacement with a simple hydrogen atom led however, to a decrease in efficiency (57% versus 87%; entry 2). The methyl group at C7 could be exchanged for a longer alkyl chain possessing a benzyl ether functionality (entry 3). In this case, the reaction was exceedingly efficient and selective since **12r** could be isolated as a single isomer in 99% yield. A limit in reactivity was attained when no substituent was present at C7 (entry 4) or when C6 and C7 were linked by a four-carbon tether (entry 5).

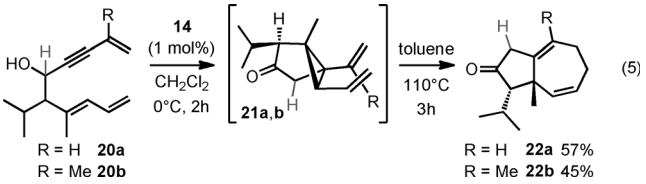
We also rapidly explored the feasibility of the tandem process using the propargylic alcohols **20a,b** instead of the propargylic carboxylates **9** [Eq. (5)].[7b,c] Gratifyingly, the corresponding hydroazulenones **22a,b** could be obtained, albeit in more modest yields. In these cases a 1,2-hydride shift occured during the cycloisomerization step to intermediately produce the ketones **21a,b**.

Table 3: Substrate scope: effects of the substitution C6 and C7.

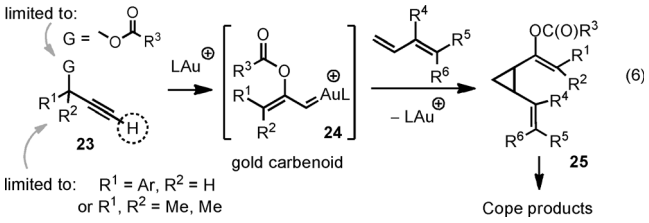


Entry	Substrate	t_1, t_2[b]	Product, yield
1	**9p** (R = Et; 2.8:1[d])	3 h, 1 h	**12p**, 76% (17:1)
2	**9q** (R = H)	3 h, 1 h	**12q**, 57%
4	**9r** (R = $(CH_2)_4OBn$; 2.7:1[d])	5 h, 1 h	**12r**, 99% (1:0)
5	**9s** (R = H; 1:1[d])	3 h, 1 h	**12s**, 24% (8:1)
8	**9t** (1.7:1[d])	–	**12t**, 0% (–)

[a] See text. [b] t_1: time required for complete consumption of the substrate. t_2: time required for completing the Cope rearrangement. [c] Yield of isolated product. The *trans*/*cis* ratio, with respect to the *i*Pr, Me relationship, is given within parentheses. [d] The d.r. value was determined by ^{1}H NMR spectroscopy.



From a mechanistic point of view, it is important to note that, in contradistinction to what has previously been reported [Eq. (6)],[9a,b,2i] the present tandem cycloisomerization/Cope rearrangement does not involve the initial formation of a gold carbenoid of type **24** which could be trapped by a diene to furnish the intermediate divinylcyclopropane **25** (compare **6** and **24**). This is a key difference with earlier work. Furthermore, the present transformation is not restricted to the use of the terminal alkyne **23** possessing acyloxy moieties as the 1,2-migrating group (G) and dimethyl or monoaryl substitution at the propargylic position.



In conclusion, we have developed a gold(I)-catalyzed tandem cycloisomerization/Cope rearrangement process which allows the formation of complex polycyclic frameworks from easily accessible linear trienyne substrates. This efficient and selective transformation represents a useful alternative to the previously reported strategies to access such structural fragments and could find direct applications in the rapid synthesis of various biologically active natural products.

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[17] Practically, CH_2Cl_2 was removed and the crude reaction mixture dissolved in $CHCl_3$ or toluene when required.

[18] A higher temperature should increase the probability of a reaction pathway involving $\mathbf{17}_{syn}$ and/or $\mathbf{18}_{anti}$ (Scheme 2).

