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Mechanistic Insights in Gold-Stabilized Nonclassical Carbocations: Gold-Catalyzed Rearrangement of 3-Cyclopropyl Propargylic Acetates

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Abstract: The reaction of 3-cyclopropyl propargylic carboxylates with Au(I) and Au(III) catalysts affords selectively 5-(*E*)-alkylidenecyclopentenyl acetates via [3,3]-sigmatropic rearrangement of the carboxylic moiety followed by cyclopropyl ring opening and cyclization. DFT calculations have been performed, supporting a two-step no-intermediate mechanism along the cyclization coordinate. The stereoselective formation of the exocyclic alkenes is kinetically controlled in the first of these events. Although stereospecific in nature through a gold-stabilized nonclassical carbocation, the chirality transfer in these cyclopentannulations is not complete. Computational and experimental evidence is provided for a Au-promoted cyclopropyl ring opening/epimerization/ring closure in both *cis*- and *trans*-cyclopropyl settings, which competes with the cyclization event, thus eroding the stereochemical information transfer. When tertiary acetates were used, products of both 1,2- and 1,3-acyloxy migration processes could be isolated, supporting the competitive coexistence of these two pathways along the reaction profile, as suggested also by DFT calculations.

Introduction

From the seminal discovery of the Zn-mediated rearrangement of propargyl acetates reported by Ohloff et al. in 1976, the chemistry of propargyl esters has experienced an exponential growth.[1] Ten years later, a related Pd-catalyzed cyclization of 1-ethynyl-2-propenyl acetates to give 2-cyclopentenones was reported by Rautenstrauch and co-workers.[2] Although an in-depth mechanistic study was lacking, the formation of a Pd−carbene intermediate was already postulated. Work from Ohe and Uemura with ruthenium[3] and from Malacria with platinum[4] reopened the interest in this class of transformations at the beginning of this decade. Later, Toste demonstrated that intermediate achiral carbenes are an insufficient explanation for the observed chirality transfer in a gold-promoted version of the Rautenstrauch reaction.[5] Now, after 30 years of research mainly driven by the irruption of platinum and gold complexes in modern catalysis, a more clear mechanistic picture has been evolved for these transformations (Scheme 1).[6] Gold in particular has proven to efficiently activate propargyl carboxylates (**I**) toward 1,2-acyloxy migration and/or [3,3]-sigmatropic acyloxy rearrangement at room temperature (red and blue paths, respectively).[7] These two competitive processes seem to be mechanistically related: 1,2-migration proceeds via metal carbene (**III**), whereas [3,3]-sigmatropic rearrangement proceeds via allenyl acetate (**V**) in a single process or stepwise by a second acetate migration from **III** (Scheme 1).[8] Allenyl acetates **V** can be further activated in the presence of the metal catalyst to give **VI**, triggering an extensive palette of transformations. It is widely accepted that terminal or electron-poor alkynes react via a 1,2-migration pathway,[9,10] whereas internal alkynes prefer the 1,3-migration pathway,[11] and only a few exceptions to this general pattern have been described.[12]

We have recently reported a new Au-catalyzed homo-Rautenstrauch rearrangement of 1-cyclopropyl propargylic esters (**1**, **2**) to give five-, six-, and also seven-membered-ring vinyl

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(6) For general reviews, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (b) Jiménez-Nuñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (c) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315.
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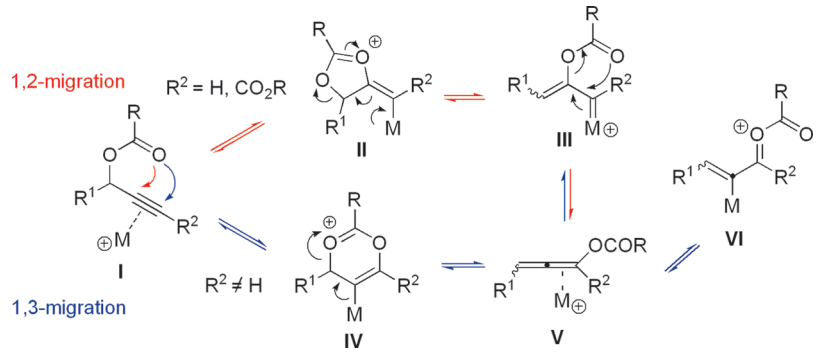
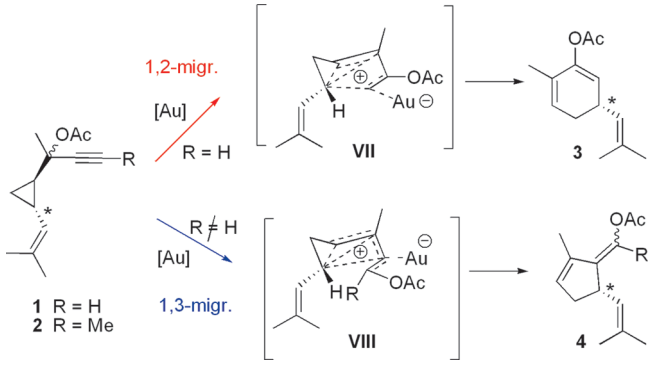
10.1021/ja909013j

Scheme 1. 1,2- vs 1,3-Carboxylate Migration

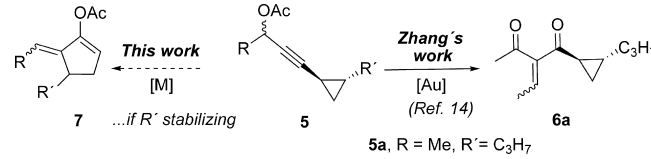


Scheme 2. Au-Catalyzed Homo-Rautenstrauch Rearrangement of 1-Cyclopropyl Propargylic Acetates



acetates under mild conditions (Scheme 2).[13] A key factor in the successful development of this transformation is the presence of a substituent at the cyclopropyl ring able to stabilize the positive electron density developed during the concomitant ring-opening process. The almost complete chirality transfer we observed in these reactions suggested that gold-stabilized nonclassical carbocations with a certain configurational stability (**VII**, **VIII**) might be involved, since enantiomerically enriched

Scheme 3. Au-Catalyzed Acetate Migration + Fission to α-Ylidene-β-diketones vs Cyclopentannulation



cyclohexadienyl (**3**) and cyclopentenyl acetates (**4**) could be obtained when optically active starting materials were employed.

To get a further insight in the reactive species involved in these transformations, we decided to explore the chemistry of related 3-cyclopropyl propargylic carboxylates **5** (Scheme 3). Such settings had already been studied by Zhang and co-workers.[14] In the presence of gold catalysts, Zhang's group developed an elegant method to obtain α-ylidene-β-diketones as a result of the 1,3-migration of the acyl group onto the alkyne moiety followed by acetate fission. The cyclopropyl ring behaved in this case as a mere spectator in the reaction (**5a** to **6a**; Scheme 3). On the basis of our previous experience, we decided to explore whether the presence of a group able to stabilize a developing positive electron density could induce the cyclopropyl ring opening to give cyclopentannulation products **7** instead.

Herein, we report our in-depth investigation on the cyclization of 3-cyclopropyl propargylic carboxylates and related species. We also present a DFT computational study on the reaction mechanism, which reveals the decisive intermediates determining the stereoselectivity of these transformations. This work also sheds light on the role of the substituents at the propargylic position in defining the reaction pathway, since products of both 1,2- and 1,3-acyloxy migration pathways have been found in these processes.

Results and Discussion

Reaction Optimization. 3-((2-Methylpropenyl)cyclopropyl propargyl)-1-phenylprop-2-ynyl acetate (**5b**) was used as a benchmark substrate to find suitable reaction conditions. The results of this optimization are summarized in Table 1. In the presence of $PtCl_2$ in toluene as solvent, no reaction was observed at room temperature (Table 1, entry 1). On heating to 80 °C, **5b** was completely consumed, affording a complex mixture of products from which the α-ylidene-β-diketone **6b** could be isolated, albeit in low yield (Table 1, entry 2). This result reflects the preference for the acetate fission pathway vs the cyclopropyl ring opening with Pt salts. We then decided to turn our attention toward gold catalysts in CH_2Cl_2 as a solvent. Treatment with

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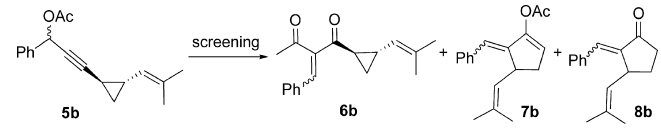
(14) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414–8415.

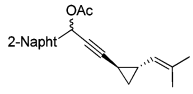
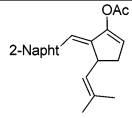
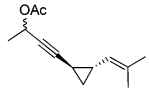
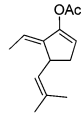
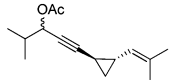
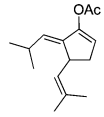
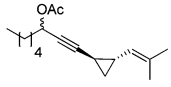
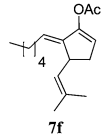
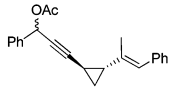
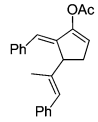
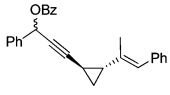
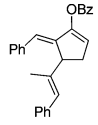
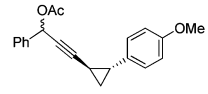
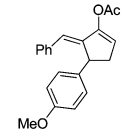
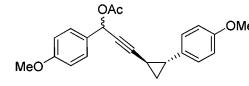
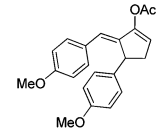
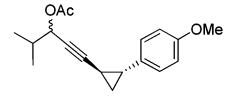
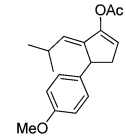
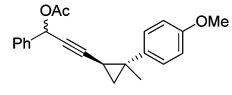
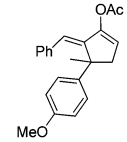
Table 1. Optimizing Reaction Conditions for the Cyclization of 3-Cyclopropyl Propargyl Acetate **5b**



entry	catalyst (mol %)	conditions	time (h)	conversn (%)[a]	yield (%)[b] (ratio **6b**:**7b**)
1	$PtCl_2$ (5)	toluene, 25 °C	15	0	
2	$PtCl_2$ (5)	toluene, 80 °C	12	100	<10 (100:0)
3	AuCl (2)	CH_2Cl_2, 25 °C	0.5	90	complex mixture
4	$[(Ph_3P)Au(NTf_2)]$ (3)	CH_2Cl_2, 25 °C	0.25	100	75 (1:8)
5	$[(Ph_3P)Au(SbF_6)]$ (3)	CH_2Cl_2, 25 °C	0.25	100	85 (1:10)
6	$LAuCl_2$[c] (5)	CH_2Cl_2, 50 °C	1	100	65 (1:>99)
7	$\{[(tBu)_2(BPH)]P\ Au(SbF_6)\}$[d] (5)	CH_2Cl_2, 25 °C	0.1	100	85 (1:>99)[e]
8	$[(IPr)Au(NTf_2)]$ (5)	CH_2Cl_2, 25 °C	0.1	100	90 (1:>99)[f]
9	$[(IPr)Au(NTf_2)]$ (5)	(i) CH_2Cl_2, 25 °C; (ii) K_2CO_3 (2 equiv), MeOH	0.1	100	75 (**8b**)[f]

[a] Conversion calculated by ^{1}H NMR. [b] Isolated yield after column chromatography. [c] L = Pyridine-2-carboxylate. [d] BPH = biphenyl. [e] Compound **7b** was obtained as a 2:1 (*E*:*Z*) mixture. [f] Compounds **7b** and **8b** were obtained as a 15:1 (*E*:*Z*) mixture.

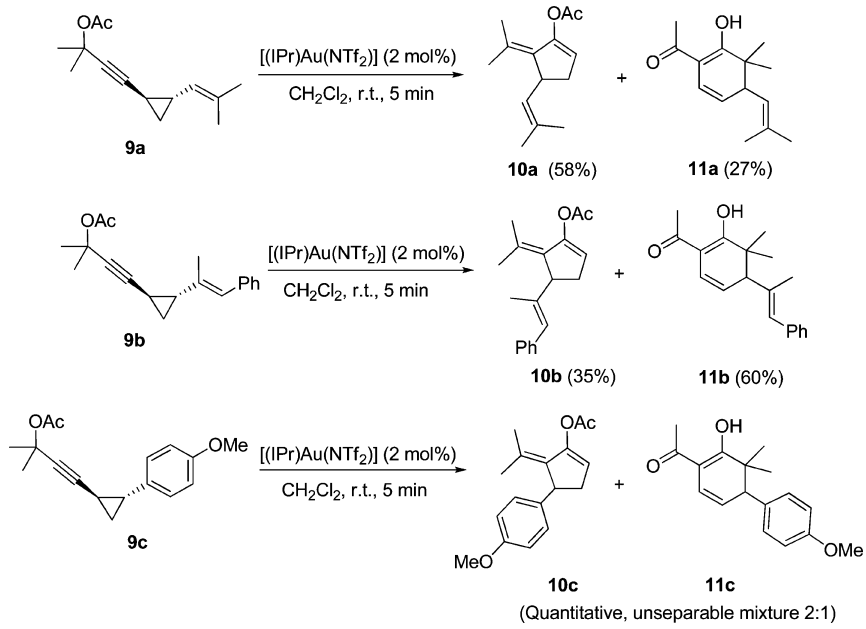
Table 2. Au-Catalyzed Cyclization of 3-Cyclopropyl Propargyl Carboxylates

Entry	substrate	conditions[a]	product[b]	yield (%)[c,d] (*E*:*Z* ratio)[e]
1	 **5c**	A	 **7c**	84 (14:1)
2	 **5d**	A	 **7d**	75 (10 : 1)
3	 **5e**	A	 **7e**	77 (7:1)
4	 **5f**	A	 **7f**	65 (50:1)
5	**5f**	B	**7f**	96 (17:1)
6	 **5g**	A	 **7g**	73 (5:1)
7	**5g**	B	**7g**	84 (10:1)
8	 **5h**	A	 **7h**	51 (14:1)
9	**5h**	B	**7h**	87 (14:1)
10	 **5i**	A	 **7i**	80 (3 : 1)
11	**5i**	B	**7i**	82 (3.4:1)
12	 **5j**	A	 **7j**	– [f]
13	**5j**	B	**7j**	75 (100:0)
14	 **5k**	A	 **7k**	84 (5:1)
15	**5k**	B	**7k**	94 (100:0)
16	 **5l**	A	 **7l**	84 (3:1)
17	**5l**	B	**7l**	86 (50:1)

[a] Reaction conditions: (A) $[(IPr)Au(NTf_2)]$ (5 mol %), CH_2Cl_2, 25 °C, 30 min; (B) dichloro(pyridine-2-carboxylato)gold(III) (5 mol %), CH_2Cl_2, 50 °C, 30 min. [b] Only the major product is shown. [c] Isolated yield after column chromatography. [d] Determined by ^{1}H NMR in the reaction mixture. [e] The yields after methanolysis of the reaction mixtures to give the corresponding ketones can be found in the Supporting Information. [f] Decomposition was observed.

gold(I) chloride delivered a complex mixture due to partial decomposition of the starting material even at room temperature (Table 1, entry 3). Cationic complexes generated by chloride abstraction from $[(Ph_3P)Au(Cl)]$ such as $[(Ph_3P)Au(NTf_2)]$ and $[(Ph_3P)Au(SbF_6)]$ provided, for the first time, cyclopentene acetate **7b** as the major product of the reaction (Table 1, entries 4 and 5). Surprisingly, dichloro(pyridine-2-carboxylato)gold(III), the catalyst of choice in Zhang's transformations,[14] did not

Scheme 4. Reaction of Tertiary Acetates with [(IPr)Au(NTf$_2$)]



produce the expected α-ylidene-β-diketone **6b** but only **7b** in moderate yield upon heating to 50 °C (Table 1, entry 6). The use of a bulky phosphine ligand as in {[(tBu)$_2$(BPH)]PAu(SbF$_6$)} afforded **7b** in 85% yield as a 2:1 (*E*:*Z*) mixture of isomers (Table 1, entry 7). Finally, [(IPr)Au(NTf$_2$)] afforded the desired alkylidene cyclopentenyl acetate **7b** in almost quantitative yield after 5 min of reaction (Table 1, entry 8). In situ methanolysis of the product produced cyclopentenone **8b** in 75% yield (Table 1, entry 9). Notably, in all the cases studied, **7b** was obtained as a variable *E*:*Z* mixture of isomers.[15]

General Reactivity. Once the reaction conditions for the selective cyclization of 3-cyclopropyl propargyl carboxylate **5b** had been established, we decided to explore the scope of this transformation. First, we focused on substrates containing secondary acetates, which proved to be unsuccessful in our previously developed homo-Rautenstrauch rearrangement reaction.[13a] The results have been summarized in Table 2. To our delight, the 2-naphthyl derivative **5c** afforded vinyl acetate **7c** in 84% yield under the optimized reaction conditions (Table 2, entry 1). The presence of alkyl substituents at the propargylic position was also examined. Thus, substrates **5d**−**f** were efficiently transformed into the corresponding cyclopentenyl acetates (**7d**−**f**) (Table 2, entries 2−5). The cyclopropyl ring cleavage can be also stabilized by a 1-phenylprop-1-en-2-yl moiety as in **5g** (Table 2, entries 6 and 7), and different migrating groups such as benzoates (**5h**) were tolerated (Table 2, entries 8 and 9). In some cases, the dichloro(pyridine-2-carboxylato)gold(III) catalyst seemed to give better results in terms of yield and/or *E*:*Z* selectivity at the exocyclic olefin compared to [(IPr)Au(NTf$_2$)] (Table 2, entries 4, 6, 8, 10, 12, 14, 16 vs 5, 7, 9, 11, 13, 15, 17). Remarkably, except for **5j**, both catalysts delivered clean and complete conversions and no α-ylidene-β-diketones (**6**) were observed. As was mentioned above, *E* isomers were always obtained as major products of these reactions.[15] Attempts to transform *Z* into thermodynamically favored *E* isomers in the presence of gold catalysts failed.[16]

(15) The *E* configuration of the major isomer was assigned on the basis of NOE studies.

The determining step for the *E* vs *Z* exocyclic alkene formation seems to be thus under kinetic control.

Cyclization of Tertiary Acetates. We focused next on the reaction of tertiary propargyl acetates, which have unraveled interesting mechanistic features of these transformations. When substrate **9a** was treated with [(IPr)Au(NTf$_2$)] (5 mol %) in CH_2Cl_2 at room temperature, the expected product **10a** was obtained in 58% yield. A careful analysis of the reaction mixture revealed the formation of 1,3-diketone **11a** isolated in 27% yield in its enolic form (Scheme 4). A similar behavior in the presence of [(IPr)Au(NTf$_2$)] as catalyst was observed for substrates **9b**,**c**, affording cyclopentenyl acetates **10b**,**c** and diketones **11b**,**c** in 1:2 and 2:1 ratios, respectively. *In our view, formation of* **11a**−**c** *can be explained by a 1,2-acetoxy migration pathway followed by cyclopropyl ring opening and cyclization terminating with the fission of the acetate group.* Formation of products from both 1,2- and 1,3-acyloxy migration pathways from the same substrate under a certain set of conditions is rare and deserves further attention. Computational studies on these systems have been performed, and the results will be discussed in a later section.

After extensive experimentation, we found that treatment of **9a** with [(PhO)$_3$PAu(SbF$_6$)] (5 mol %) allowed the clean formation of cyclopentenyl acetate **10a** in 81% yield (Table 3, entry 1). Similarly, **10b**−**d** were efficiently produced under the same reaction conditions (Table 3, entries 2−4). The reaction of cyclopentyl- and cyclohexyl-substituted derivatives **9e**,**f** proceeded cleanly at −20 °C to give products **10e**,**f** in 85%

(16) Compound **7b** was treated with catalytic amounts of IPrAuNTf$_2$, LAuCl$_2$ (L = pyridine-2-carboxylate), and [(Ph$_3$P)Au(NTf$_2$)], first at room temperature and then at 50 °C without any remarkable change in the isomeric ratio of the exocyclic alkene.

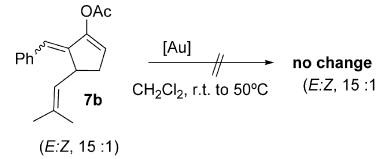
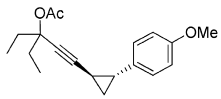
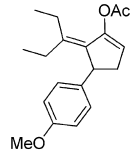
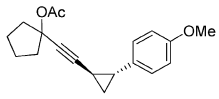
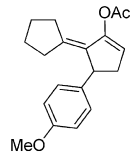
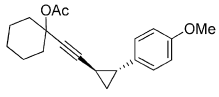
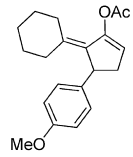
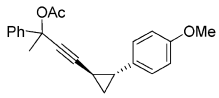
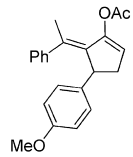


Table 3. Au-Catalyzed Cyclization of 3-Cyclopropyl Propargyl Tertiary Carboxylates

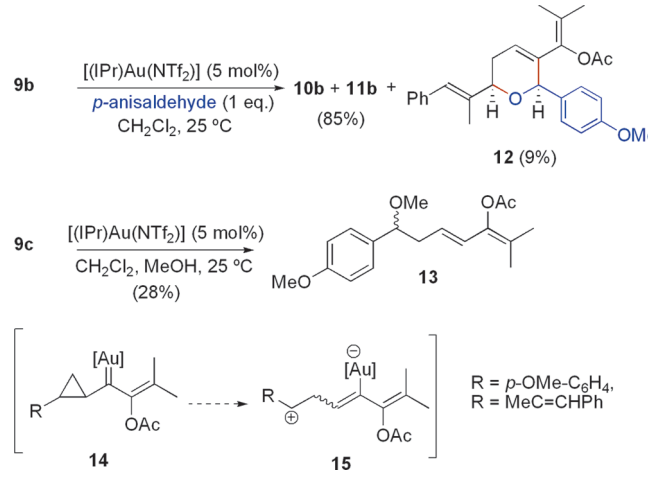
Entry	substrate	reaction conditions[a]	product[b] (yield, %)
1	**9a**	$[(PhO)_3PAu(SbF_6)]$, T^a = 25 °C, 30 min	**10a** (81)
2	**9b**	$[(PhO)_3PAu(SbF_6)]$, T^a = 25 °C, 30 min	**10b** (90)
3	**9c**	$[(PhO)_3PAu(SbF_6)]$, T^a = 25 °C, 1 h	**10c** (78)
4	 **9d**	$[(PhO)_3PAu(SbF_6)]$, T^a = 25 °C, 1 h	 **10d** (71)
5	 **9e**	$[(PhO)_3PAu(SbF_6)]$, T^a = - 20 °C, 1 h	 **10e** (85)
6	 **9f**	$[(PhO)_3PAu(SbF_6)]$, T^a = - 20 °C, 1 h	 **10f** (85)
7	 **9g**	$[(PhO)_3PAu(SbF_6)]$, T^a = 25 °C, 1 h	 **10g** (78)[c]

[a] Reactions run in CH_2Cl_2 as solvent with 5 mol % catalyst. [b] Isolated yield after column chromatography. [c] Obtained as a 4:1 (*E*:*Z*) mixture of isomers.

yield (Table 3, entries 5 and 6). Finally, compound **9g** was cyclized to give **10g** as a 4:1 mixture of isomers (Table 3, entry 7).[15]

To further confirm the 1,2-acetoxy migration pathway operating in the reaction of tertiary acetates with $[(IPr)Au(NTf_2)]$ as catalyst, the following experiments were designed (Scheme 5). Reaction of **9b** in the presence of 1 equiv of *p*-anisaldehyde gave a mixture of **10b** and **11b** in 85% yield together with dihydropyran **12** in 9% yield. The latter can be explained by a [4C + 2C] cycloaddition reaction between the 1,4-dipole **15** (generated in situ along the 1,2-migration path) and *p*-anisaldehyde as dipolarophile.[17] On the other hand, when **9c** was treated with $[(IPr)Au(NTf_2)]$ in MeOH as a cosolvent, compound **13** was isolated in 28% yield. Formation of both **12** and **13** is a clear indication of a 1,2-acyloxy migration manifold via

Scheme 5. Evidence for the 1,2-Acyloxy Migration Pathway in the Reaction of Tertiary Acetates with $[(IPr)Au(NTf_2)]$ as Catalyst



intermediates **14** and **15** operating in competition with the predicted [3,3]-acyloxy rearrangement.

The results summarized in Schemes 4 and 5 and Table 3 can be explained in light of the distinct nature of the reaction intermediates depending on the ligand bound to the gold center.[18] $[(PhO)_3PAu(SbF_6)]$ displays a more electrophilic character compared to $[(IPr)Au(NTf_2)]$, due to the π-acceptor phosphite ligand. The decrease in the gold-to-C π-donation might enhance the carbocationic character of the reaction intermediates, thus favoring the cyclopentannulation products (**10**). In contrast, the IPr (1,3-bis(2,6-disiopropylphenyl)imidazol-2-ylidene) ligand is strongly σ-donating and only weakly π-acidic, thus increasing the carbene-like reactivity favoring intermediate **14** (also preferred by steric reasons) over the allene intermediate and thus triggering the formation products such as **11**−**13**.

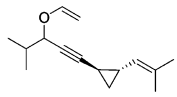
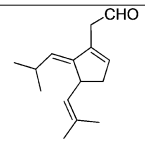
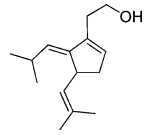
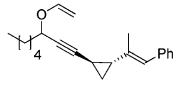
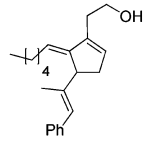
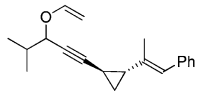
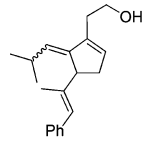
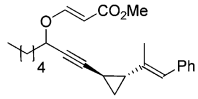
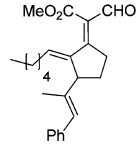
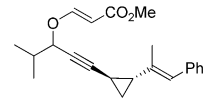
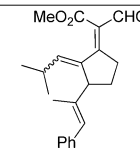
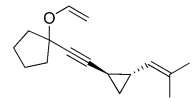
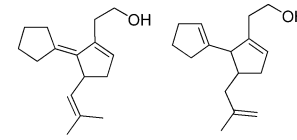
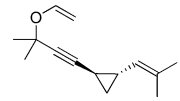
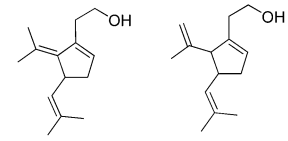
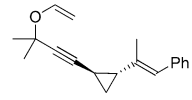
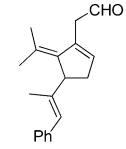
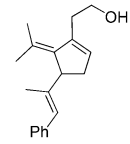
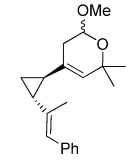
Cyclization of Propargyl Vinyl Ethers. In addition to carboxylic groups (acetates, benzoates, etc.), propargyl vinyl ethers are also suitable motifs for rearrangement across the triple bond upon metal activation.[19] We expected to form two new C−C bonds by coupling the [3,3]-sigmatropic rearrangement to the cyclopropyl ring-opening reaction. Thus, substrate **16a** was treated with $[(IPr)Au(NTf_2)]$ (5 mol %), delivering the corresponding cyclopent-1-enyl aldehyde **17a** in 71% yield (Table 4, entry 1).[15] To achieve higher yields, the Au-catalyzed cyclization was coupled to an in situ reduction of the aldehyde with $NaBH_4$, as previoustly reported by Toste and co-workers (Table 4, entry 2).[19b] A similar protocol was applied for substrates **16b**,**c**, which gave the corresponding alcohols **18b**,**c** in excellent yields (Table 4, entries 3 and 4). Interestingly, electron-deficient vinyl ethers such as **16d**,**e** were cleanly transformed into the corresponding (*Z*)-methyl-2-(2-methylenecyclopentylidene)-3-oxopropanoates **17d**,**e** under the aforementioned reaction conditions (Table 4, entries 5 and 6).[15] It is important to note that no heterocyclization on the allenyl carbonyl intermediate to give 3-cyclopropyl-substituted furans was observed, as previously reported by Kirsch and co-workers for similar settings.[20] In contrast to the mechanistic dichotomy

(17) (a) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814–1815. (b) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598–12599.

(18) (a) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nature* **2009**, *1*, 482–486. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.

(19) (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979. (b) Benjamin, D. S.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132–8133.

Table 4. Au-Catalyzed Cyclization of 3-Cyclopropyl Propargyl Enol Ethers

Entry	substrate	conditions[a]	product(s), (yield, %),[b,c] (*E*:*Z* ratio)[d]
1	 **16a**	A	 **17a** (71), (2:1)
2	**16a**	B	 **18a** (97), (2:1)
3	 **16b**	B	 **18b** (88), (3:1)
4	 **16c**	B	 **18c** (88), (1:1)
5	 **16d**	A	 **17d** (97), (5:1)
6	 **16e**	A	 **17e** (82), (1:1)
7	 **16f**	B[e]	 **18f** + **18f′** (90, 17:1 ratio)
8	 **16g**	B[e]	 **18g** + **18g′** (75, 5:1 ratio)
9	 **16h**	A[e]	 **17h** (58)
10	**16h**	B[e]	 **18h** (70)  **19** (10)

[a] Reaction conditions (A) [(IPr)Au(NTf_2)] (5 mol %), CH_2Cl_2, 25 °C, 30 min; (B) (i) [(IPr)Au(NTf_2)] (5 mol %), CH_2Cl_2, 25 °C, 30 min, (ii) $NaBH_4$ (5 equiv), MeOH. [b] Only the major product is shown. [c] Isolated yield after column chromatography. [d] Determined by ^1H NMR in the reaction mixture. [e] Reaction time 90 min.

manifold observed in the migration of tertiary acetates with [(IPr)Au(NTf_2)], the rearrangement of tertiary vinyl ethers under similar reaction conditions delivered only the products derived from a propargyl-Claisen rearrangement. Substrates **16f**,**g** with a 2-methyl-2-propen-1-yl substituent at the cyclopropyl ring delivered upon $NaBH_4$ reduction the expected alcohols **18f**,**g** together with **18f′**,**g′** (Table 4, entries 7 and 8).[21] The reaction of **16h** afforded aldehyde **17h** in modest yield (Table 4, entry 9), whereas the reductive workup in MeOH allowed us to isolate alcohol **18h** in 70% yield and a small amount of **19**. The latter is presumably formed by trapping the carbocationic intermediate formed during [3,3]-rearrangement in the first step of the reaction with MeOH, which is used as solvent in the subsequent step (Table 4, entry 10).[19b]

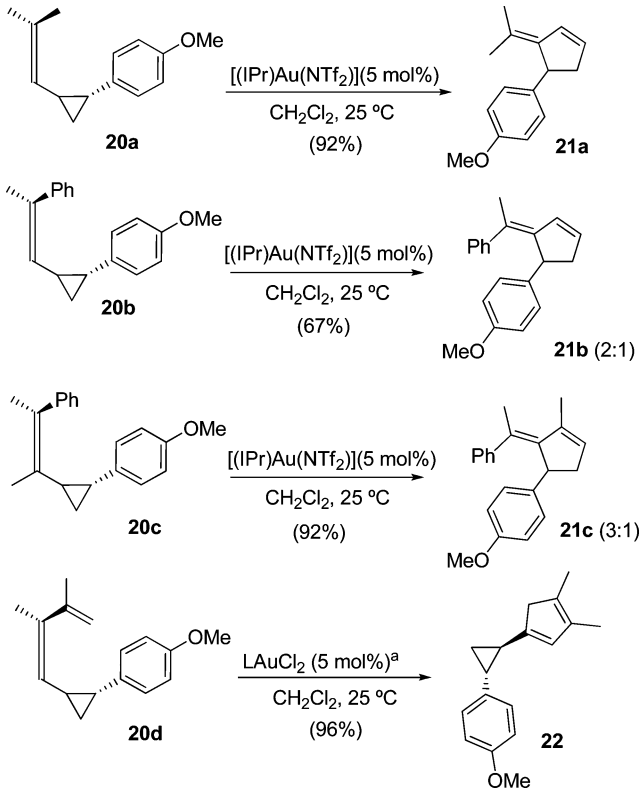
Cyclization of Non-activated Allenes. The cyclization of propargylic esters and enol ethers presented above presumably proceed by the formation of an oxo-allene intermediate (see **V** in Scheme 1) upon Au-catalyzed [3,3]-sigmatropic rearrangement. To further confirm this hypothesis, we decided to explore the reactivity of "non-activated" cyclopropyl allenes in the presence of gold complexes. We were pleased to observe that substrate **20a** reacted in the presence of 5 mol % of [(IPr)Au(NTf_2)] to afford the 2-(ethylidene)cyclopent-3-enyl species **21a** in excellent yield following the previously proposed sequence: gold activation of the allene−cyclopropyl ring-opening−cyclization (Scheme 6). Tri- and tetrasubstituted allenes were well tolerated, as shown by the reactions of **20b**,**c** to give cyclopentenes **21b**,**c** in 67 and 92% yields, respectively. When a 1-methyleth-2-enyl substituent is placed at the terminal position of the allene (**20d**), the reaction in the presence of [(IPr)Au(NTf_2)] afforded a complex reaction mixture. In the presence of dichloro(pyridine-2-carboxylato)gold(III), a clean 6-π-electron cyclization takes place to give bicyclic compound **22** in almost quantitative yield, as previously reported by other groups.[22]

Mechanistic Discussion. A simplified vision of the cyclization of 3-cyclopropyl propargylic acetate **5** presumably involves allenyl intermediate **IX**, which undergoes ring expansion to form the 1,5-dipole **X**, where the carbocation is stabilized by aromatic

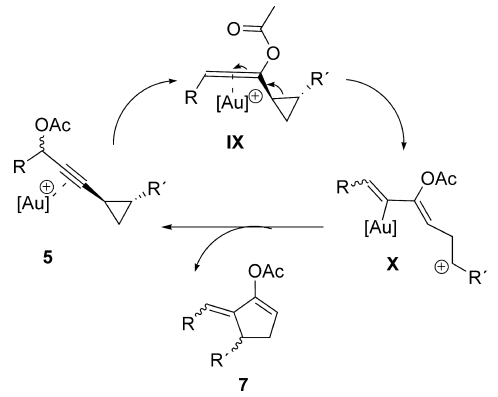
(20) (a) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925–3927. (b) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151–2153.

(21) Longer reaction times and the Au catalyst seem to be crucial for this somewhat unexpected isomerization,which is currently the focus of further mechanistic studies.

Scheme 6. Cyclization of 3-Cyclopropyl Allenes



Scheme 7. Simplified Mechanism for the Cyclopentannulation Reaction of 3-Cyclopropyl Propargyl Acetates



or vinylic groups. From **X**, a cyclization to form alkylidene cyclopentenyl acetates **7** can be proposed (Scheme 7).

To gain a deeper insight into the reaction intermediates defining the stereochemistry of the exocyclic double bond, the different behavior of secondary vs tertiary carboxylates, and a potential chirality transfer in this process, we performed DFT calculations on the model gold(I) complex **XI**.[23]

Allenyl Acetate Formation. The Au(I) complex of (*S*)-4-((1*R*,2*S*)-2-vinylcyclopropyl)but-3-yn-2-yl acetate **XIa** reacts through $\mathbf{TS_{XIa\text{-}XIIa}}$ ($\Delta H^{\ddagger} = 6.5$ kcal/mol) and $\mathbf{TS_{XIIa\text{-}XIIIa}}$ ($\Delta H^{\ddagger} = 2.8$ kcal/mol) to give gold coordinated allene **XIIIa** in a reversible and slightly endothermic process ($\Delta H = 0.4$ kcal/mol) (Scheme 8).[24] **XIIIa** shows a clear "allene" character, with gold coordinated to the more external double bond and the four allenyl substituents disposed perpendicularly resembling the gold-coordinated minimized structures of simple allenes **20a**−**d** (Scheme 6). **XIIIa** is in equilibrium with the more cationic-type derivative **XIVa** through $\mathbf{TS_{XIIIa\text{-}XIVa}}$ ($\Delta H^{\ddagger} = 3.4$ kcal/mol) thermodynamically more stable ($\Delta H = -4.0$ kcal/mol), where the internal double bond is now activated, leaving the gold almost exclusively coordinated to the central carbon atom of the allene.[25] From **XIIIa**, the formation of the *E*-configured vinyl gold derivative **XIVd** can also be envisioned, although, for the sake of clarity, only **XIIIa** will be considered here (a complete version of Scheme 8 summarizing all possible isomers can be found in the Supporting Information).[26] The stereochemical information of the acetate at the propargylic position is lost by the low barrier transition state $\mathbf{TS_{XIVa\text{-}XIVb}}$ ($\Delta H^{\ddagger} = 3.1$ kcal/mol), which converts **XIVa** into its enantiomer **XIVb** in a slightly exothermic transformation ($\Delta H = -0.7$ kcal/mol). On the other hand, **XIVb** could also arise from **XIb** in a manner analogous to that described above. Such an epimerization event is well precedented experimentally[27] and was recently studied by the groups of Malacria[25] and Toste.[13b,19]

Cyclization Step. The next step along the reaction coordinate involves cyclopropyl ring opening and C−C bond formation to give the cyclopentannulation products. The parallel reactions of the four isomers **XIVa**−**d** were computed, although for the sake of clarity, only the structures of intermediates derived from **XIVa** are explicitly shown (Scheme 9, left). The relative energies for the other isomers (**XIVb**, epimer at the carbon bearing the acetate; **XIVc**,**d**, (*E*)-vinyl gold isomers) have been summarized in the right-hand side of Scheme 9. Thus, from **XIVa** two adjacent transition states, one higher in energy ($\mathbf{TS_{XIVa}(1)}$; $\Delta H^{\ddagger} = 19.9$ kcal/mol) and a second one being lower in the reaction profile ($\mathbf{TS_{XIVa}(2)}$; $\Delta H^{\ddagger} = 10.9$ kcal/mol) were found to deliver cyclopentene acetate **XVa** without an intervening intermediate.[28] Interestingly, $\mathbf{TS_{XIVa}(1)}$ can be described as a gold-stabilized nonclassical carbocation related to those proposed in Scheme 2.[13a,29] On the other hand, $\mathbf{TS_{XIVa}(2)}$ constitutes a "bifurcation point" in the reaction profile, which can evolve either to cyclopentenyl **XVa** or toward the six-membered ring **XVIa**, although formation of **XVa** is thermodynamically much more favorable ($H_{\mathbf{XVa}} = -36.7$ kcal/mol vs $H_{\mathbf{XVIa}} = -17.1$ kcal/mol). The product of a β-hydride elimination in **XVIa** would yield cyclohexadiene **XVIIa**, which was never detected experimentally.

(22) (a) Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207–2209. (b) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006. (c) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 909–911. (d) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912–914.

(23) Calculations performed with Gaussian 03 (full reference in the Supporting Information).

(24) Alternatively, a double 1,2-migration of the acetoxy moiety could also explain the formation of allenyl intermediate **XIII**. For an in-depth study on this possibility, see ref 8.

(25) Gandon, V.; Lemière, G.; Hours, A.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7534–7538.

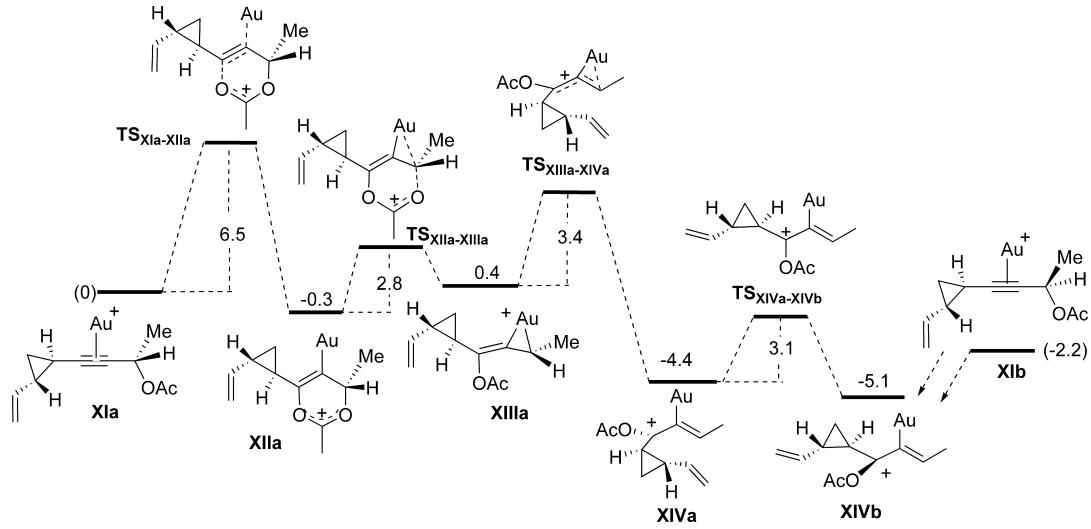
(26) Further details can be found in the Supporting Information.

(27) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875–944.

(28) $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVa}(2)}$ form a two-step no-intermediate system. For related examples, see: Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 1319–1328.

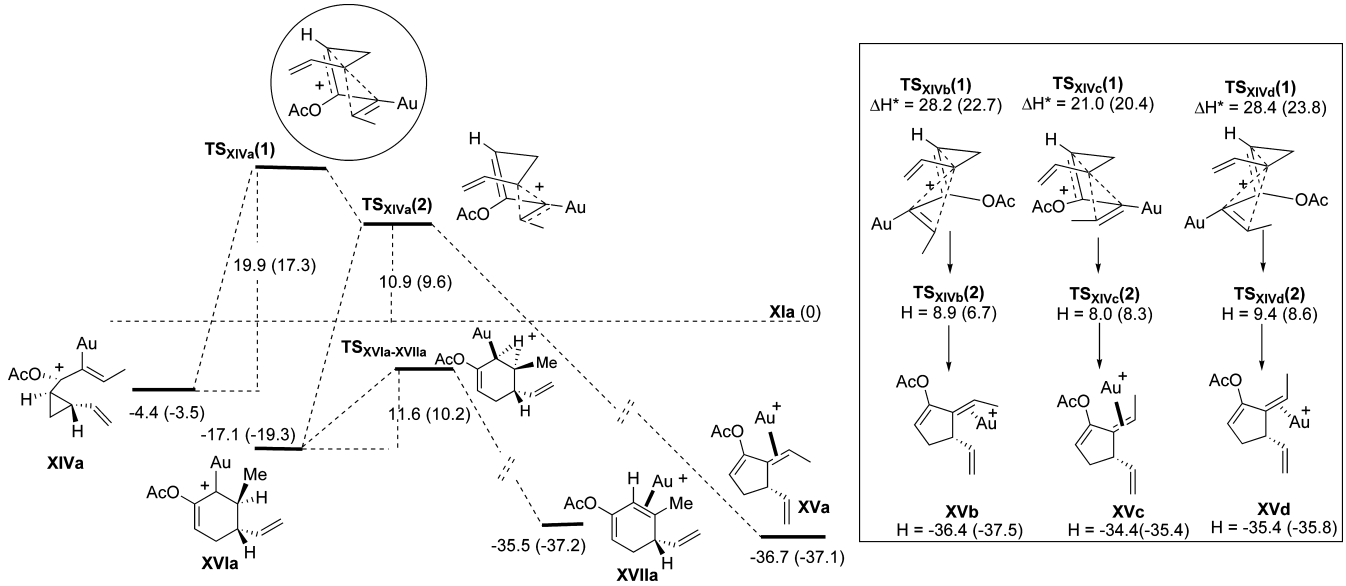
(29) (a) Olah, G.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69–95. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869. (c) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245. (d) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030–5033.

Scheme 8. Reaction Coordinate Diagram for the [3,3]-Acetoxy Migration of **XIa** to Cationic Intermediate **XIVa**,**b**[a]



[a] Calculations were carried out at the B3LYP/6-31G(d) (C, H, O) and LANL2DZ (Au) levels (+ZPE corrected energies are given in kcal/mol). Au = (IPr)Au.

Scheme 9. Reaction Coordinate Diagram for the Cyclopentannulation of **XIVa**[a]



[a] Calculations were carried out at the B3LYP/6-31G(d) (C, H, O) and LANL2DZ (Au) levels (+ZPE corrected energies are given in kcal/mol; values in brackets are those considering solvent effects (CH_2Cl_2)). Au = (IPr)Au.

Solvent effects (CH_2Cl_2) were considered in these calculations (energy values in brackets in Scheme 9). As expected, the energies of all **TS(1)** species are lower than those in the gas phase, since the stabilization of the carbocation retards the cyclopropyl ring opening and promotes the formation of the cycle. More importantly though, the energies of all **TS(1)** species are still higher than those of **TS(2)**, so that the first step remains the rate-limiting step.

Since the stereochemistry observed in the exocyclic olefin of cyclopentene acetates **7** seems to be under kinetic control,[16] transition states $\mathbf{TS_{XIVa\text{-}d}(1)}$, higher in energy than $\mathbf{TS_{XIVa\text{-}d}(2)}$, were closely examined. In $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVc}(1)}$, we observe that the configuration at C_6 of the cyclopropyl ring forces an "endo" reaction, where the Au−C bond is always oriented toward the cyclopropyl ring, whereas $\mathbf{TS_{XIVb}(1)}$ and $\mathbf{TS_{XIVd}(1)}$, higher in energy, present an "exo" approach, where the cyclization takes place from the opposite side of the cyclopropyl ring (Scheme 9). $\mathbf{TS_{XIVa\text{-}d}(1)}$ shows an early carbocation being formed at C_6 with the cyclopropyl unit almost intact. The δ^+ developing in the incipient carbocation interacts with the electron-rich vinyl gold forming a pseudo-six-membered ring cycle in a boat conformation (Figure 1).

In the two transition states of lower energy, $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVc}(1)}$, the substituents at C_1 and C_6 are eclipsed. This unfavorable eclipsing interaction is enhanced in $\mathbf{TS_{XIVc}(1)}$, where methyl and vinyl groups are in pseudoaxial positions (Figure 1, right upper row). Therefore, for each couple, the transition states displaying the Au and Me in a "syn" disposition have an activation energy lower than those with both groups in a "trans" disposition ($\mathbf{TS_{XIVa}(1)} < \mathbf{TS_{XIVc}(1)}$ and $\mathbf{TS_{XIVb}(1)} < \mathbf{TS_{XIVd}(1)}$). These observations led us to conclude that the lower energy reaction path goes from **XIVa** via $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVa}(2)}$, yielding (*E*)-cyclopentenyl acetate **XVa** as a major product under

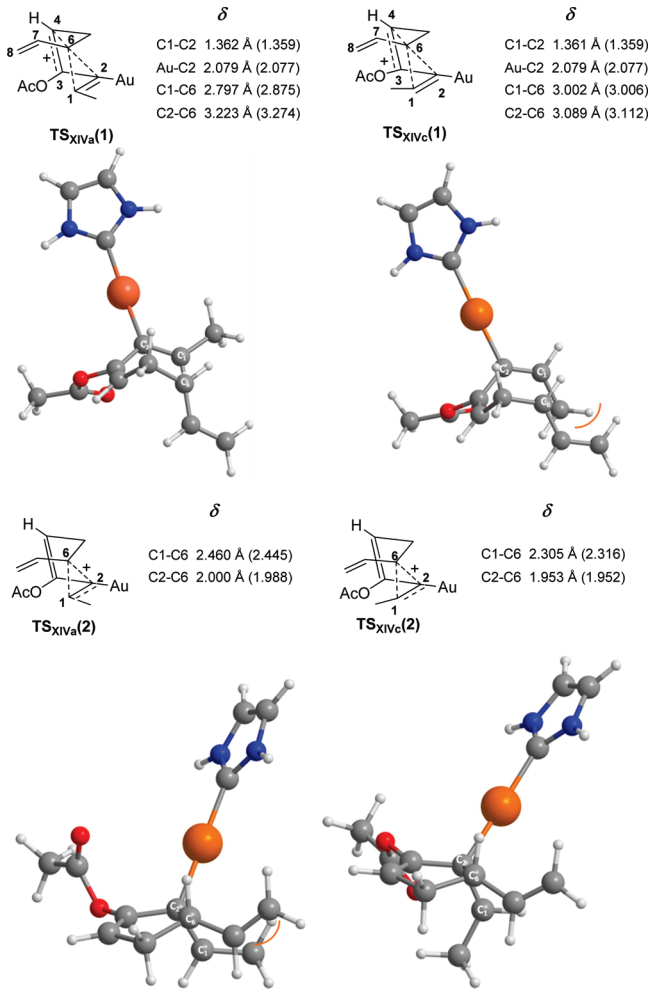


Figure 1. (Upper row) Structures of transition states $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVc}(1)}$, highlighting the interaction between the cyclopropyl ring and the vinyl gold moiety and the eclipsed interaction between substituents C_1 and C_6 and relevant distances (values in brackets are those considering solvent effects). (Lower row) Structures of transition states $\mathbf{TS_{XIVa}(2)}$ and $\mathbf{TS_{XIVc}(2)}$ highlighting the steric interaction between methyl at C_1 and vinyl at C_6 and relevant distances (values in brackets are those considering solvent effects). Au = (IPr)Au.

kinetic control, although the *E* product (**XVa**) is also thermodynamically more stable than **XVc**.[16]

The stabilizing effect of the vinylic (or aromatic) substituent by delocalization of the δ^+ generated upon cyclopropyl ring opening can be easily rationalized by looking at the key C−C distances in the transition states. In fact, the C_6-C_7 and the $C_7=C_8$ distances measured in **XIa** and **XIVa** are 1.48, 1.47 Å and 1.33, 1.34 Å, respectively. In contrast, in $\mathbf{TS_{XIVa(1)}}$, the distances reflect the more allylic character of the vinyl moiety with values of 1.42 and 1.36 Å. Furthermore, the NBO analysis of $\mathbf{TS_{XIVa(1)}}$ shows a strong interaction (63.8 kcal/mol) between the π orbital of the double bond and the empty developing orbital on C_6, which is not present either in **XIa** or in **XIVa**. This strong interaction is also reflected in the analysis of the partial charges, which shows an increasing positive charge (+0.2 e) in the vinyl moiety of $\mathbf{TS_{XIVa(1)}}$ vs the value measured in **XIa** (+0.06 e).

In the second transition states ($\mathbf{TS_{XIVa}(2)}$, $\mathbf{TS_{XIVc}(2)}$) a complete rupture of the cyclopropyl ring can be observed, with the fully developed carbocation in close interaction with the metal−vinyl bond ($\mathbf{TS_{XIVa}(2)}$, $d(C_2-C_6) = 2.0$ Å and $\mathbf{TS_{XIVc}(2)}$, $d(C_2-C_6) = 1.953$ Å). In contrast with the steric interactions analyzed for $\mathbf{TS_{XIVa}(1)}$ vs $\mathbf{TS_{XIVc}(1)}$, the stronger steric congestion occurs between vinyl and methyl groups in $\mathbf{TS_{XIVa}(2)}$, disfavoring it compared to $\mathbf{TS_{XIVc}(2)}$ (Figure 1, lower row). Nevertheless, since these are the lower energy transition states in the reaction coordinate, they have no influence in the structure of the final products. Solvent effects also influence the key C−C distances (C_1-C_2, C_1-C_6, C_2-C_6, $Au-C_2$), which are slightly shorter in the gas phase (Figure 1).

1,2- vs 1,3-Acyloxy Migration. The results obtained with tertiary acetates and [(IPr)Au(NTf_2)] (Schemes 4 and 5), where products presumably arising from both 1,2- and 1,3-acyloxy migration paths could be isolated, prompted us to study this mechanistic dichotomy more in depth. Previous work in this area has shown how minimal changes in the structure of starting materials, catalysts, etc. can play a key role in the preference for one of these two reaction manifolds.[8] Our computational models were the IPrAu complexes of (*S*)-4-((1*R*,2*S*)-2-*p*-methoxyphenylcyclopropyl)but-3-yn-2-yl acetate (**XVIII**) and 2-methyl-4-((1*R*,2*S*)-2-*p*-methoxyphenylcyclopropyl)but-3-yn-2-yl acetate (**XVIII′**), respectively (Scheme 10).

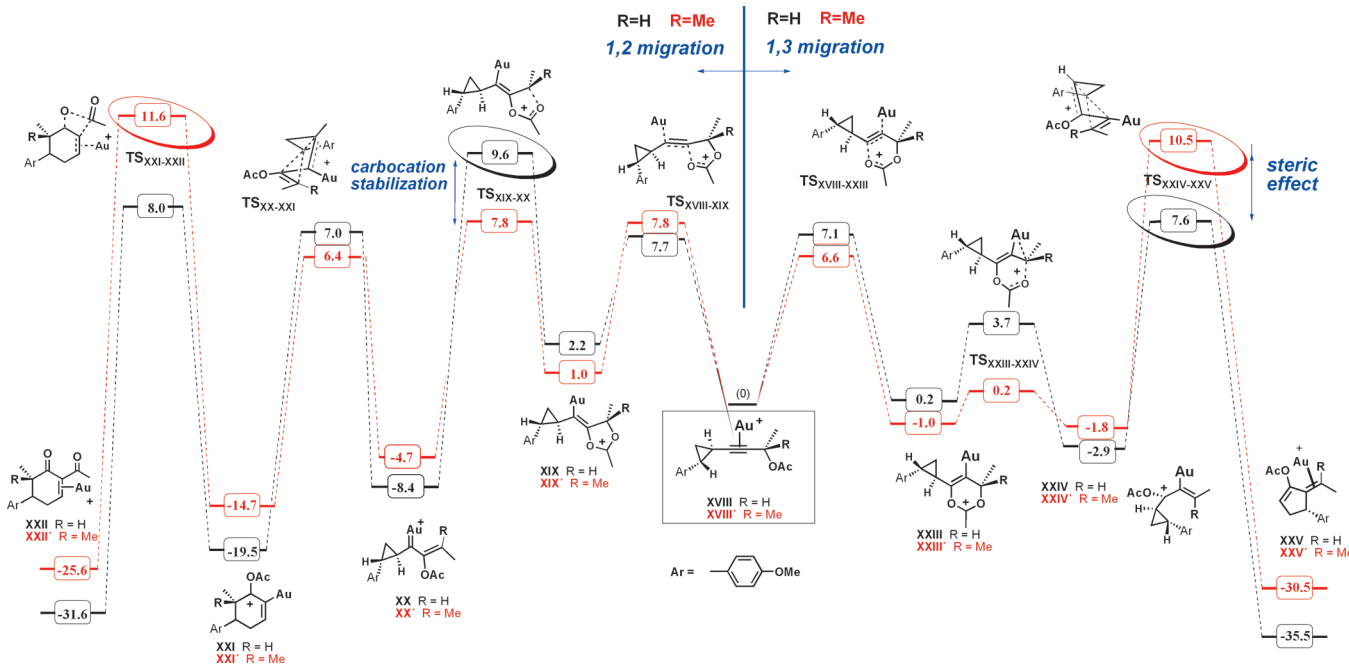
For the secondary acetate **XVIII** (route in black), the reaction coordinate following a 1,2-acetoxy migration (left path) has in $\mathbf{TS_{XIX\text{-}XX}}$ the higher energy barrier ($\Delta H^{\ddagger} = 9.6$ kcal/mol), whereas the 1,3-migration (right path) proceeds smoothly by the previously described intermediates, with lower activation energy for the determining step $\mathbf{TS_{XXIV\text{-}XXV}}$ ($\Delta H^{\ddagger} = 7.6$ kcal/mol), which could explain why no products derived from a 1,2-acetoxy migration were found in the reaction of secondary acetates.

In sharp contrast, for the tertiary acetate **XVIII′** (route in red) the steric hindrance caused by the presence of two methyl groups at the propargylic position raises the activation energy along the 1,3-migration pathway (right path) to almost 10.5 kcal/mol for $\mathbf{TS_{XXIV\text{-}XXV}}$. This barrier is now comparable to the energy needed in the 1,2-migration path via $\mathbf{TS_{XXI\text{-}XXII}}$ (11.6 kcal/mol). Since the system can be considered under Curtin−Hammet conditions (from **XVIII′** to **XXI′**−**XXIV′**), the product composition will depend on the difference in energies between the respective transition states ($\Delta\Delta H^{\ddagger} = 1.1$ kcal/mol) thus becoming competitive. It is important to mention that, as shown in Scheme 5, products arising from the cyclopropyl ring opening of **XVIII′** have been isolated in the reaction, which has never been the case for the secondary acetate derivatives **XVIII**.

Chirality Transfer. The interesting issue of a possible chirality transfer in these systems was addressed both experimentally and computationally. The optically active substrates **23** and **24** were prepared from (1*R*,3*R*)-(−)-*trans*-chrysanthemum acid (99% ee) (Scheme 11).[26] In sharp contrast with our previous results obtained with 1-cyclopropyl propargyl acetates,[13a] the cycloisomerization of **23** (dr = 1:1, 99% de) under standard conditions with different catalytic systems afforded, after methanolysis, cyclopentanone **25** in 61% ee in the best case using pyridine-2-carboxylate gold(III) catalyst. A similar behavior was observed for tertiary acetate **24**, which upon treatment with [$(PhO)_3PAu(SbF_6)$] (5 mol %) and methanolysis afforded **26** in only 50% ee.[30]

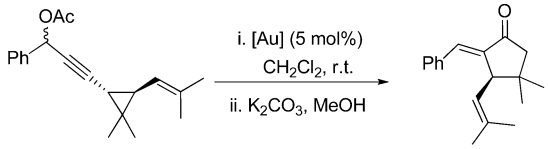
These results prompted us to re-examine our mechanistic proposal for these cycloisomerizations. According to the calculations presented in Scheme 9, the reaction is stereospecific,

Scheme 10. Reaction Coordinate Diagrams for the 1,2- vs 1,3-Acyloxy Migration of Secondary vs Tertiary Propargyl Acetates [a]



[a] Calculations were carried out at the B3LYP/6-31G(d) (C, H, O) and LANL2DZ (Au) levels (+ZPE corrected energies are given in kcal/mol). Au = (IPr)Au.

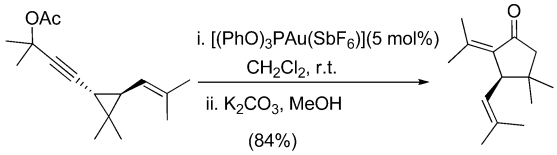
Scheme 11. Chirality Transfer of Compounds **23** and **24**



23 (d.r. 1:1, 99% de) **25**

[Au]	ee %
$[(IPr)Au(NTf)_2$	35%
$LAuCl_2$[a]	61%
$[(Ph_3P)Au(SbF_6)]$	35%
$[(PhO)_3PAu(SbF_6)]$	19%

[a] Pyridine-2-carboxylate



24 (ee > 99%) **26** (50 % ee)

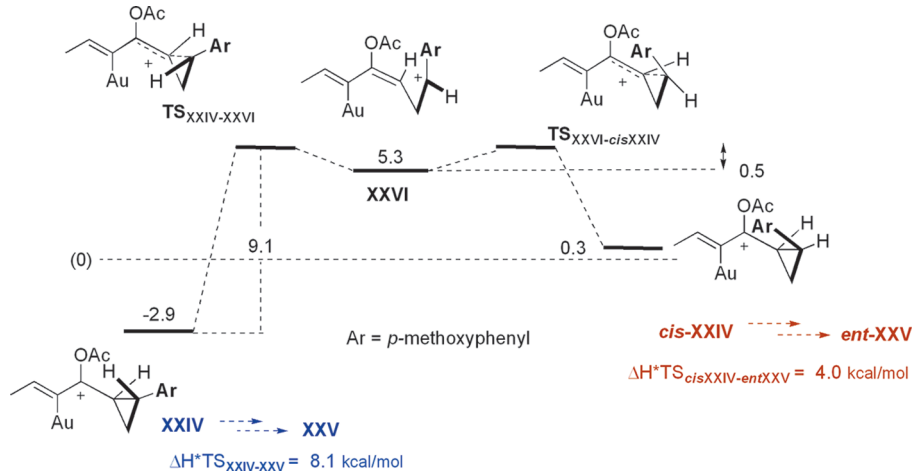
since the ring opening of the cyclopropyl via gold-stabilized carbocations $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVa}(2)}$ takes place with retention of the configuration, which in principle should be translated in the final products. A careful ^{1}H NMR analysis of the reaction of *trans*-**5k** in the presence of $[(IPr)Au(NTf_2)]$ or pyridine-2-carboxylate gold(III) showed that, in addition to the expected scrambling at the propargylic position as predicted in Scheme 8,[31] a partial epimerization at the cyclopropyl occurred prior to the cyclization event.[26] A computational study revealed a reaction pathway that could account for such configurational instability (Scheme 12).[26] First, **XXIV** can undergo a cyclopropyl ring opening via $\mathbf{TS_{XXIV\text{-}XXVI}}$ to give the high-energy intermediate **XXVI**. The process is endothermic due to the intrinsically unstable nature of such a purely carbocationic intermediate, even if the calculation takes into account solvent effects (ΔH = 8.2 kcal/mol). Upon C−C rotation via $\mathbf{TS_{XXVI\text{-}\textit{cis}\text{-}XXIV}}$, the minor isomer ***cis*-XXIV** is formed. The activation barriers to transform **XXIV** into ***cis*-XXIV** are comparable to those obtained for the cyclopentannulation process and summarized in Scheme 10. Therefore, we have to assume that even if the cycloisomerization is an intrinsically stereospecific process, a competitive epimerization at the cyclopropyl moiety can erode the chirality transfer of these transformations. To understand the loss of chirality by such a mechanism, **XXIV** should be in equilibrium with cyclopropyl propargyl acetate **XVIII** (or analogously, **XIVa** with **XIa**), which seems to be the case according to the energy barriers summarized in Schemes 8 and 10. A final requirement involves the transformation of ***cis*-XXIV** into the final cyclopentenyl acetate ***ent*-XXV**, which seems to be possible according to the $\Delta H^{\ddagger}$ values obtained for such process, comparable to those obtained for the trans product ($\Delta H^{\ddagger}(\mathbf{TS_{XXIV\text{-}XXV}})$ = 8.1 vs $\Delta H^{\ddagger}(\mathbf{TS_{\textit{cis}\text{-}XXIV\text{-}\textit{ent}XXV}})$ = 4.0 kcal/mol, considering solvent effects in both cases).

Acetate Fission vs Cyclopropyl Ring Opening. Finally, from intermediates of type **XIVa**, we decided to study the competitive acetate fission process to give α-ylidene-*β*-diketones **XXVIIa**, as previously described by Zhang and co-workers.[14] The activation energy for the attack of a metal−vinyl bond into the acetate $\mathbf{TS_{XIVa\text{-}XXVIIa}}$ is approximately 25−26 kcal/mol, independent of the substituent at the cyclopropyl ring (Scheme 13,

(30) The absolute configuration shown here for the cyclopentenone products was proposed on the basis of our previous results on the cyclization of 1-cyclopropyl propargyl acetates.[13a]

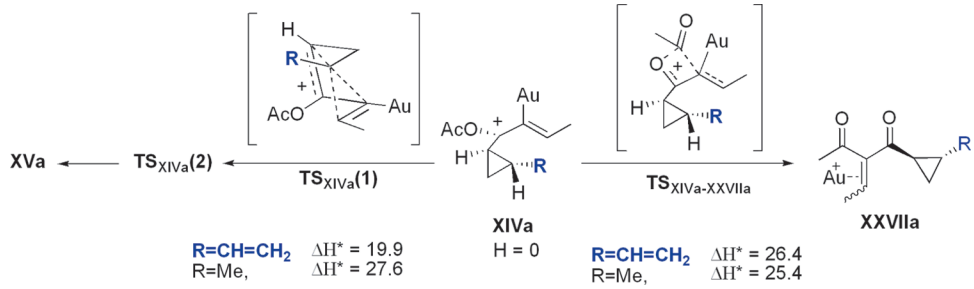
(31) In ref 13b Toste et al. have shown that scrambling in the *cis*-1-cyclopropyl propargyl acetates at both propargylic and cyclopropyl positions takes place before the cyclization is complete. However, no such phenomenon was detected for the *trans*-cyclopropyl derivatives they studied nor could the responsible intermediates for the second of these processes be fully characterized computationally.

Scheme 12. Reaction Coordinate Diagrams for the Cyclopropyl Epimerization of **XXIV**[a]



[a] Calculations were carried out at the B3LYP/6-31G(d) (C, H, O) and LANL2DZ (Au) levels (+ZPE corrected energies are given in kcal/mol; calculations considering solvent effects (CH_2Cl_2)). Au = (IPr)Au.

Scheme 13. Reaction Coordinate Diagrams for the Cyclopentannulation vs the Acetate Fission Reaction[a]



[a] Calculations were carried out at the B3LYP/6-31G(d) (C, H, O) and LANL2DZ (Au) levels (+ZPE corrected energies are given in kcal/mol). Au = (IPr)Au.

right). However, the activation barrier for the ring opening of the methyl-substituted cyclopropyl rises to more than 27.6 kcal/mol (vs 19.9 kcal/mol for the vinyl-substituted one), thus highlighting the importance of the cyclopropyl substituent in the reaction mechanism (Scheme 13, left).

Conclusion

We present here a complete study on the reactivity of 3-cyclopropyl propargylic acetates and enol ethers with Au(I) and Au(III) catalysts. The intelligence gathered in the development of the gold-catalyzed homo-Rautenstrauch rearrangement previously reported by our group aided the selection of substituents at the cyclopropyl ring able to tune the reactivity of these settings in favor of a cyclopentannulation vs an acetate fission process to give α-ylidene-*β*-diketones. Supported by DFT calculations, this study sheds light on the key gold-stabilized "nonclassical carbocationic" intermediates involved in the stereocontrolled synthesis of 5-(*E*)-alkylidene cyclopentenyl acetates and reveals the intrinsic stereospecific nature of these transformations. Further experimental and computational evidence is disclosed to explain the lack of a complete chirality transfer in optically active settings: the cyclopentannulation process competes with a gold-triggered cyclopropyl opening/closure prior to the cyclization event. Surprisingly, such cyclopropyl scrambling has been found for both cis and trans settings, thus highlighting the configurational promiscuity of these motifs. The rearrangement of tertiary acetates has been highly illuminative of the competitive nature of the 1,2- and 1,3-acyloxy migration pathways, opening the venue for new transformations orchestrated in that regard, which is currently being pursued and will be reported in due course.

Acknowledgment. We thank the Organic Chemistry Institute of the University of Zürich, Givaudan, and the Swiss National Science Foundation for financial support and the SGI/IZO-SGIker UPV/EHU and Matterhorn (UZH) for allocation of computational resources.

Supporting Information Available: Text, figures, and tables giving experimental and computational details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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