

Tandem Gold(I)-Catalyzed Cyclization/ Electrophilic Cyclopropanation of Vinyl Allenes

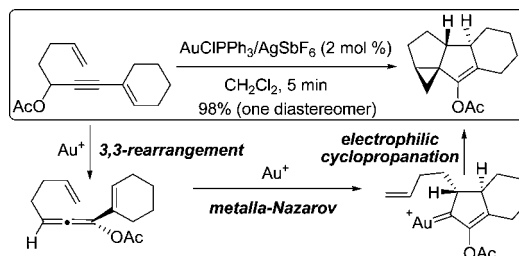
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ABSTRACT

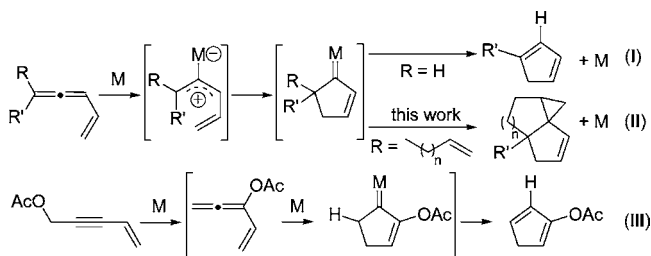


We have developed an expedient method for the synthesis of polycyclic compounds from propargyl acetates or vinyl allenenes involving up to three Au(I)-catalyzed elemental steps: 3,3-rearrangement, metalla-Nazarov reaction, and electrophilic cyclopropanation. The reaction proceeds under very mild conditions and in short times. The mechanism has been studied by DFT computations.

Gold and platinum salts are exquisite catalysts that activate alkynes, alkenes, and allenes toward nucleophilic attack.¹ In that respect, vinyl allenenes are converted into five-membered ring systems, presumably via complexation of the allene

moiety and subsequent Nazarov-like cyclization² leading to a cyclopentenylidene intermediate (Scheme 1, eq I). Cyclo-

Scheme 1. Trapping of Cyclopentenylidene Complexes



pentadienes are finally obtained via 1,2-hydride migration ($R = H$, $R' = \text{aryl, alkyl}$).³ Alternatively, CH insertion ($R = R' = \text{Me}$)^{3b} or intramolecular nucleophilic addition of an alkoxy group ($R = \text{Me}$, $R' = (\text{CH}_2)_2\text{OH}$)^{3c} has been observed. Cyclopentadienyl acetate (or cyclopentenone

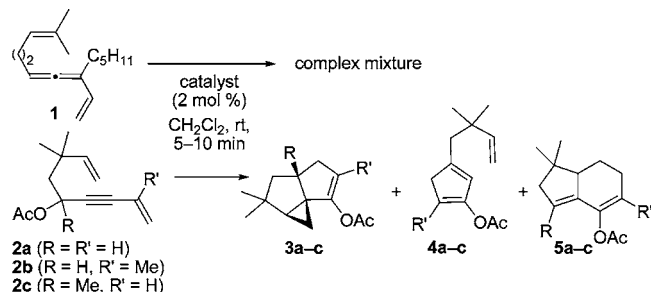
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(1) For general reviews on “electrophilic” transition-metal-catalyzed cycloisomerization reactions, see: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (b) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, 44, 2328–2334. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, 104, 1317–1382. (d) Hashmi, A. S. K. *Gold Bull.* **2003**, 36, 3–9. (e) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, 39, 4237–4239. For selected recent examples of Au- and Pt-catalyzed reactions involving allenes, see: (f) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, 128, 10352–10353. (g) Morita, N.; Krause, N. *Angew. Chem., Int. Ed.* **2006**, 45, 1897–1899. (h) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2006**, 71, 8658–8660. (i) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Kian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, 128, 9066–9073. (j) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, 45, 7596–7599. (k) Hashmi, A. S. K.; Blanco, M. C.; Fisher, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387–1389. (l) Zhou, C.-Y.; Chan, P. W. H. C.; Che, C.-M. *Org. Lett.* **2006**, 8, 325–328. (m) Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, 126, 3408–3409.

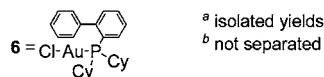
after hydrolysis) was also formed via Au(I)-catalyzed 3,3-rearrangement of enynyl acetates, Nazarov reaction, and 1,2-H migration (eq III).^{3a,4,5}

We anticipated that cyclopentenylidenegold species could be trapped by carbon–carbon double bonds.⁶ If successful, metalla-Nazarov cyclization followed by intramolecular electrophilic cyclopropanation would give rise to highly valuable polycyclic compounds in a single operational step (eq II). Our initial attempts using precursor **1** were disappointing, with complex mixtures being systematically obtained using both Au(I) and Au(III) catalysts (Table 1).

Table 1. Catalyst Optimization and Substrate Scope



Entry	Substrate	Catalyst	Yield (3 / 4 / 5) ^a
1	2a	AuCl ₃	no reaction
2	2a	6/AgSbF ₆	44% (3a:4a = 1.9:1) ^b / 0%
3	2b	AuCl ₃	12% / 0% / 0%
4	2b	6/AgSbF ₆	quant (3b:4b = 2.6:1) ^b / 0%
5	2b	AuCIPPh ₃ /AgSbF ₆	92% / 0% / 0%
6	2c	AuCl ₃	0% / – / 70%
7	2c	AuCIPPh ₃ /AgSbF ₆	0% / – / 69%



^a isolated yields
^b not separated

^a Isolated yields. ^b Not separated.

On the other hand, acetates **2a–c** gave promising results; although AuCl₃ failed to convert **2a** (entry 1), the desired tricyclic compound **3a**⁷ admixed with cyclopentadienylic

(2) For recent reviews about the Nazarov reaction and related transformations, see: (a) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, 61, 7577–7606. (b) Pellissier, H. *Tetrahedron* **2005**, 61, 6479–6517. (c) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206.

(3) (a) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, 128, 1442–1443. (b) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2007**, 46, 909–911. (c) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, 46, 912–914.

(4) The Pt- and Au-catalyzed 3,3-rearrangement of propargyl acetates is a well-known process; see inter alia: (a) Marion, N.; Díez-González, S.; De Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, 45, 3647–3650. (b) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, 128, 8414–8415. (c) Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, 60, 9745–9755. (d) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, 43, 2280–2282. (e) Fürstner, A.; Hanen, P. *Chem. Commun.* **2004**, 2564–2547 and references therein.

(5) For homologue reactions leading to acetoxy bicyclo[3.1.0]hexenes, see: Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, 128, 12614–12615.

(6) For related intramolecular trappings of alkylidenegold species by olefins, see: Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cardenas, D. J.; Echavaren, A. M. *Angew. Chem., Int. Ed.* **2004**, 43, 2402–2406.

(7) When possible, the configuration of compounds of type **3** and **8** appearing in this study was ascertained by nOe experiments.

acetate **4a** (1.9:1 ratio) was obtained in 44% total yield when 2 mol % of ClAu(2-biphenyldicyclohexylphosphine) **6**⁸ and AgSbF₆ were used (entry 2). We next reacted compound **2b**, which displays a methyl group at the internal position of the 1,3-enyne framework. Whereas AuCl₃ still proved poorly efficient (entry 3), a quantitative yield was obtained with a catalytic mixture of **6** and AgSbF₆ (entry 4). However, the formation of cyclopentadiene could not be suppressed (**3b**: **4b** = 2.6:1). The selective conversion of **2b** into **3b** was finally realized in 92% yield using 2 mol % of AuCIPPh₃ and AgSbF₆ (entry 5). Surprisingly, tertiary acetate **2c** was selectively converted into bicyclo[4.3.0]nonadiene **5c** with both AuCl₃ and cationic triphenylphosphinegold(I) (entries 6 and 7). We suspect that this product arose from an intramolecular (gold)-catalyzed type I Diels–Alder reaction of the putative vinyl allene intermediate with the terminal double bond.⁹

From this set of results, we anticipated that substitution at the internal 1,3-enyne position would favor the formation of compounds of type **3** compared to **5**. Using the AuCIPPh₃/AgSbF₆ catalytic mixture, methyl-substituted substrates **2d–g** were efficiently converted into the corresponding 5/5/3 or 5/6/3 fused systems (Table 2, entry 1). Compounds **3d–g**

Table 2. Gold(I)-Catalyzed Cycloisomerizations^a

Entry	Substrate	Product	Yield ^b
1	2d–h	3d, n = 1, R ¹ = R ² = R ³ = H 3e, n = 1, R ¹ = Me, R ² = R ³ = H 3f, n = 2, R ¹ = Me, R ² = R ³ = H 3g, n = 1, R ¹ = R ³ = Me, R ² = H	92% 97% 88% 95%
2	2i	4h, n = 2, R ¹ = R ² = R ³ = H	72% ^c
3	2j	3i	98%
4	2k	3ja : 3jb = 1.7 : 1	90%
5	7a–c	8a, R ¹ = C ₄ H ₉ , R ² = H 8b, R ¹ = R ² = Me 8c, R ¹ = C ₄ H ₉ , R ² = Me	62% 72% ^d 80% ^d

^a Reaction conditions: AuCIPPh₃ (2 mol %), AgSbF₆ (2 mol %), substrate in CH₂Cl₂, rt, 10 min. ^b Isolated yields after column chromatography. ^c Overall yield including 30% of **4h** and 42% of cyclopentenone formed during column chromatography; reaction time 24 h. ^d GC purity of 85% after column chromatography; yields are corrected accordingly.

were isolated in excellent yields as single diastereomers. That the formation of compounds of type **4** can be avoided using tertiary acetates is a sufficient, but not necessary feature, was revealed by the selective conversion of **2d** into **3d**. Still, the

(8) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavaren, A. M. *Angew. Chem., Int. Ed.* **2006**, 45, 5455–5459.

tether length seems to dictate the outcome, as shown by the selective conversion of **2h** into cyclopentadiene **4h** (entry 2). Tetracyclic fused structures could also be assembled using **2i** and **2j** (entries 3 and 4). Although **3i** was obtained as a single diastereomer, **3j** was isolated as an inseparable diastereomeric mixture. Nevertheless, the construction of angular triquinanes such as **3j** has always been the target of many synthetic efforts.¹⁰ Since the substitution at the internal enyne position facilitates the production of compounds of type **3**, we finally decided to reinvestigate the case of preformed vinyl allenes. Gratifyingly, unlike compound **1**, vinyl allenes **7a–c** proved to be suitable substrates for the stereoselective cycloisomerizations into **8a–c** (entry 5).

The mechanism of the title reaction is hypothesized in Figure 1 and supported by DFT/B3LYP computations.

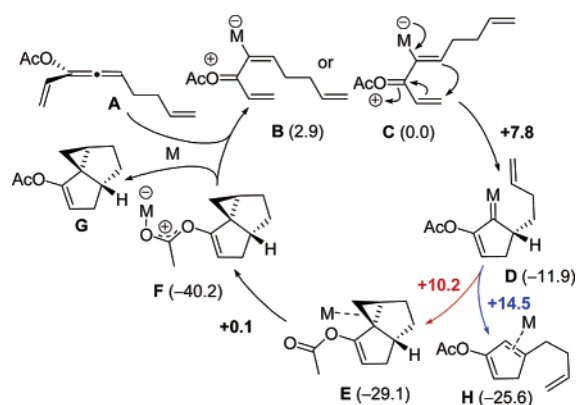


Figure 1. Proposed reaction mechanism supported by DFT/B3LYP calculations ($M = \text{AuPMe}_2\text{Ph}^+$). ΔH_{298} (kcal/mol) values relative to **C** are given in parentheses. ΔH^\ddagger_{298} values are depicted in bold.

Isomerization of propargyl acetates into 3-acetoxy 1,2,4-trienes such as **A** was taken for granted at this stage.⁴ Coordination of gold to the allene framework gives rise to diastereomers **B** and **C**, the latter being more stable by 2.9

kcal/mol. From **C**, Nazarov-type cyclization leads to carbene **D**.¹¹ It requires 7.8 kcal/mol of enthalpy of activation and is exothermic by 11.9 kcal/mol.¹² Concerted electrophilic cyclopropanation follows (red pathway), giving complex **E** which exhibits two cis ring fusions. This step requires 10.2 kcal/mol of enthalpy of activation and is exothermic by 17.2 kcal/mol.

Alternatively, 1,2-hydrogen migration may occur (blue pathway), leading to gold-complexed cyclopentadiene **H**. This hydrogen shift appears less favored kinetically and thermodynamically compared to the electrophilic cyclopropanation, the enthalpy of activation being evaluated as 14.5 kcal/mol and the exothermicity as 13.7 kcal/mol. This result is in satisfactory agreement with the experimental results described in Table 1. In **E**, gold still coordinates to a cyclopropyl bond. It then migrates to the acetoxy group via a very low-lying transition state ($\Delta H^\ddagger_{298} = 0.1$ kcal/mol). This shift is appreciably exothermic by 11.1 kcal/mol. Decomplexation of the species **F** gives the final product **G** and regenerates the catalyst.^{13,14}

In conclusion, we have developed a novel method for the synthesis of polycyclic compounds from propargyl acetates and vinyl allenes involving up to three Au(I)-catalyzed elemental steps: 3,3-rearrangement, metalla-Nazarov reaction, and electrophilic cyclopropanation. Application of this new methodology to asymmetric and total synthesis is currently under active investigation in our laboratory.

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Supporting Information Available: An additional experiment in which the incipient vinyl allene can be isolated and transformed into a 6,6-fused system via thermal Diels–Alder cycloaddition, experimental procedures, and spectral data; computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) (a) For related thermal examples, see: Gibbs, R. A.; Bartels, K.; Lee, R.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 3717–3725. (b) For a general discussion, see: Regás, D.; Ruiz, J. M.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Tetrahedron Lett.* **2003**, *44*, 8471–8474. (c) For a discussion about gold-catalyzed Diels–Alder reactions, see: Rabaã, H.; Engels, B.; Hupp, T.; Hashmi, A. K. *Int. J. Quantum Chem.* **2007**, *107*, 359–365.

(10) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671–719.

(11) The C–Au distance is 2.04 Å. Gold carbenes present Au–C bonds of 2.0–2.1 Å; see inter alia: Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.–Eur. J.* **2003**, *9*, 2627–2635.

(12) From **B**, the enthalpy of activation is 10.4 kcal/mol (13.3 kcal/mol relative to **C**).

(13) For related computations on gold(I)-catalyzed Rautenstrauch rearrangement, see: Faza, O. N.; Silva López, C.; Álvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437. For precedent computed cyclopropanations involving gold carbenes, see ref 11.

(14) Once **E** is formed, the demetalation could also be assisted by a molecule of the starting substrate to release **G**.