Homogeneous Catalysis

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Gold-Catalyzed Cycloisomerization of Cyclopropyl Alkynyl Acetates: A Versatile Approach to 5-, 6-, and 7-Membered Carbocycles**

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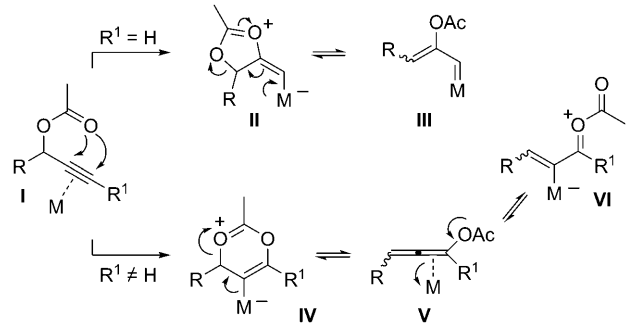
In memory of Yoshihiko Ito

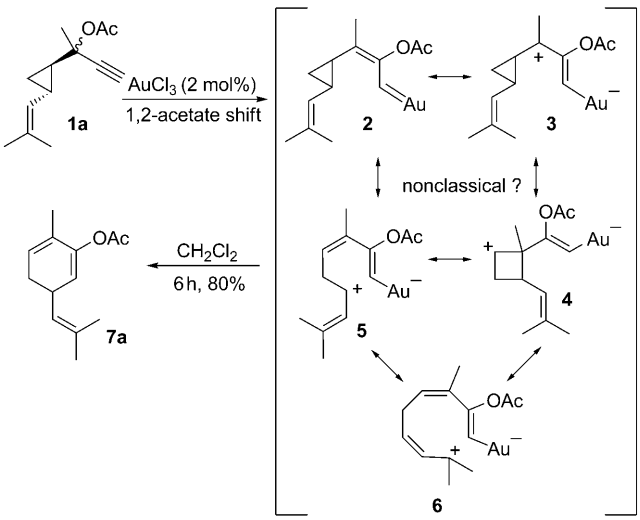
During the last decade, late-transition-metal-catalyzed cycloisomerizations have emerged as a powerful tool to access unprecedented structural and mechanistic diversity.[1] In this context, a rapidly developing area involves the use of propargylic esters, preferably acetates, in which the carbonyl unit acts as a nucleophile onto the metal-activated alkyne complex **I** (Scheme 1). Two distinct mechanistic scenarios



Scheme 1. 1,2- versus 1,3-acetate migration.

arise from this intermediate.[2] If terminal alkynes are used, 1,2 migration of the acetate affords vinyl metal species **II**, which can result in the formation of "carbenoid" **III**.[3] In contrast, internal alkynes undergo a [3,3]-sigmatropic rearrangement to form allenyl acetate **V**, which can be additionally activated in the presence of the metal catalyst to give **VI**, triggering an extensive palette of transformations.[4,5]

Intermediates of type **III** were proposed by Rautenstrauch et al. for the Pd-catalyzed cycloisomerization/in situ hydrolysis of vinyl propargyl acetates to give 2-cyclopentenones.[6] Recently, Toste and co-workers expanded the scope of this cyclopentenone synthesis by application of cationic Au^I catalysts.[7,8] To access the Rautenstrauch rearrangement products of larger ring sizes we decided to construct a homologous system such as **1a** (Scheme 2).[9] The reaction in the presence of catalytic amounts of $AuCl_3$ was aimed to



Scheme 2. Au-catalyzed homo-Rautenstrauch rearrangement.

probe the behavior of canonical carbenoid **2** which could subsequently arise from the Au-promoted 1,2-acetate migration.[3] However, a look at intermediate **2** in light of the recently discussed nonclassical carbocationic nature of carbenoid-like intermediates of gold-catalyzed enyne cyclizations[1b,g] would be more insightful. Resonance structures **3**–**6** visualize the possibilities for consecutive cyclizations more clearly. Intermediate **2** could lead to 7-membered ring products by a Cope (divinylcyclopropane) rearrangement, and allylcations **5** or **6** may cyclize to give 6- or 8-membered ring systems, respectively. We were pleased to find that compound **1a** exclusively led to cyclohexadienyl acetate **7a**. Herein, we report our investigation on this novel gold-catalyzed homo-Rautenstrauch rearrangement and hope it

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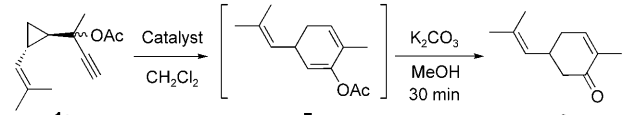
will help to further unravel the mechanistic blur of gold catalysis.

To provide insight into this initial result several optimization and control reactions were carried out (Table 1). The primary product, **7a**, is a sensitive dienol acetate and it was generally converted into 2-hexenone **8a** by an in situ methanolysis. To investigate the cationic gold(I) complexes for

Table 1: Catalyst optimization.



1a **7a** **8a**

Entry	Catalyst (mol%)	*t* [min]	Yield [%][a]
1	$AuCl_3$ (2)	360	75
2	$[Au(PPh_3)]SbF_6$ (1)	2	85
3	$[Au(PPh_3)]SbF_6$ (0.1)	30	80
4	$[Au(PPh_3)]OTf$ (5)	5	0[b]
5	$[Au(PPh_3)]Cl$ (5)	360	0[c]
6	$AgSbF_6$ (5)	5	0[b]
7	$[PdCl_2(MeCN)_2]$ (5)	360	0[b]

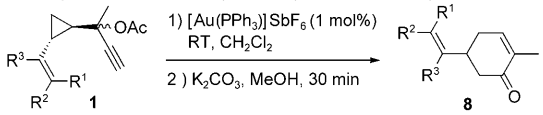
[a] Yield of isolated product **8a** after column chromatography. [b] Decomposition occurred. [c] Starting material was recovered.

alkyne activation, compound **1a** was treated with a variety of catalysts (Table 1). Using 1 mol% of the pregenerated cationic complex $[Au(PPh_3)]SbF_6$ in CH_2Cl_2 produced acetate **7a** within 2 minutes, and the product was isolated in an 85% yield after hydrolysis (Table 1, entry 2). Even at a catalyst loading of 0.1 mol%, the reaction was fast and no significant decrease in yield was observed (Table 1, entry 3). Interestingly, decomposition of substrate **1a** was observed when the counterion was changed from SbF_6^- to TfO^- (Table 1, entry 4). Control experiments employing either 5 mol% $[Au(PPh_3)]Cl$ or 5 mol% $AgSbF_6$ as the sole catalyst did not lead to product **7a** (Table 1, entries 5 and 6). Notably, under the original reaction conditions reported by Rautenstrauch et al.,[6] decomposition of **1a** was observed (Table 1, entry 7).

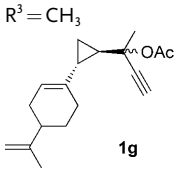
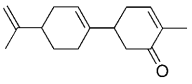
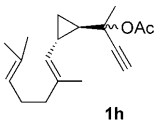
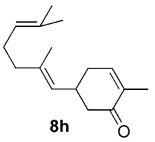
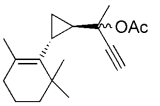
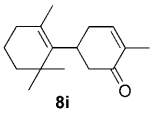
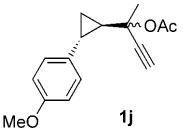
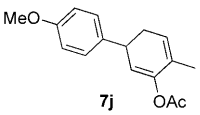
With good working conditions in hand, the scope of the gold(I)-catalyzed cycloisomerization of 1-cyclopropyl-propargyl esters **1** was examined (Table 2). The reactions were all carried out on gram scale under very mild conditions.[9] Alkyl (Table 2, entries 1–4) and aryl (Table 2, entry 5) substituents on the double bonds were tolerated, and the products (**8**) were obtained in good to excellent yields. As expected, sterically hindered substrate **1i** resulted in a slower reaction, but full conversion was achieved after 6 hours, giving bicyclic compound **8i** in an excellent yield of 90% upon isolation (Table 2, entry 8). The cyclopropyl ring cleavage can be also stabilized by a *para*-methoxyphenyl substituent (**1j**), affording **7j** in good yield (Table 2, entry 9).

Apparently, the stabilization of positive charge in intermediates **3** and **5** (Scheme 2) is essential for a smooth conversion of **1** into the cyclization products (**7**); even under harsh conditions, secondary acetate **9** did not cyclize but instead ring-opened to trienone **10** after hydrolysis, albeit in

Table 2: Scope of the Au^I-catalyzed 2-cyclohexenone synthesis.[a]



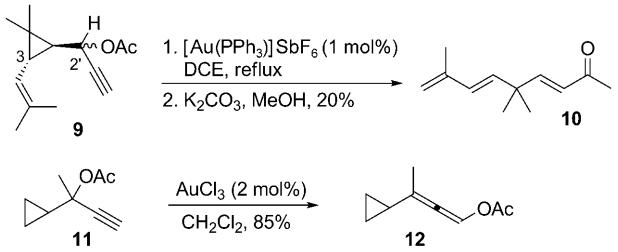
1 **8**

Entry	Substrate	Product	*t* [min][b]	Yield [%][c]
1	**1b**: $R^1=R^2=Et$, $R^3=H$	**8b**	5	78
2	**1c**: $R^1=H$, $R^2=nPr$, $R^3=H$	**8c**	10	62
3	**1d**: $R^1=CH_3$, $R^2=Et$, $R^3=H$	**8d**	10	82
4	**1e**: $R^1=H$, $R^2=Et$, $R^3=CH_3$	**8e**	10	96
5	**1f**: $R^1=H$, $R^2=Ph$, $R^3=CH_3$	**8f**	10	88[10]
6	 **1g**	 **8g**	10	56
7	 **1h**	 **8h**	10	71
8	 **1i**	 **8i**	360	90
9	 **1j**	 **7j**	60	70[d]

[a] Reaction conditions: 1) Substrate (10 mmol, 1 M in CH_2Cl_2), $[Au(PPh_3)]SbF_6$ (1 mol% in CH_2Cl_2), RT. 2) K_2CO_3 (20 mmol), MeOH (10 mL), RT, 30 min. [b] Reaction time for the first step with 100% conversion determined by GC-MS methods. [c] Yield of isolated products after 2 steps. [d] Yield of isolated product after the first step.

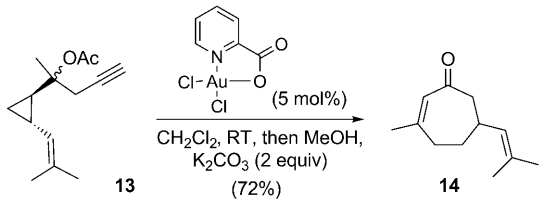
low yield (Scheme 3). Likewise, the simple cyclopropyl derivative **11** did not cyclize but rearranged to allene **12**.

We also extended this process to homopropargyl acetates (Scheme 4), which have been reported to undergo acetate migration to the internal position of the alkyne, even though serious limitations were observed when restricted conformations were not achieved.[11] To our delight, cyclization of



9 **10** **11** **12**

Scheme 3. Side reactions of the cycloisomerization.

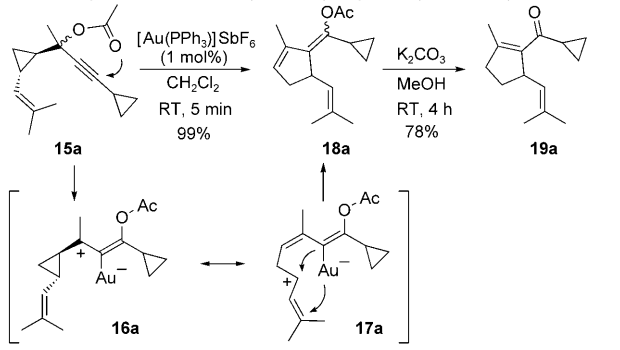


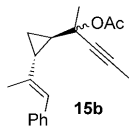
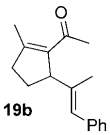
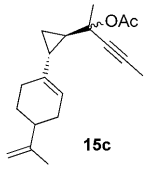
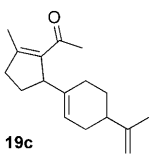
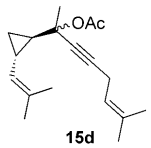
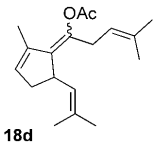
Scheme 4. Homopropargyl acetate cycloisomerization.

substrate **13** occurred smoothly affording cycloheptenone **14** in 72% yield.

As shown in Scheme 1, substitution at the terminal position of the acetylene unit may initiate a 6-*endo*-*dig*-like 1,3 migration of the carboxylate group.[2,4] We envisioned that treatment of substrates, such as **15a**, with $[Au(PPh_3)]SbF_6$ would generate cyclopropylalkyl carbenium ion **16a**, which is mesomeric to intermediate **17a** (Table 3). Cyclization of these species at the allyl cationic positions may occur, but only trienyl acetate **18a** was obtained in almost quantitative yield as a mixture of *cis* and *trans* isomers. Methanolysis and concomitant isomerization led to **19a** as a single isomer.

Table 3: Scope of the Au^I-catalyzed 1-cyclopentenylketone synthesis.[a]

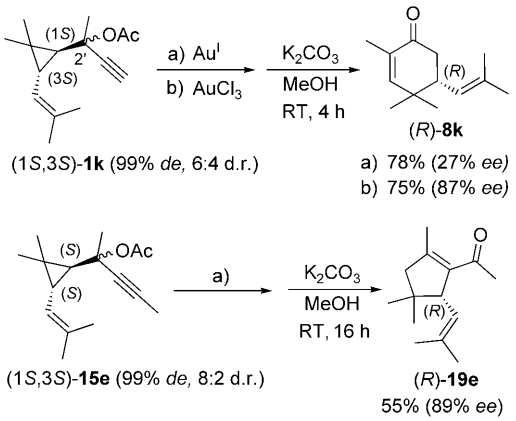


Entry	Substrate	Product	t [min][b]	Yield [%][c]
1	 **15b**	 **19b**	5	88
2	 **15c**	 **19c**	2	87
3	 **15d**	 **18d**	10	90[d]

[a] Reaction conditions: 1) Substrate (10 mmol, 1 M in CH_2Cl_2), [Au-(PPh_3)]SbF_6 (1 mol% in CH_2Cl_2), RT. 2) K_2CO_3 (20 mmol), MeOH (10 mL), RT, 16 h. [b] Reaction time of first step with 100% conversion determined by GC-MS methods. [c] Yield of isolated product after column chromatography. [d] Yield of isolated product **18d** after column chromatography.

Additional investigations (Table 3) revealed that the cyclization also tolerates a variety of differently substituted substrates.

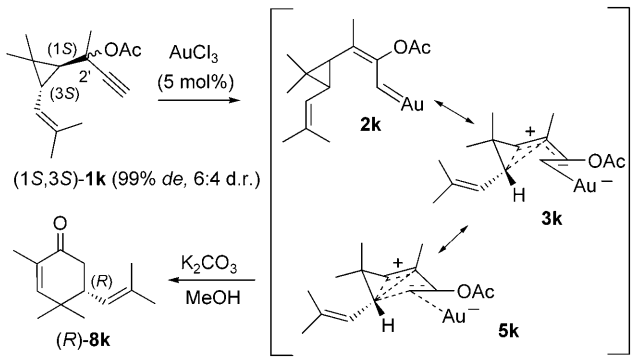
The interesting question of a possible chirality transfer in these systems was addressed using optically active substrates **1k** and **15e**, which are both easily available from optically pure (1*S*,3*S*)-(−)-*trans*-chrysanthemum acid (99% *ee*; Scheme 5).[9,12] Cycloisomerization of **1k** (d.r. 6:4, 99% *de*) under standard conditions ($[Au(PPh_3)]SbF_6$, CH_2Cl_2, RT) cleanly afforded (*R*)-**8k** after methanolysis, albeit with only



Scheme 5. Chirality transfer of compounds **1k** and **15e** to 6- and 5-membered ring products.

27% *ee*. Lowering the temperature to −20 °C only increased the reaction time to 24 hours without significantly improving the *ee* value (31% *ee*). Performing the reaction in various solvents also did not improve these results. Surprisingly, using $AuCl_3$ as the catalyst retained the enantioselectivity most effectively, leading to (*R*)-**8k** with 87% *ee*. In contrast, $[Au(PPh_3)]SbF_6$-promoted cycloisomerization of compound **15e** delivered acetylcyclopentenone (*R*)-**19e** with good chirality transfer (89% *ee*; Scheme 5). The absolute configuration of both enantiomerically enriched samples was unequivocally determined by Raman optical activity (ROA) measurements.[13]

In our view, these results disfavor mechanisms of chirality transfer through the stereogenic propargyl ester unit as reported earlier for other systems:[8] the stereochemical information at the 2′-position in substrate **1k** (Scheme 5) does not overrule that which is inherent at C1 and C3.[14] In contrast, the reaction clearly depends on the stabilization of a positive charge, particularly at positions 3 and 2′ in **1k** (see Scheme 3 and reference [10]), but only to an extent that prevents formation of achiral cation **5** (Scheme 2). We propose a more concerted mechanism, wherein carbene **2k** can be redefined as a nonclassical carbonium ion[1b,15] complex **3k** or, under participation of the vinyl/gold unit species **5k**,[16] as the intermediate that preserves the enantioselectivity (Scheme 6). Depending on the electronic stabilization and geometry, these species display a certain configurational stability by which stereochemical information is retained throughout the reaction.



Scheme 6. Proposed nonclassical intermediates for the chirality transfer to product **8k**.

In conclusion, we have found a new Au-catalyzed homo-Rautenstrauch rearrangement of 1-cyclopropylpropargylic esters to give cyclohexenones **8** and cyclopentenyl ketones **19** under mild conditions. In addition, enantiomerically enriched cyclohexenones and cyclopentenyl ketones can be prepared by the gold-catalyzed cyclization of optically active propargyl acetates. Although the rearrangements are cationic in nature, the high degree of chirality transfer in these reactions suggests that gold-stabilized nonclassical carbocations with a certain configurational stability are involved.

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[1] For recent general reviews, see: a) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338 – 4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268 – 4315; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478 – 3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449; c) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431 – 436. For specific Au-catalyzed transformations: d) E. Jiménez-Nuñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326 – 3350; e) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395 – 403; f) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180 – 3211; g) A. S. Hashmi, *Angew. Chem.* **2008**, *120*, 6856 – 6858; *Angew. Chem. Int. Ed.* **2008**, *47*, 6754 – 6756; h) S. Ma, S. Yu, Z. Gu, *Angew. Chem.* **2006**, *118*, 206 – 209; *Angew. Chem. Int. Ed.* **2006**, *45*, 200 – 203; i) J.-M. Tang, S. Bhunia, S. M. Abu Sohel, M.-Y. Lin, H.-Y. Liao, S. Datta, A. Das, R.-S. Liu, *J. Am. Chem. Soc.* **2007**, *129*, 15677 – 15683.

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[4] a) N. Marion, S. Díez-González, P. de Frémont, A. R. Noble, S. P. Nolan, *Angew. Chem.* **2006**, *118*, 3729 – 3732; *Angew. Chem. Int. Ed.* **2006**, *45*, 3647 – 3650; b) A. Buzas, F. Istrate, F. Gagosz, *Org. Lett.* **2006**, *8*, 1957 – 1959; c) S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 8414 – 8415; d) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804 – 16805; e) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442 – 1443.

[5] Recent computational studies suggest that both Au-mediated pathways could be interconnected, see: A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan, L. Cavallo, *Angew. Chem.* **2008**, *120*, 730 – 733; *Angew. Chem. Int. Ed.* **2008**, *47*, 718 – 721.

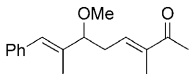
[6] a) V. Rautenstrauch, *J. Org. Chem.* **1984**, *49*, 950 – 952; b) V. Rautenstrauch, U. Burger, P. Wirthner, *Chimia* **1985**, *39*, 227 – 228.

[7] X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802 – 5803.

[8] Herein, an interesting chirality transfer from an optically active propargyl pivaloate was postulated to proceed by the cyclic oxonium ion similar to mechanisms proposed for such conservation of stereochemical information in other cases such as: a) A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *12*, 3006 – 3019; b) C. Fehr, J. Galindo, *Angew. Chem.* **2006**, *118*, 2967 – 2970; *Angew. Chem. Int. Ed.* **2006**, *45*, 2901 – 2904. In a subsequent calculation, a helical intermediate was found to retain the stereochemical information of the starting material: c) O. N. Faza, C. S. López, R. Álvarez, A. R. de Lera, *J. Am. Chem. Soc.* **2006**, *128*, 2434 – 2437.

[9] For the preparation of new compounds and additional experimental details, see the Supporting Information.

[10] When the reaction was performed using $AuCl_3$ and MeOH as solvent, substrate **1f** reacted through a 1,2-acetate shift and solvolysis of the cyclopropane unit to give a methoxy adduct:



[11] S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 14274 – 14275.

[12] G. Rosini, C. Ayoub, V. Borzatta, E. Marotta, A. Mazzanti, P. Righi, *Green Chem.* **2007**, *9*, 441 – 448.

[13] The absolute configurations of (*R*)-**8k** and (*R*)-**19e** were determined by comparing the vibrations of the measured ROA spectra with those of the theoretical spectra, calculated at the B97-1/pc-2 level with the Gaussian program. See: a) W. Hug, *Continuum Solvation Models in Chem. Physics* **2007**, 220 – 237; b) ROA calculations at the TDHF/DPS level was carried out with the Dalton program: G. Zuber, W. Hug, *J. Phys. Chem. A* **2004**, *108*, 2108 – 2118; c) J. Haesler, W. Hug, *Chimia* **2008**, *62*, 482; for applications see: d) M. A. Lovchik, G. Frater, A. Goeke, W. Hug, *Chem. Biodiversity* **2008**, *5*, 126 – 139; e) M. A. Lovchik, A. Goeke, G. Frater, *J. Org. Chem.* **2007**, *72*, 2427 – 2433; f) J. Haesler, I. Schindelholz, E. Riguet, C. G. Bochet, W. Hug, *Nature* **2007**, *446*, 526 – 529.

[14] A diastereomeric ratio of 6:4 would account for a chirality transfer of a maximum 20% *ee*.

[15] a) For a general review on nonclassical cations, see: G. Olah, V. P. Reddy, G. K. S. Prakash, *Chem. Rev.* **1992**, *92*, 69 – 95; b) For a related case, see: M. Motamed, E. M. Brunnelle, S. W. Singaram, R. Sharpong, *Org. Lett.* **2007**, *9*, 2167 – 2170.

[16] Species **3k** (see also **3** in Scheme 2) could be most likely represented as the *E* configured vinyl gold intermediates. Nevertheless, *Z* isomer has been postulated to be plausible, being generated by anchimeric assistance allowing the cyclization with minimal steric hindrance, see: E. Soriano, J. Marco-Contelles, *J. Org. Chem.* **2005**, *70*, 9345 – 9353.

