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Generation and Trapping of Cyclopentenylidene Gold Species: Four Pathways to Polycyclic Compounds

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Abstract: Cyclopentenylidene gold complexes can easily be formed from vinyl allenes through a Nazarov-like mechanism. Such carbenes may transform in four different ways into polycyclic frameworks: electrophilic cyclopropanation, C−H insertion, C−C migration, or proton shift. We have studied the selectivity of these different pathways and used our findings for the expedient preparation of valuable complex molecules. An application to the total synthesis of a natural product, $\Delta^{9(12)}$-capnellene, is presented. DFT computations were carried out to shed light on the mechanisms.

1. Introduction

Electrophilic activation of alkynes by gold or platinum complexes may give rise to carbenic intermediates that can be trapped in various ways to provide valuable compounds (Scheme 1).[1−3] For instance, these species can react inter- or intramolecularly with alkenes to give polycyclic molecules incorporating one or more cyclopropyl units.[4] On the other hand, the opportunity to generate carbenes from allenes has been much less investigated,[5] and their reactivity has been mostly limited to 1,2- or higher shifts of hydrides or alkyl groups (R = H or alkyl).[6]

In analogy with the oxidative rearrangement of vinyl allenes (Scheme 2), [7] we reasoned that ene vinyl allenes would be suitable substrates to achieve this goal.[8] Indeed, vinyl allenes can be activated by an electrophilic oxygen donor (e.g., *m*-CPBA) to give a vinyl epoxide which opens next to give a pentadienyl cation. This intermediate undergoes Nazarov-type cyclization[9] leading to a cyclopentenone. In a similar fashion,

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(1) The rendition as gold-carbene or gold-stabilized carbocation is a matter of debate that is beyond the scope of this article, see: (a) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030. (b) Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7892. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754.

(2) For recent reviews on gold-mediated homogeneous catalysis, see: (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (e) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (f) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (g) Skouta, R.; Lie, C.-J. *Tetrahedron* **2008**, *64*, 4917. (h) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (i) Hashmi, S. A. *Chem. Rev.* **2007**, *107*, 3180. (j) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (k) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (l) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698. (m) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (n) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *248*, 2271. (o) Malacria, M.; Goddard, J.-P.; Fensterbank, L. In *Comprehensive Organometallic Chemistry*, 3rd ed.; Crabtree, R., Mingos, M., Eds.; Elsevier: Amsterdam, 2006; Vol. 10, Chapter 10.07, p 299. (p) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (q) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555.

(3) For selected examples of generation and trapping of platinum or gold carbenes from alkynes, see: (a) Takaya, J.; Udagawa, S.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *46*, 4906. (b) Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Org. Lett.* **2008**, *9*, 4049. (c) Kirsch, S. F. *Synthesis* **2008**, 3183. (d) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156. (e) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (f) Cabello, N.; Jiménez-Nùñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, 4217. (g) Genin, E.; Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Synlett* **2007**, 1780. (h) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698. (i) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427. (j) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916. (k) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem.-Eur. J.* **2006**, *11*, 1694. (l) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146. (m) Zhang, L.; Kozmin, S. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (n) Nevado, C; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. C.; Méndez, M.; Rager, M.-N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706. (o) Méndez, M; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511.

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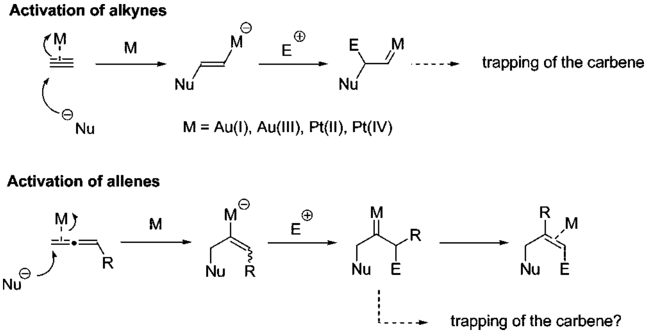
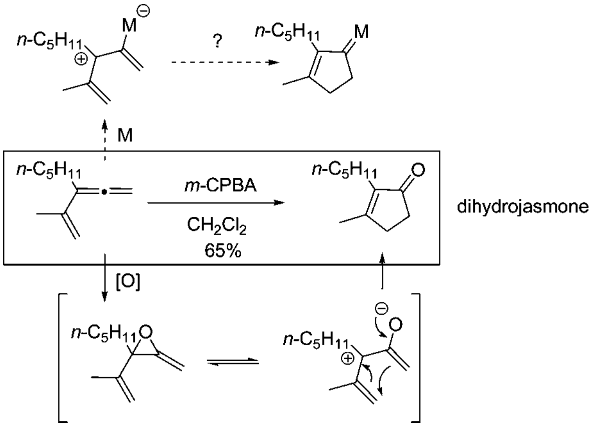
10.1021/ja808872u CCC: $40.75

Scheme 1. Activation of Alkynes and Allenes Leading to Carbenes



Scheme 2. Hypothetical Transposition of the Oxidative Rearrangement of Vinyl Allenes (Leading to Cyclopentenones) to the Formation of Cyclopentenylidenes

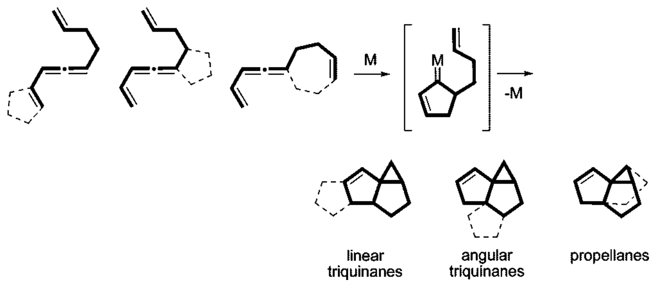


one might expect that an electrophilic metal such as gold would allow the formation of a cyclopentenylidene.[10,11]

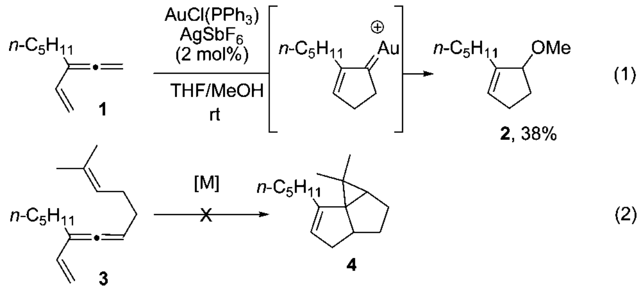
Thus, we decided to use vinyl allenes bearing a pendant double bond to build polycyclic molecules in an intramolecular fashion. Interestingly, this strategy would grant an easy access to tricyclic systems that can be found in important classes of compounds of biological interest, such as linear and angular triquinanes,[12] as well as propellanes (Scheme 3).[13]

In this article, we deliver new experimental and theoretical advances on the gold-catalyzed cycloisomerization of ene vinyl allenes.[14] We have also explored ways to trap cyclopentenylidenes and disclosed new synthetic opportunities. The total synthesis of a natural product, $\Delta^{9(12)}$-capnellene, is also described.

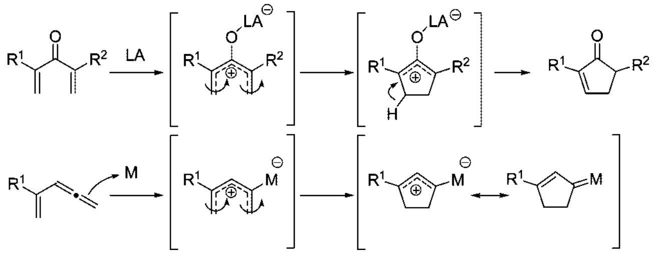
Scheme 3. Cycloisomerization of Ene Vinyl Allenes: New Access to Polyquinanes?



Scheme 4. Initial Attempts to Trap Cyclopentenylidene Intermediates Inter- and Intramolecularly



Scheme 5. Analogy with the Nazarov Reaction



2. Scope and Limitations

In order to probe the formation of cyclopentenylidene gold derivatives from vinyl allenes, the simple substrate **1** was treated at room temperature with 2 mol % of a cationic gold(I) species generated in situ by chlorine abstraction of AuCl(PPh$_3$) promoted by AgSbF$_6$ in a mixture of THF and MeOH (Scheme 4). As expected, the 3-methoxycyclopentene **2**, possibly arising from 1,2- or 1,4-nucleophilic addition of MeOH, could be

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(5) With the exception of allenyl acetates, which can be easily generated from propargyl acetates by 3,3-rearrangement, see: (a) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718. (b) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (c) Marco-Contelles, J.; Soriano, E. *Chem. Eur. J.* **2007**, *13*, 1350, and references therein.

(6) (a) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (b) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (c) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 909. (d) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912. (e) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398. (f) Trillo, B.; López, F.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 951. (g) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614. (h) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414. (i) Crone, B.; Kirsch, S. F. *Chem. Eur. J.* **2008**, *14*, 3514. (j) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488.

(7) (a) Grimaldi, J.; Bertrand, M. *Tetrahedron Lett.* **1969**, *38*, 3269. (b) Grimaldi, J.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1971**, *3*, 957. (c) Roumestant, M. L.; Malacria, M.; Goré, J.; Grimaldi, J.; Bertrand, M. *Synthesis* **1976**, 755. (d) Malacria, M.; Roumestant, M. L. *Tetrahedron* **1977**, *33*, 2813. (e) Doutheau, A.; Goré, J.; Malacria, M. *Tetrahedron* **1977**, *33*, 2393. (f) Malacria, M.; Goré, J. *J. Org. Chem.* **1979**, *44*, 885. (g) Malacria, M.; Goré, J. *Tetrahedron Lett.* **1979**, *52*, 5067.

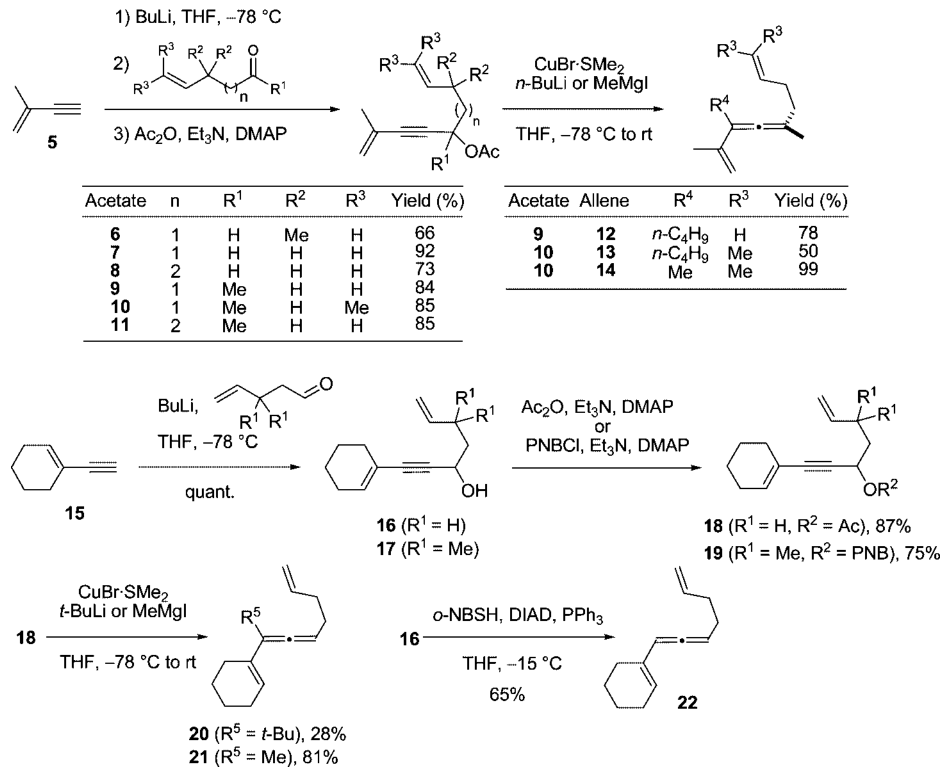
(8) For gold-catalyzed cycloisomerizations of higher eneallene homologues, see: Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6670.

(9) For recent reviews on Nazarov cyclization, see: (a) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (c) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193 See also. Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N.Y.)* **1994**, *45*, 1–158.

(10) For a seminal work on transition-metal mediated activation of vinyl allenes, see: (a) Delbecq, F.; Goré, J. *Tetrahedron Lett.* **1976**, *38*, 3459. (b) Baudouy, R.; Delbecq, F.; Gore, J. *Tetrahedron* **1980**, *36*, 189.

(11) For gold-catalyzed transformations involving Nazarov cyclizations, see: (a) Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059. (b) Lin, C.-C.; Teng, T.-M.; Tsai, C.-C.; Liao, H.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16417.

Scheme 6. Synthesis of Enyl Acetates and Vinyl Allenes



Acetate	n	R^1	R^2	R^3	Yield (%)
6	1	H	Me	H	66
7	1	H	H	H	92
8	2	H	H	H	73
9	1	Me	H	H	84
10	1	Me	H	Me	85
11	2	Me	H	H	85

Acetate	Allene	R^4	R^3	Yield (%)
9	**12**	*n*-C_4H_9	H	78
10	**13**	*n*-C_4H_9	Me	50
10	**14**	Me	Me	99

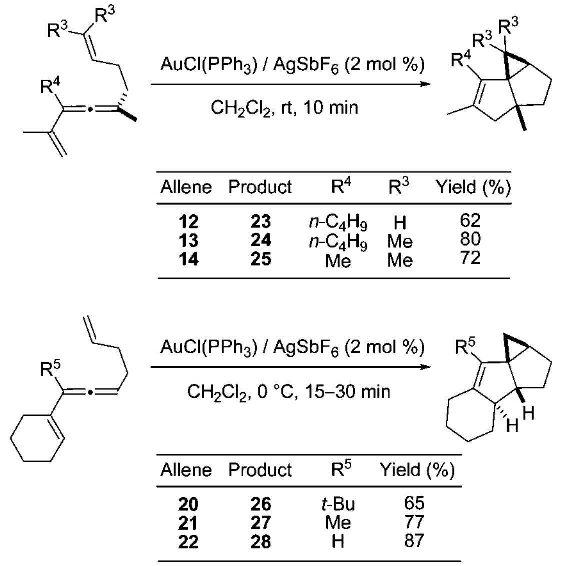
isolated from the mixture in 38% yield (eq 1).[15] On the other hand, the reaction of **3**, similar to **1** but exhibiting a pendant double bond, with various catalytic systems based on Au^I or Au^{III}, did not allow the formation of **4**, but gave rise to complex mixtures (eq 2).

We reasoned that the introduction of a substituent at the internal vinylic carbon of the vinyl allene framework could enhance the cyclization rate relatively to other potential competitive processes. This rationale was inspired by the mechanism of the Nazarov reaction,[9] which can benefit from bulky groups α to the carbonyl favoring the reactive s-*trans*/s-*trans* conformation (Scheme 5).

To validate this hypothesis, vinyl allenes **12**−**14**, **20**, and **21** were prepared from enyl acetates using *n*-BuLi or methylmagnesium iodide in the presence of copper(I) bromide (Scheme 6). These acetates were easily synthesized by treating various enones with enynes **5** or **15** previously deprotonated with *n*-BuLi. The resulting crude propargyl alcohols were reacted next with acetic anhydride or *p*-nitrobenzoyl chloride to give the corresponding enyl esters. On the other hand, the preparation of vinyl allene **22** from the propargyl alcohol **16** was achieved using *o*-nitrobenzenesulfonylhydrazine (*o*-NBSH) following a described procedure.[16]

Gratifyingly, in the presence of $AuCl(PPh_3)/AgSbF_6$ (2 mol %), vinyl allenes **12**−**14** and **20**−**22** cyclized in 10−30 min at room temperature (**12**−**14**) or 0 °C (**20**−**22**) to give the desired tricyclic compounds (Scheme 7). They were isolated in good yields as single diastereomers. The stereochemical assignment was based upon NOE experiments.

Scheme 7. Cycloisomerization of Vinyl Allenes **12**−**14** and **20**−**22**



Allene	Product	R^4	R^3	Yield (%)
12	**23**	*n*-C_4H_9	H	62
13	**24**	*n*-C_4H_9	Me	80
14	**25**	Me	Me	72

Allene	Product	R^5	Yield (%)
20	**26**	*t*-Bu	65
21	**27**	Me	77
22	**28**	H	87

In principle, acetates **6**−**11**, **18**, and **19** could themselves give rise to the same kind of transformation. Indeed, the rearrangement of propargyl acetates into allenyl esters is a well-known process,[17] that can notably be catalyzed by gold. This transformation would provide the vinyl allene moiety exhibiting the

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(12) Angular triquinanes have been prepared in several steps using gold-catalysis, but not directly: Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315.

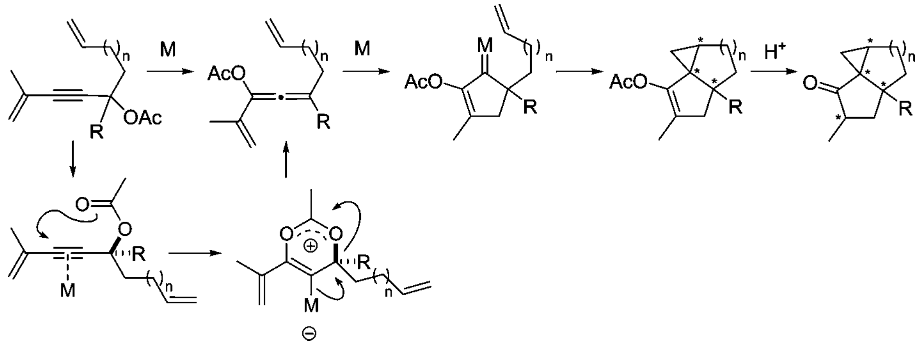
(13) (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671. (b) Pihko, A. J.; Koskinen, A. M. P. *Tetrahedron* **2005**, *61*, 8769.

(14) For two preliminary communications, see: (a) Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207. (b) Gandon, V.; Lemière, G.; Hours, A.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7534.

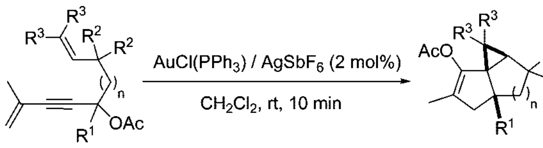
(15) Simultaneously to our work, Toste et al. disclosed an intramolecular variant of this transformation, see ref 6d.

(16) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

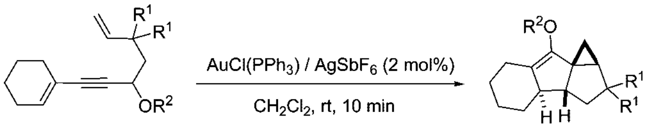
Scheme 8. Cycloisomerization of Enyl Acetates via 3,3-Rearrangement, Metalla-Nazarov, and Electrophilic Cyclopropanation



Scheme 9. Cycloisomerization of Enyl Acetates



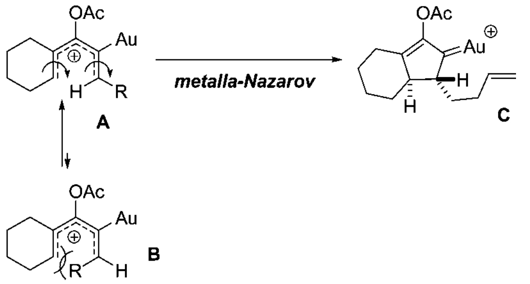
Acetate	Product	n	R^1	R^2	R^3	Yield (%)
6	**29**	1	H	Me	H	92
7	**30**	1	H	H	H	92
9	**31**	1	Me	H	H	97
10	**32**	1	Me	H	Me	95
11	**33**	2	Me	H	H	88



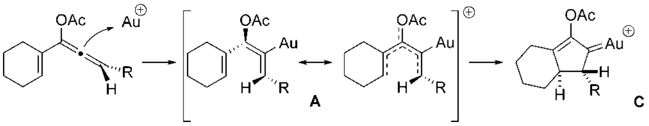
18 (R^1 = H, R^2 = Ac)
19 (R^1 = Me, R^2 = PNB)

34, 98%
35, 96%

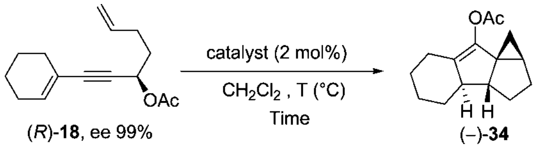
Scheme 10. Reactive Conformation of the Metalla-Nazarov Step



Scheme 11. Structure of the Allene Complex **A**



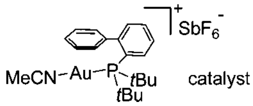
Scheme 12. Cycloisomerization of Enantioenriched Enyl Acetate **18**



(*R*)-**18**, ee 99%

(–)-**34**

Catalyst	T (°C)	Time (h)	Yield (%)	ee (%)
AuCl(PPh$_3$)/AgSbF$_6$	–20	2	93^a	84
AuCl(PPh$_3$)/AgSbF$_6$	–30	4	100^b	89
cat **I**	–20	2	100^b	90
cat **I**	–30	4	100^b	92



catalyst **I**

^{a} Isolated Yield
^{b} NMR Yield

required substitution pattern for the next step. This strategy would lead to polycyclic vinyl acetates, or to the corresponding ketones after protolysis (Scheme 8).

As anticipated, we were able to transform enyl acetates **6**, **7**, and **9−11** into polycycles **29−33** in a completely diastereoselective fashion (Scheme 9; the case of acetate **8** will be exposed later, see Scheme 14).[18] Interestingly, not only 5/5/3 fused systems could be assembled in excellent yields (**29−32**) but also the 5/6/3 tricyclic compound **33**, which was isolated in 88% yield. As in the case of the preformed vinyl allenes **12−14,** the reaction times were very short (∼10 min at room temperature), and the presence of substituents at the terminal double bond could be tolerated as well. The secondary acetates **18** and **19** could also be cycloisomerized successfully into tetracyclic products. These two reactions proved very efficient, both in terms of yields and stereoselectivity, **34** and **35** being isolated in 98% and 96% yield, respectively, as single diastereomers. Crystals suitable for X-ray diffraction were obtained with

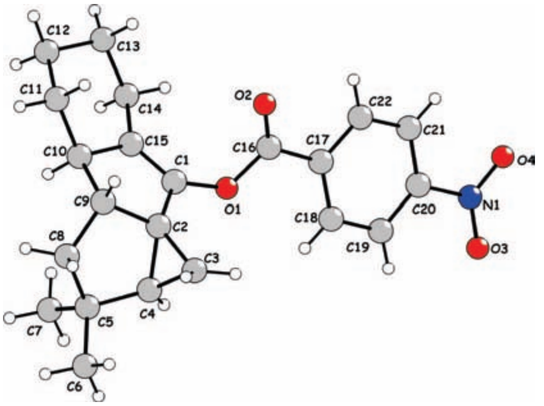


Figure 1. X-ray Structure of Compound **35**.

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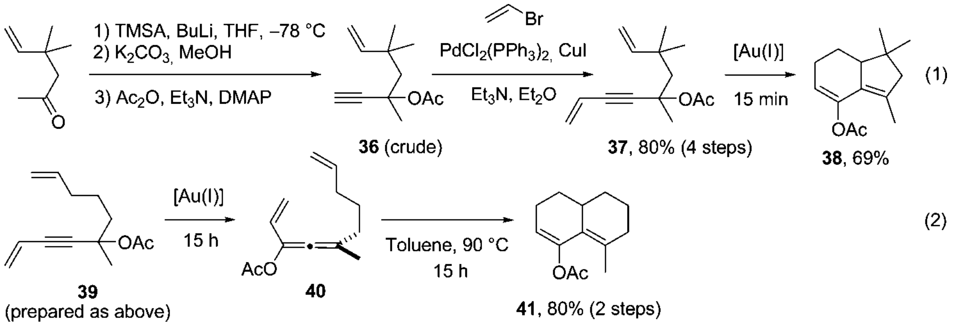
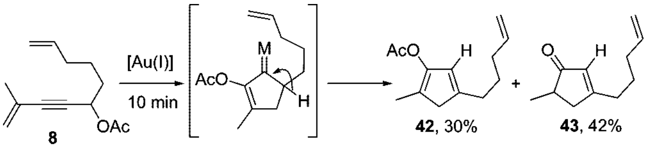
(17) See inter alia ref 6h and (a) Marion, N.; Díez-González, S.; De Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. (b) Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745. (c) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280. (d) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546. (e) Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408, and references therein.

Scheme 13. Synthesis and 3,3-Rearrangement/[4 + 2] Cycloaddition of Enyl Acetates **37** and **39** [Au(I)] = AuCl(PPh$_3$) (2 mol %), AgSbF$_6$ (2 mol %), CH$_2$Cl$_2$, rt



[Au(I)] = AuCl(PPh$_3$) (2 mol%), AgSbF$_6$ (2 mol%), CH$_2$Cl$_2$, rt

Scheme 14. Cycloisomerization of Enyl Acetate **8**: Formation of a Cyclopentadiene [Au(I)] = AuCl(PPh$_3$) (2 mol %), AgSbF$_6$ (2 mol %), CH$_2$Cl$_2$, rt



[Au(I)] = AuCl(PPh$_3$) (2 mol%), AgSbF$_6$ (2 mol%), CH$_2$Cl$_2$, rt

p-nitrobenzoate **35** (Figure 1).[19] This analysis confirmed the cis relationship of the two five-membered rings, whereas the two vicinal hydrogen of the 6/5 and 5/5 ring junctions were found trans.

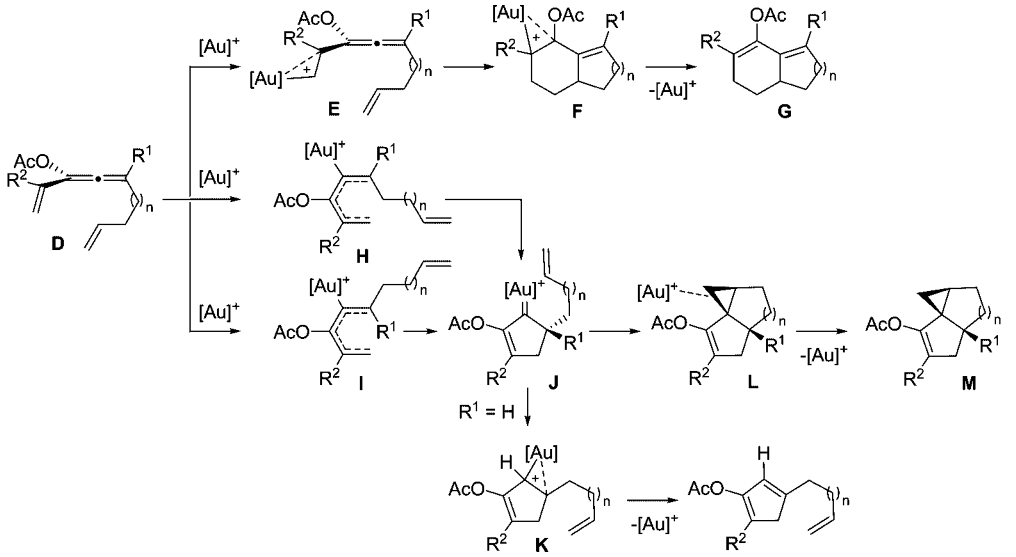
Again, this trans relationship can be explained by considering some of the mechanistic aspects of the Nazarov cyclization (Scheme 10): intermediate **B**, which suffers from steric interactions, preferably isomerizes into **A**; the latter undergoes conrotatory electrocyclization, giving **C**, which displays the expected stereochemical arrangement.

The structure of **A** deserves some comments: we recently disclosed that the coordination of gold to the central carbon of an allene may give rise to a so-called "bent-allene" complex.[14b,20] The importance of such intermediates lies in their ability to retain the chirality of the starting allene (Scheme 11). Indeed, inversion of configuration of these species, and hence racemization of the substrate, would occur via planar transition states that are quite difficult to reach if the starting allene is at least trisubstituted. In other words, owing to allylic interactions, planar conformations of these species are disfavored compared to twisted ones.

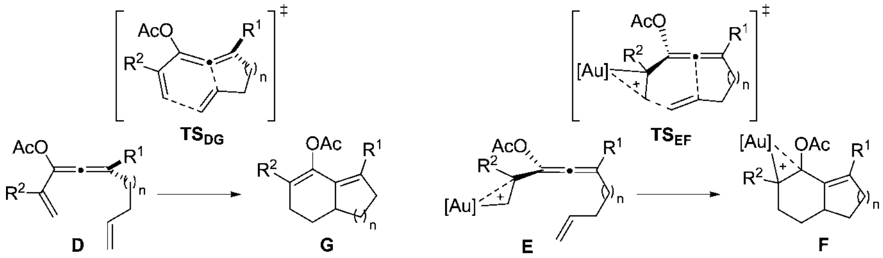
This being the case, chirality transfers from enantioenriched substrates become possible. This was shown by the cycloisomerization of (*R*)-**18**, which was prepared by lipase-catalyzed transesterification[21] in 99% ee. At low temperatures, we obtained (−)-**34** in up to 92% ee when using catalyst **I**[22] (Scheme 12).

We wanted to check whether the substitution at the internal position of the enyne framework was still a requirement for selective cyclopropanation with the enyl acetates. For that purpose, we prepared **37** and **39**, similar to **9** and **11** without the methyl group at the enyne (Scheme 13). No cyclopropanation product ensued after reacting **37** with AuCl(PPh$_3$) and AgSbF$_6$. Instead, we obtained the bicyclic compound **38** in 69% yield (eq 1). How this product was formed became clear after the reaction of **39**: this compound, which displays one more carbon in the tether and no *gem*-dimethyl substitution, transformed slowly at room temperature into vinyl allene **40**, which could be isolated and fully characterized (eq 2). It cyclized cleanly in hot toluene into the bicyclic product **41**.[23] Thus, **38** and **41** arise from a [4 + 2] cycloaddition between the diene

Scheme 15. Mechanistic Rationale



Scheme 16. Calculated Enthalpies at 298 K (kcal·mol^{-1}) for Thermal and Gold-Catalyzed [4 + 2] Cycloaddition of Ene Vinyl-Allenes ([Au] = Au(PMe$_2$Ph))



n	R^1	R^2	$\Delta H^{\ddagger}_{298}$	ΔH_{298}
1	H	H	22.6	–53.3
1	Me	H	22.6	–52.3
2	H	H	23.6	–56.3
2	Me	H	23.9	–47.7
1	H	Me	23.4	–54.3
2	H	Me	23.9	–57.1

n	R^1	R^2	$\Delta H^{\ddagger}_{298}$	ΔH_{298}
1	H	H	18.3	–49.5
1	Me	H	17.7	–49.6
2	H	H	19.7	–53.9
2	Me	H	19.4	–45.2
1	H	Me	23.5	–47.0
2	H	Me	24.5	–50.6

moiety and the double bond,[24] a process that can be avoided by substitution at the internal carbon of the enyne fragment as shown above.

However, the formation of a cyclopentenylidene gold species is not a guarantee of success. We found another possible limitation, the 1,2-H shift leading to a cyclopentadienyl acetate (Scheme 14). This was the case with the secondary acetate **8**, which displays one more carbon in the tether compared to its congeners **6** and **7**. In the presence of the Au^I catalytic system, it transformed into **42**, admixed with cyclopentenone **43** arising from the partial hydrolysis of **42** during purification.

In spite of this possible difficulty, secondary acetates may still be used safely providing that the alkyl chain does not become too long (e.g., **6**, **7**, **18**, and **19**).

3. DFT Computations

We undertook some DFT calculations in order to gain some insights into the mechanism of the various transformations reported above. The 3,3-rearrangement of propargyl acetates into allenyl acetates being already described,[5,17] we started our investigations on substrates of type **D** (Scheme 15). At least two scenarios can be envisaged. (i) A [4 + 2] cycloaddition leading to **G**, catalyzed or not by gold, accounting for the transformations depicted in Scheme 13; (ii) the formation of diastereomeric bent-allene complexes **H** or **I** leading to cyclopentenylidene **J**. This intermediate may undergo β-hydride elimination giving **K** (Scheme 14), or electrophilic cyclopropanation leading to **L**, which, in agreement with the structures of **29**−**35** in Scheme 9, should display a cis relationship between the cyclopropyl ring and R^1.

3.1. Computational Details. All geometries of intermediates and transition states were optimized fully without symmetry constraints using the Gaussian 03 program.[25] The DFT computations were carried out using the B3LYP functional as implemented in Gaussian. The computations were done using the LACVP(d,p) basis set: the gold atom was described by a double-ζ basis set with the effective core potential of Hay and Wadt (LANL2DZ),[26] and the 6-31G(d,p) basis set[27] was used for the other elements. Frequency calculations were performed to confirm the nature of the stationary points and to obtain zero-point energies (ZPE). The connectivity between stationary points was established by intrinsic reaction coordinate calculations (IRC). The Chemcraft program was used to draw the calculated structures.[28]

We were able to model the [4 + 2] cycloaddition, either with or without the assistance of the metal.[29,30] Without gold, we found transition states corresponding to a concerted asynchronous transformation, the bond at the central carbon of the allene being formed first (Scheme 16, see also Figure 2).

Neither the length of the tether (n = 1 or 2) nor the substitution at the allene (R^1) or at the internal 1,3-diene carbon (R^2) influences the quite high barrier heights of ~23 kcal·mol^{-1}. Several minima corresponding to the coordination of gold to one of the four C−C double bonds of the precursors were optimized. However, a [4 + 2] cycloaddition process could be modeled from one type of complex only, the one at the external 1,3-diene double bond. The cyclization also occurs in a concerted asynchronous manner; however, the bond between the external carbons of the substrate is formed first, followed

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(18) In the case of acetate **7**, we checked that neither AuCl(PPh$_3$) nor AgSbF$_6$ alone were able to promote this reaction. The starting material was recovered intact.

(19) CCDC 684838, see Supporting Information of ref 14b.

(20) For reports on bent-allenes and their transition metal complexes, see: (a) Dyker, C. A.; Lavallo, V.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 3206. (b) Kaufhold, O.; Hahn, F. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4057. (c) Fürstner, A.; Alcarazo, M.; Goddard, R.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 3210. (d) Tonner, R.; Frenking, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8695. (e) Yamaguchi, T.; Yamamoto, Y.; Kinoshita, D.; Akiba, K.-a.; Zhang, Y.; Reed, C. A.; Hashizume, D.; Iwasaki, F. *J. Am. Chem. Soc.* **2008**, *130*, 6894.

(21) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129.

(22) Herrero-Gomez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

(23) The fact that the formation of the decaline system **41** requires higher temperature compared to **38** has been previously observed, see:(a) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370. (b) Okamura, W. H.; Curtin, M. L. *Synlett* **1990**, 1.

(24) Examples of Diels−Alder reaction involving vinyl allenes as diene are scarce; for a seminal work, see: (a) Bertrand, M.; Grimaldi, J.; Waegell, B. *Chem. Commun. (London)* **1968**, *19*, 1141. (b) Marcel, B.; Grimaldi, J.; Waegell, B. *Bull. Soc. Chim. Fr.* **1971**, *3*, 962. This reaction has been used as key-step in the total synthesis of natural products: (c) Deutsch, E. A.; Snider, B. B. *J. Org. Chem.* **1982**, *47*, 2682. (d) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487. (e) Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791. (f) Gibbs, R. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 4062. (g) Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 3717.

(25) Gaussian 03, Revision D.02, Frisch, M. J.,; Gaussian, Inc.: Wallingford CT, 2004.

(26) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

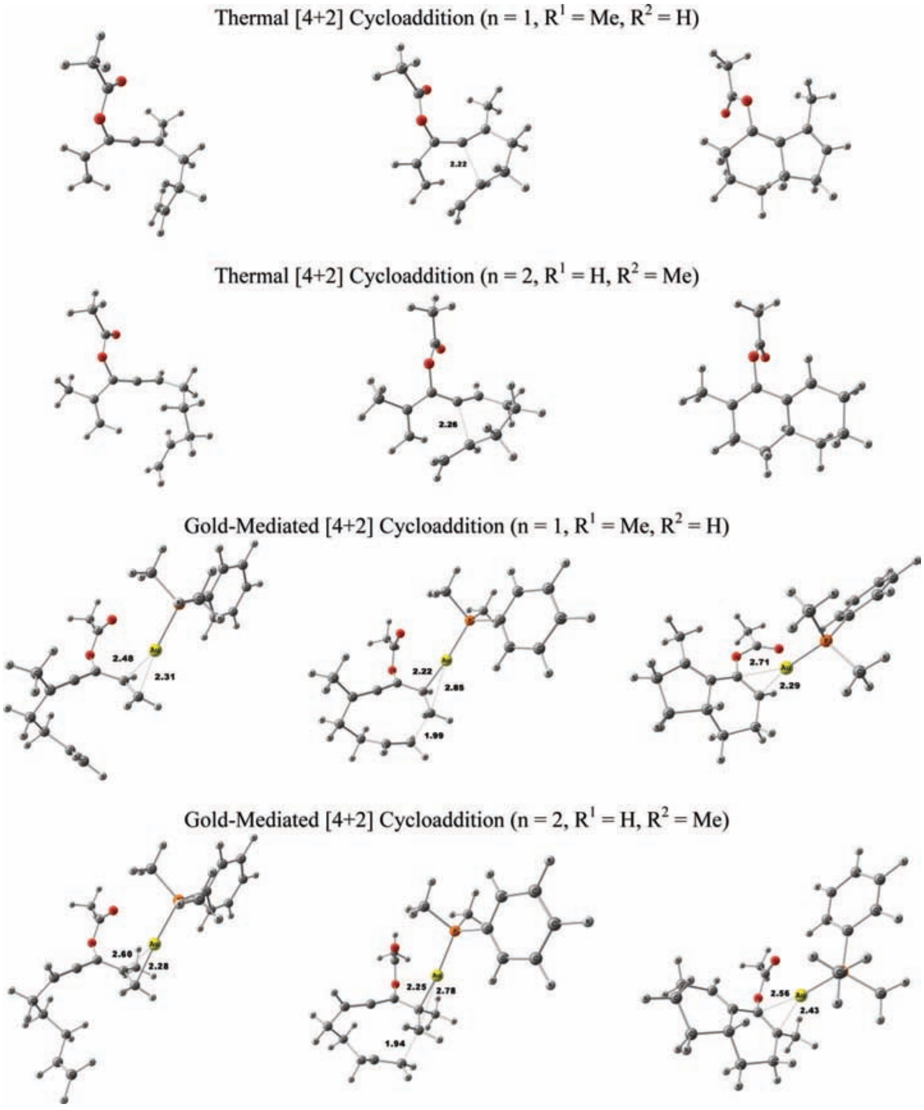

Figure 2. Selected computed structures (distances in Å).

by the one at the internal allene carbon. Interestingly, gold-coordination lowers the barrier heights by ~4 kcal·mol^{-1}, except with R^2 = Me. In this case, the kinetics are similar with or without gold. This phenomenon might be explained as follows. In the minima, the coordination of gold is slipped in a η^1-fashion toward the less-hindered carbon.[31] The slippage is therefore more pronounced with R^2 = Me than with R^2 = H. In the transition states, the coordination of gold is also slipped, but the other way around, to allow the nucleophilic attack of the distance double bond. As a matter of fact, the shift of the gold atom from one carbon to another will be harder with R^2 = Me than with R^2 = H. Lastly, one notes that an increase in the length of the tether slightly increases the barrier heights by ~1−2 kcal·mol^{-1}.

Table 1. Calculated at Enthalpies at 298 K (kcal·mol^{-1}) Relative to **I** in Scheme 15 ([Au] = Au(PMe_2Ph))[a]

	R^1 = H			
	n = 1 R^2 = H	*n* = 1 R^2 = Me	*n* = 2 R^2 = H	*n* = 2 R^2 = Me
H	2.9	2.8	3.5	1.3
I	0.0	0.0	0.0	0.0
$\mathbf{TS_{IJ}}$	7.8	4.0	8.9	3.6
J	−11.9	−18.7	−11.3	−20.1
$\mathbf{TS_{JK}}$	2.6 (14.5)	−2.3 (16.4)	2.9 (14.2)	−3.5 (16.5)
K	−25.6	−32.4	−25.1	−33.3
$\mathbf{TS_{JL}}$	−1.7 (10.2)	−7.4 (11.3)	0.1 (11.4)	−7.3 (12.8)
L	−29.1	−22.1	−21.2	−26.3
M + $[Au]^+$	−0.9	−2.5	−3.7	−6.7
E	1.0	−1.2	1.5	−2.6
$\mathbf{TS_{EF}}$	19.4 (18.4)	22.3 (23.5)	21.2 (19.7)	21.9 (24.5)
F	−48.5	−48.2	−52.4	−53.1
G + $[Au]^+$	−17.7	−18.8	−18.6	−13.6

[a] For clarity, barrier heights for the step considered are also indicated in parentheses.

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(27) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. (d) Hariharan, P. C.; Pople, J. A. *Mol. Phys.* **1974**, *27*, 209. (e) Gordon, M. S. *Chem. Phys. Lett.* **1980**, *76*, 163.

(28) http://www.chemcraftprog.com.

(29) For another type of gold-catalyzed [4 + 2] cycloaddition, see: Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269.

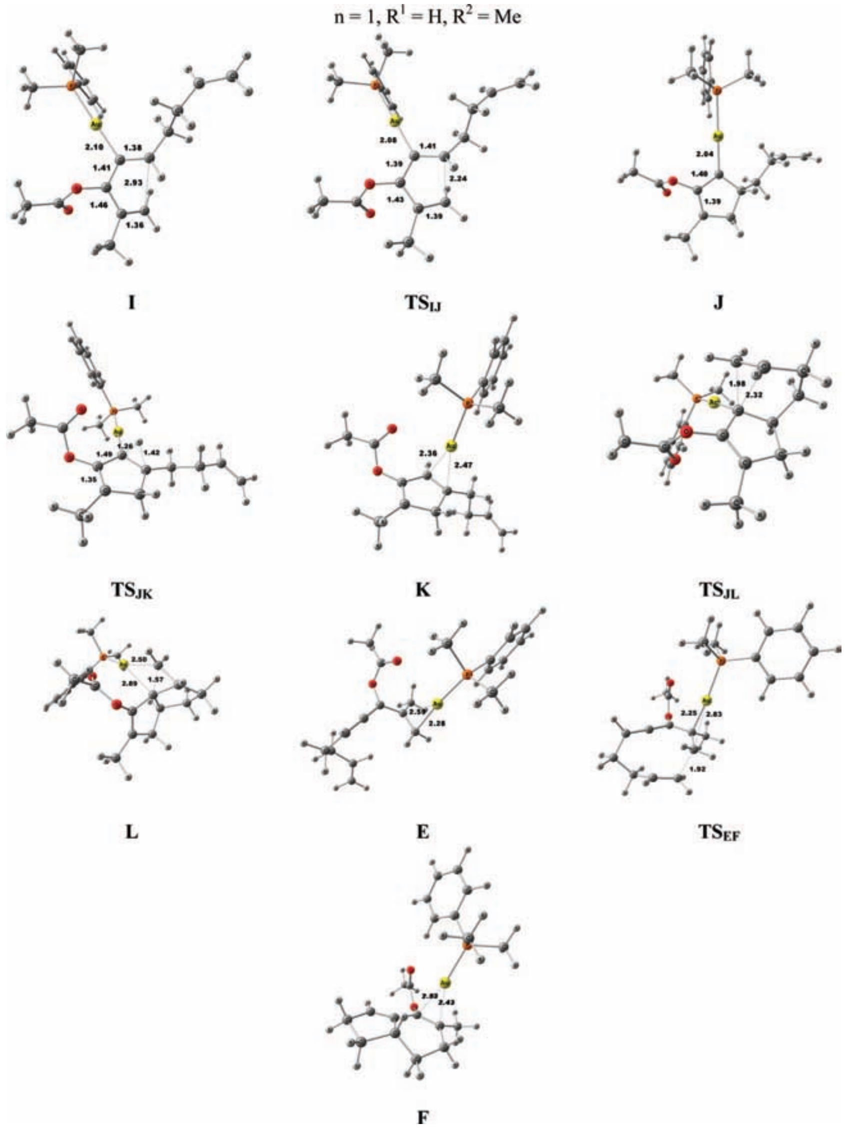

Figure 3. Selected computed structures (distances in Å).

The energetics of the other processes described in Scheme 15 were estimated next (Table 1, see also Figure 3). With $R^1 =$ H, isomer **I** was always found more stable than **H** by 1.3−2.9 kcal·mol^{-1}. Relative to **I**, the barrier height for the cyclization of **H** into **J** (not depicted) always lies at least 5 kcal·mol^{-1} higher than that of **I** into **J** ($\mathbf{TS_{IJ}}$). The length of the tether does not influence the barrier heights. On the other hand, the presence of a substituent at the internal 1,3-diene carbon (R^2 = Me) divides them by two. Besides, the transformations are much more exothermic with R^2 = Me, perhaps because the electron-donating group stabilizes the delocalized vinyl carbene framework of **J**. As a consequence of this stabilization, the β-hydride elimination is somewhat slower with R^2 = Me ($\mathbf{TS_{JK}}$). Thus, the benefits of a substituent at the enyne for the metalla-Nazarov step is reproduced computationally. The calculations predict the cyclopropanation step to be always favored compared to the β-elimination process. Thus, the clean switch over from cyclopropanation to β-elimination in the conversions of **7** and **8** in Schemes 9 and 14 could not be reproduced computationally, even in terms of free energies or by introducing computational sophistications such as solvent effects (PCM, solvent = CH_2Cl_2).[32] However, the trend is respected in the calculations: with R^2 = H, the difference between $\mathbf{TS_{JK}}$ and $\mathbf{TS_{JL}}$ decreases from 4.3 to 2.8 kcal·mol^{-1} as *n* increases from 1 to 2, and with R^2 = Me, this difference diminishes from 5.1 to 3.8 kcal·mol^{-1}. Lastly, as far as the [4 + 2] cycloaddition steps is concerned, species **E** were found slightly less stable than their congeners **I** with R^2 = H, but slightly more stable with R^2 = Me. However, transitions states $\mathbf{TS_{EF}}$ lie much higher in energy than $\mathbf{TS_{IJ}}$; therefore, no cycloadduct is expected with R^1 = H, as observed experimentally.

To account for the formation of the Diels−Alder products depicted in Scheme 13, we next introduced substituents at the allene (R^1) and at the alkyl chain (R^3) and compared the barrier

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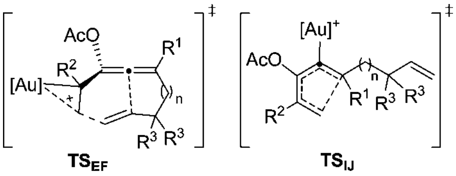
(30) For a computational study dealing with hetero Diels−Alder reaction of vinyl allenes and aldehydes, see: Regás, D.; Ruiz, J. M.; Afonso, M. M.; Palenzuela, J. A. *J. Org. Chem.* **2006**, *71*, 9153.

(31) For the concept of slippage, see: (a) Eisenstein, O.; Hoffmann, R *J. Am. Chem. Soc.* **1981**, *103*, 4308. See also: (b) Senn, H. M.; Blöchl, P. E.; Togni, A. *J. Am. Chem. Soc.* **2000**, *122*, 4098.

(32) As shown by Gevorgyan et al., the H-migration could also be assisted by traces of water. This might explain why the switch over could not be reproduced computationally. See: Xia, Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6940.

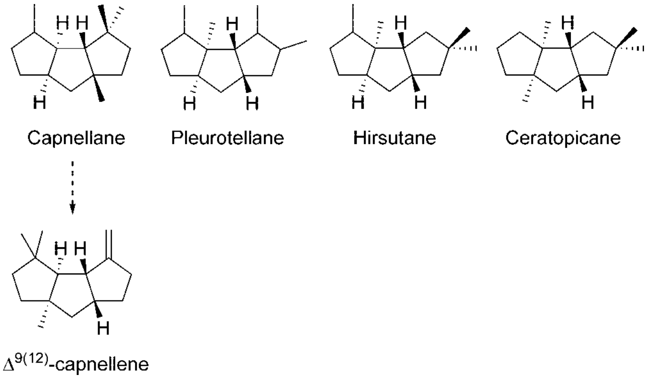
Scheme 17. Calculated Enthalpy Differences at 298 K (kcal·mol^{-1}) for **TS$_{EF}$** and **TS$_{IJ}$** ([Au] = Au(PMe$_2$Ph))



n	R^1	R^2	R^3	$\Delta\Delta H^{\ddagger}_{298}$ (**TS$_{IJ}$** favored)
1	H	H	H	11.5
1	Me	H	H	5.2
1	H	Me	H	18.2
2	H	H	H	12.3
2	Me	H	H	6.8
2	H	Me	H	18.3
1	H	H	Me	10.4
1	Me	H	Me	2.5
1	H	Me	Me	17.3
2	H	H	Me	11.1
2	Me	H	Me	5.6
2	H	Me	Me	16.8

heights for the [4 + 2] cycloaddition (**TS$_{EF}$**) and the "Nazarov cyclization" (**TS$_{IJ}$**) (Scheme 17). We found no strong influence of the tether length, whereas the presence of a *gem*-dimethyl substitution slightly decreases the barriers of each process by $\sim$1−2 kcal·mol^{-1}. On the other hand, both R^1 and R^2 play an important role: with R^1 = Me, the "Nazarov" becomes much less favored over the [4 + 2] cycloaddition, while with R^2 = Me, it is the [4 + 2] cycloaddition that becomes more difficult to achieve, for the reasons exposed previously.

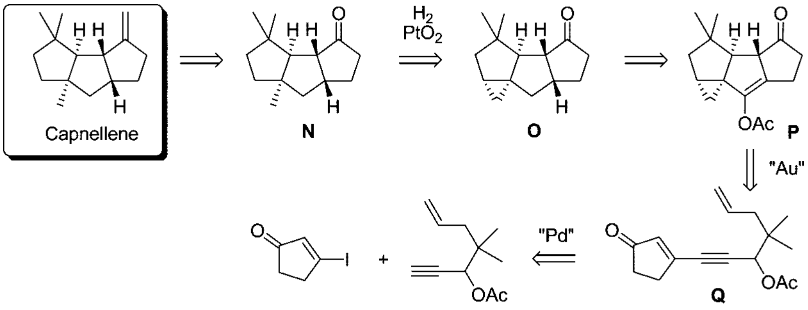
Chart 1. Important Natural Linear Triquinanes



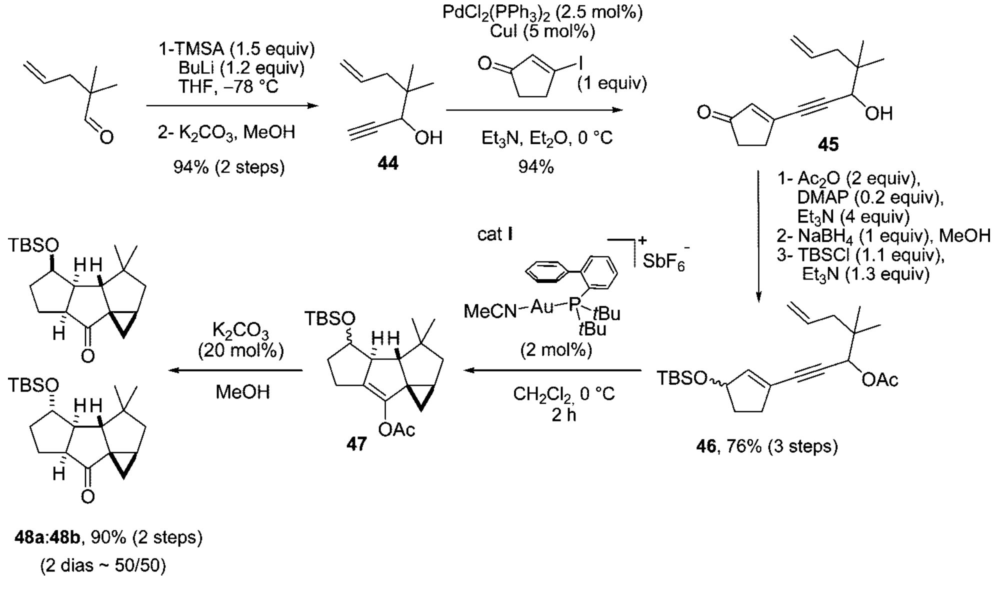
These results are corroborated with the transformation of **37** into **38** (Scheme 13), which corresponds to R^1 = Me, R^2 = H, and R^3 = Me in the computations. In this case, the energy difference of the two transition states is only of 2.5 kcal·mol^{-1}. Here again, even with additional techniques (PCM calculations) the switch over was not reached computationally, but the correct trend was observed.

To summarize this section, the coordination of gold to vinyl allenes may give rise to two types of reactive complexes **E** and **I**. The former may easily transform into a bicyclic compound **F** via concerted asynchronous gold-catalyzed cycloaddition, providing that the allene is tetrasubstituted and that the vinyl moiety is monosubstituted. Otherwise, the formation of a cyclopentenylidene gold species **J** takes place. This intermediate

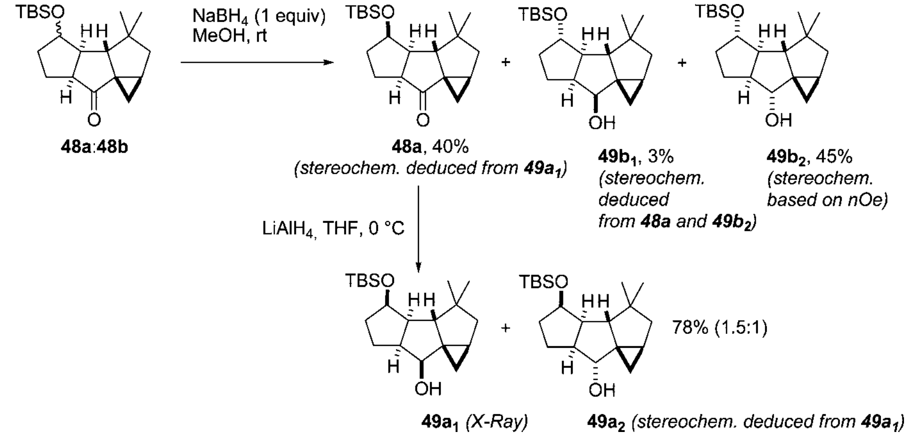
Scheme 18. Retrosynthetic Approach to Capnellene



Scheme 19. Total Synthesis of Capnellene (Part 1)



Scheme 20. Total Synthesis of Capnellene (Part 2): Reduction of Ketones **48a** and **48b**



undergoes exclusive diastereoselective intramolecular cyclopropanation giving **L** with a short tether, but may also give rise to compounds of type **K** via β-elimination with a longer alkyl chain. This mechanistic rationale is well substantiated by DFT computations.

4. Applications

4.1. Linear Triquinanes: Total Synthesis of $\Delta^{9(12)}$-Capnellene. Polyquinanes constitute an important class of natural products with various biological activities (sesqui-, di-, and sesterpenoid).[33] Among them, $\Delta^{9(12)}$-capnellene, a marine sesquiterpene of the capnellane family, has been a frequent target on which to test the utility of a new methodology. It was isolated from *Capnella imbricata* in 1978[34] and is supposed to be a biosynthetic precursor of some capnellenols that have antibacterial and antitumoral activities.[35] About 20 synthetic ways to this product have been reported,[36] including three enantioselective ones.[37] While in most of these syntheses the triquinane skeleton was obtained in several steps via a diquinane system, quite a few propose the formation of the tricyclopentanoid framework in one step. This was achieved by intramolecular trapping of a 1,3-diradical,[36a] photothermal metathesis,[36g] radical cascade,[36k] palladium-catalyzed tandem cyclization,[36s] and domino organocatalyzed reactions.[36o]

Our approach to capnellene was based on the deprotection and olefination of precursor **N**, obtained by hydrogenation of cyclopropane **O** (Scheme 18). The polycyclic framework would be formed during the cycloisomerization of the polyunsaturated acetate **Q**, previously assembled by Sonogashira coupling between a propargyl acetate and 3-iodocyclopent-2-enone.

Thus, 2,2-dimethylpent-4-enal was treated with trimethylsilylacetylene, previously deprotonated by *n*-BuLi (Scheme 19). The crude was reacted with MeOH in the presence of a catalytic amount of K$_2$CO$_3$, to give **44** in 94% yield over the two steps. Enynol **45** was next prepared in 94% yield by Pd-catalyzed coupling of **44** with 3-iodocyclopent-2-enone. Esterification with acetic anhydride, reduction of the ketone into the corresponding alcohol using sodium borohydride and protection of the alcohol as *tert*-butyldimethylsilyl ether furnished **46** in 76% overall yield as a 1:1 diastereomeric mixture. In the presence of 2 mol % of cat. **I**, triquinane **47** was obtained, also as a 1:1 mixture of diastereomers, and directly converted into ketones **48a** and **48b** in 90% yield over the two steps.[38]

The reduction of **48a/48b** using NaBH$_4$ resulted in the derivatization of the mixture (Scheme 20). While **48a** was recovered in 40% yield, **48b** led to the expected alcohols **49b$_1$**

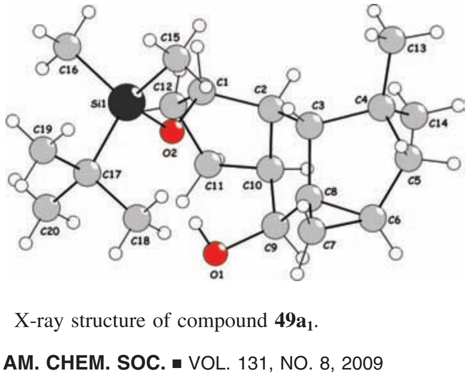


Figure 4. X-ray structure of compound **49a$_1$**.

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[33] (a) Paquette, L. A.; Doherty, A. M. *Recent Synthetic Developments in Polyquinane Chemistry*; Springer-Verlag: New York, 1987. (b) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occuring Compounds*; Academic Press: New York, 1972; Vol. II, 180. (c) Comer, F. W.; Trotter, J. *J. Chem. Soc. B* **1966**, *1*, 1.

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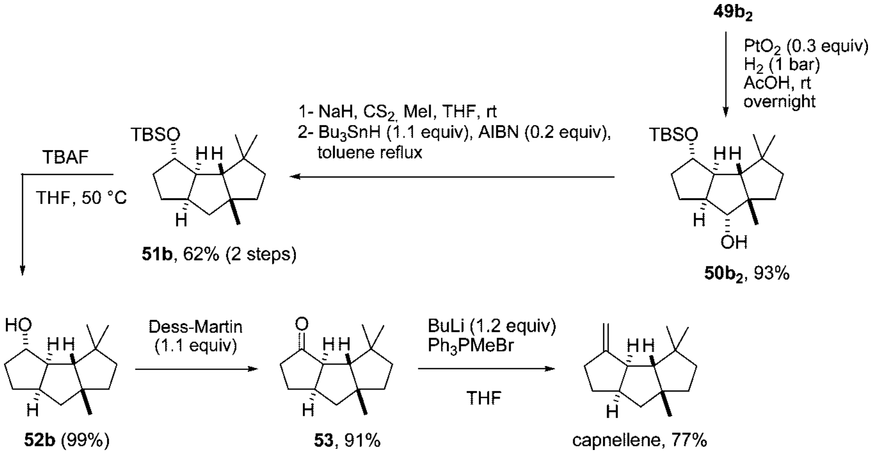
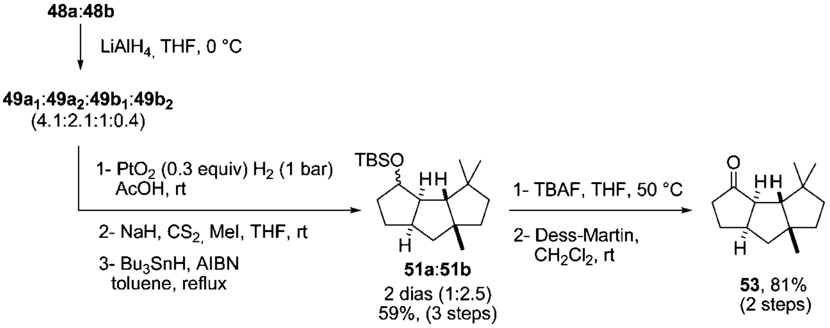
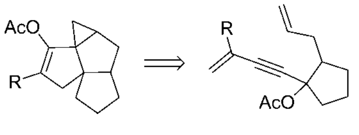
Scheme 21. Total Synthesis of Capnellene (Part 3)



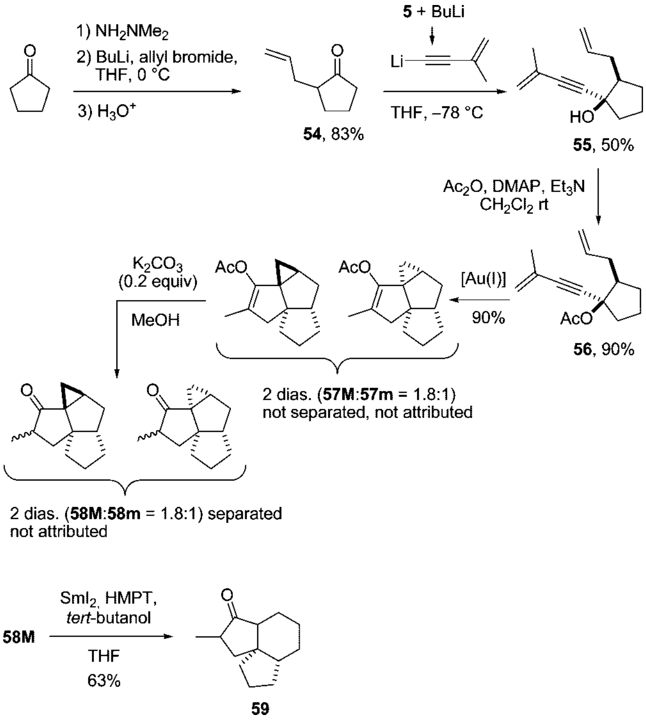
Scheme 22. Convergent Approach to Key Intermediate **53**



Scheme 23. Retrosynthetic Approach to Angular Triquinanes



Scheme 24. Synthesis of Angular Triquinane **57**, Methanolysis and Radical Opening of the Cyclopropyl Ring



and **49b₂** in 48% overall yield, the latter being the major component of the mixture (1:15 mixture). The stereochemical assignment of **49b₂** was based on NOE experiments. Alcohols **49a₁** and **49a₂** could be obtained in a 1.5:1 ratio by reduction of **48a** with LiAlH₄. The structure of **49a₁** could be unambiguously established by X-ray crystallography (Figure 4).[39] Thus, the stereochemistry of **49a₂** could be deduced, and as a matter of fact, the relative arrangement of the substituents in the four important capnellenol derivatives **49** was unambiguously established.

Alcohol **49b₂** was submitted to hydrogenation over platinum oxide (Scheme 21).[40] As expected, the reduction occurred at the less-hindered bond of the cyclopropane unit, giving **50b₂** in 93% yield. This alcohol was reduced using the Barton−McCombie procedure,[41] providing **51b** in 62% overall yield. It was desilylated into **52b** using tetrabutylammonium fluoride in excellent yield. This alcohol was oxidized into the corresponding ketone **53** using Dess−Martin periodinane.[42] Lastly, a Wittig methylenation transformed **53** into $\Delta^{9(12)}$-capnellene in 77% yield.

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(38) It is worth noting that a complex mixture ensued when starting either from the acetate of **45**, even when protected as acetal using ethylene glycol, or from the alcohol resulting from the reduction with NaBH₄.

(39) CCDC 706846.

(40) For an example of such transformation, see:Taber, D. F.; Nakajima, K.; Xu, M.; Rheingold, A. L. *J. Org. Chem.* **2002**, *67*, 4501 See also. Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K. *Tetrahedron* **1993**, *49*, 11189.

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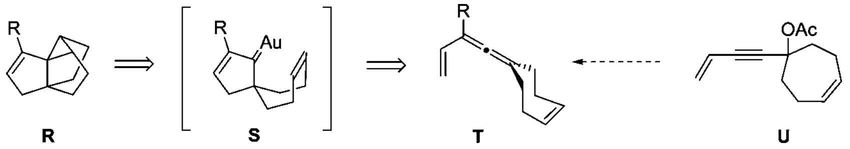
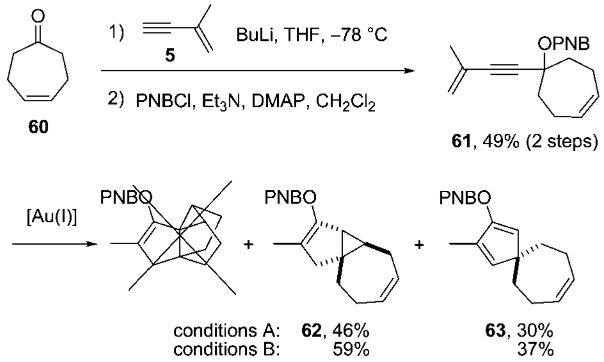
Scheme 25. Retrosynthetic Approach to Propellanes

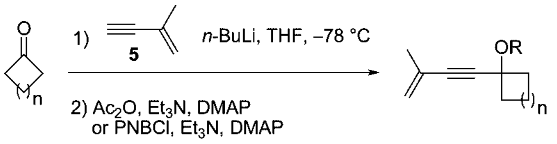


Scheme 26. Synthesis and Cycloisomerization of Benzoate **61**[a]



[a] Conditions A: AuCl(PPh_3) (2 mol %), $AgSbF_6$ (2 mol %), CH_2Cl_2, rt; Conditions B: Cat **I** (2 mol %), CH_2Cl_2, rt.

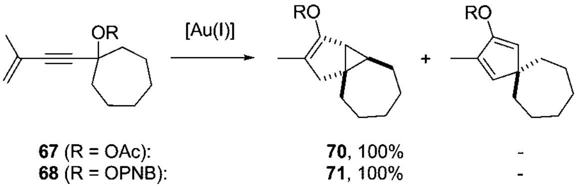
Scheme 27. Synthesis of Enyl Esters **64**−**69**



n	Product	Yield (%)
1	**64**	89[a]
2	**65**	86[a]
3	**66**	71[a]
4	**67**	87[a]
4	**68**	76[b]
5	**69**	74[a]

[a] R = Ac; [b] R = PNB

Scheme 28. Cycloisomerization of Enyl Acetates **67** and **68**[a]

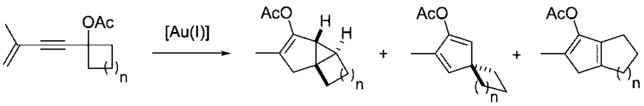


[a] [Au(I)]: Cat **I** (2 mol %), CH_2Cl_2, rt, 10 min.

It is worth noting that it was not necessary to start from a diastereomerically pure alcohol such as **49b₂** to achieve the synthesis of the key compound **53**. Any of the four diastereomers **49** would provide this ketone as a single diastereomer, as shown by the transformation of the mixture obtained after reduction of **48a/48b** by $LiAlH_4$ (Scheme 22).

To summarize this section, $\Delta^{9(12)}$-capnellene has been prepared via a 15-step synthesis with an overall yield of 17%, which is one of the most efficient to date. The key step is the formation of the linear triquinane skeleton via gold-catalysis. The remote stereogenic center does not influence the diastereoselectivity of this process which remains complete. Interestingly, our strategy also grants access to capnellenol derivatives.

Scheme 29. Cycloisomerization of Enyl Acetates **64**−**67** and **69** with Calculated Energies of Activation (kcal·mol^{-1})[a]



Precursor	n	Product, Yield, (calculated $\Delta G^{\ddagger}_{298}$)				
64	1	-	(29.6)	-	**72**, 83%	(11.9)
65	2	-	(26.9)	-	**73**, 97%	(18.7)
66	3	-	(23.9)	**74**, 86%[b]	-	(22.2)
67	4	**70**, 100%	(17.8)	-	-	(23.4)
69	5	**75**, 99%	(16.4)	-	-	(26.0)

[a] [Au(I)]: Cat **I** (2 mol %), CH_2Cl_2, rt. [b] Yield including this product and the corresponding ketone arising from the partial hydrolysis of the vinyl acetate framework during workup.

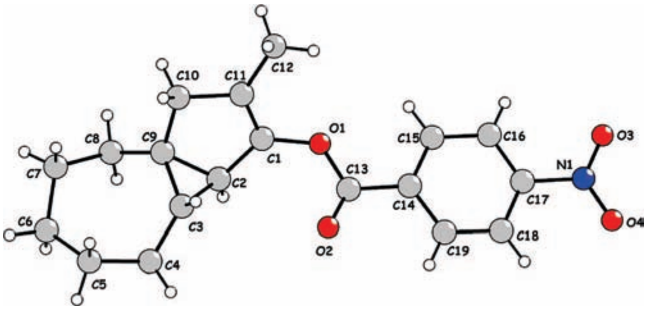


Figure 5. X-ray structure of compound **71**.

4.2. Angular Triquinanes. Angular triquinanes are usually pretty difficult to assemble. We reasoned that our tandem reaction could provide an expedient access to these compounds, starting from cyclopentylacetates (Scheme 23).

One such substrate, **56**, was prepared stereoselectively from enone **54** and enyne **5** (Scheme 24). Gratifyingly, the cycloisomerization step proceeded smoothly. Compound **57** could be isolated in 90% yield as an unseparable 1.8:1 mixture of two diastereomers. The components of this mixture, which includes a *cis*−*cis* and a very rare *cis*−*trans* angular triquinane,[43] could not be structurally assigned unambiguously by spectroscopic techniques. We carried out the methanolysis of the mixture to get the corresponding ketones **58M** and **58m** diastereoselectively, which could be separated. However, we still could not determine the stereochemistry of these compounds. One of the stereogenic center was removed by radical opening using samarium(II) iodide, but again, the relative arrangement of the stereogenic centers could not be ascribed unambiguously.

To summarize this section, the very efficient conversion of **56** into **57** validated our new approach to angular triquinanes, even if in the specific case that we studied, it was not possible to determine the stereochemistry of the products.

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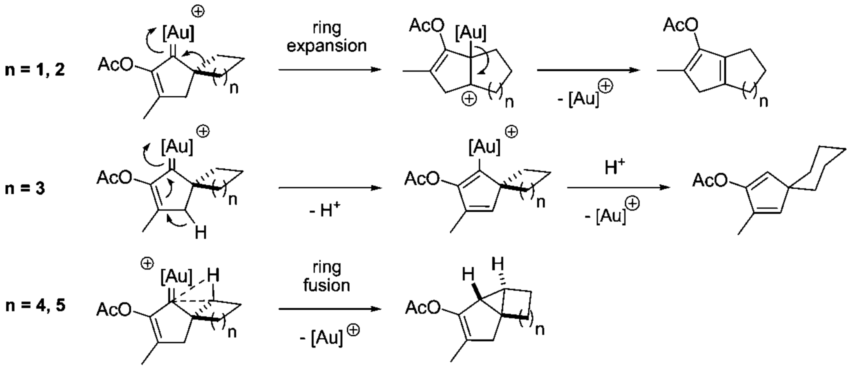
Scheme 30. Mechanistic Rationale for the Formation of Products **70** and **72**−**75** from Cyclopentenylidenes



4.3. Attempted Preparation of Propellanes Leading to New Synthetic Opportunities. After having prepared linear and angular triquinanes, we turned our attention to propellanes. At first glance, they could be obtained by the same strategy from vinyl allenes of type **T** (Scheme 25). However, a closer look at the structure of the spiranic intermediate **S** revealed that the cyclopropanation step could be quite difficult. Indeed, the double bond supposed to interact with the carbenic center lies perpendicular to the plane of the cyclopentenylidene. However, a somewhat parallel arrangement is required for the cyclopropanation (see Figure 3, $\mathbf{TS_{JL}}$). Thus, even in the case where **T** or **U** incorporate a large ring, the formation of a propellane might be thwarted by other competing pathways.

Indeed, no propellane was found in the mixture resulting from the reaction of ester **61** displaying a seven-membered ring (Scheme 26). Instead, we found two interesting products: the tricyclic compound **62** and the spiro-cyclopentadiene **63**.

To make sure that the double bond of the seven-membered ring was actually not required and also to study the influence of the ring size, we prepared acetates **64**−**67** and **69** and the *p*-nitrobenzoate **68** (Scheme 27).

Fortunately, in the case of the seven-membered ring systems **67** and **68**, only the tricyclic products **70** and **71** ensued, in 100% yield in each case (Scheme 28). The structure of **71** was confirmed by a single-crystal X-ray analysis (Figure 5).[44]

We reasoned that the difference in outcome between the reaction of **61** and that of **67** and **68** might be due to the greater rigidity of the seven-membered ring induced by the double bond. To probe this hypothesis, we carried out the gold-catalyzed cycloisomerizations of enyl acetates **64**−**66** and **69**, incorporating rings of various sizes (Scheme 29). All of these compounds were transformed in high yields with perfect chemo- and diastereoselectivities. Substrates **64** and **65**, displaying a four- and a five-membered ring, respectively, transformed into the bicyclic fused cyclopentadienes **72** and **73** in 83% and 97% yield. With a six-membered ring, **66** gave rise to the spiro-cyclopentadiene **74** (and the corresponding ketone) in 86% yield (overall). Lastly, with a seven- and an eight-membered ring, respectively, **67** and **69** furnished the tricyclic products **70** and **75**, isolated nearly quantitatively as single diastereomers.

We believe that these compounds arise from the intermediate spiranic cyclopentenylidene that evolved following different

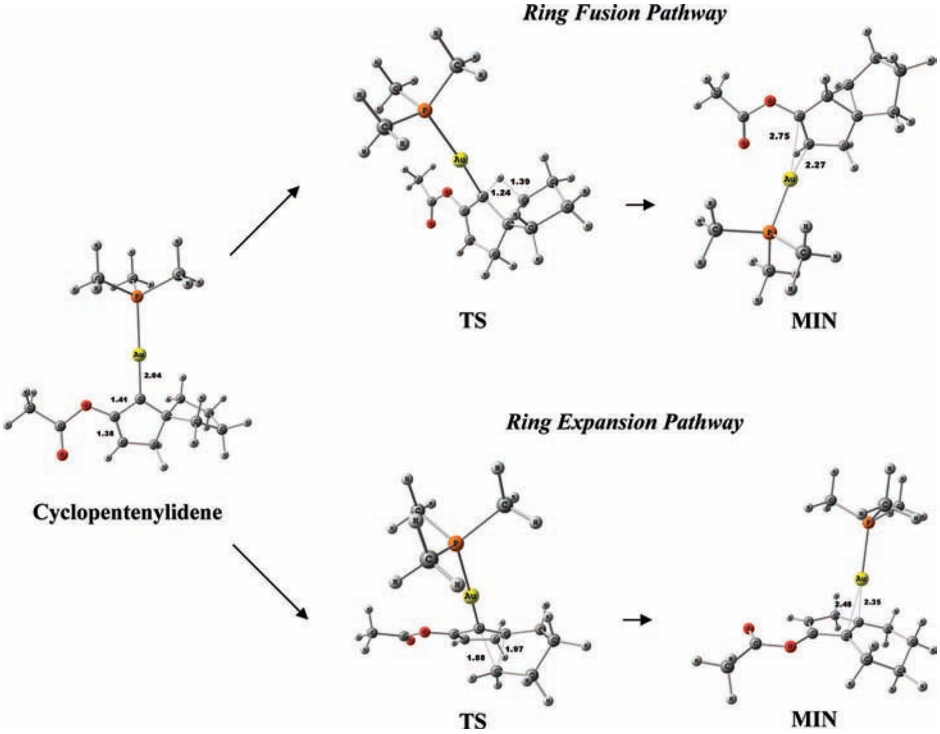


Figure 6. Selected computed structures ($n = 2$, distances in Å).

pathways according to the size of the joint ring (Scheme 30). With short rings ($n = 1$ or 2), in order to release some strain energy, a carbocation 1,2-rearrangement resulting in ring expansion occurs (eq 1). One such reaction was reported by Toste and co-workers.[6d] With larger rings ($n = 4$ or 5), C−H insertion resulting in ring fusion is observed (eq 3), a process that might be driven by entropic factors. Whereas 1,5 C−H insertions at metallic carbene centers are quite common,[45] 1,3-processes are rare.[46] A related nondiastereoselective example has been described by Iwasawa and co-workers with platinum.[6d] Lastly, with a six-membered ring ($n = 3$), another process takes place, unprecedented for that kind of system, a proton transfer giving rise to a spiro-cyclopentadiene. Since the intermediate carbene suffers no ring strain in this case, the ring fusion pathway would be disfavored at least enthalpically and so would be the expansion pathway to a cycloheptene for which both enthalpic and entropic factors would contribute to increase the energy of activation.

Whereas this last proton-elimination is not possible to model, we carried out DFT computations on the ring-expansion and ring-fusion steps (see DFT Computations section for computational details, $Au(PMe_3)^+$ was chosen as metallic fragment in the calculations). The corresponding energies of activation, reported in Scheme 29, match perfectly with the observed results, giving credit to the intermediacy of cyclopentenylidene species and their proposed modes of evolvement. Along the series, as n increases, the energy to reach the ring fusion transition state decreases from 29.6 to 16.4 $kcal\cdot mol^{-1}$. Conversely, the energies corresponding to ring expansion increase from 11.9 to 26.0 $kcal\cdot mol^{-1}$. Interestingly, with $n = 3$, both processes require quite high activation energies above 22 $kcal\cdot mol^{-1}$, leaving space for an alternative transformation as observed.

5. Conclusion and Perspectives

Our combined experimental and theoretical study clearly establishes the intermediacy of cyclopentenylidenes in gold(I)-catalyzed cycloisomerization of vinylallenes. These carbenes can be trapped in various ways to give rise to organic structures of interest. Notably, the reaction with a double bond allows the diastereoselective formation of valuable polycyclic compounds. The usefulness of this strategy for organic chemistry was demonstrated by the total synthesis of $\Delta^{9(12)}$-capnellene. Since this type of cycloisomerization proceeds with chirality transfer, it is likely that natural products could be prepared in an enantioselective manner using this strategy. We will now orient our ongoing program around this key feature, as well as around the valorization of the side issues that were revealed during our study. Indeed, in the absence of a double bond to trap the gold carbenes, other evolution modes become possible, all leading with great selectivities to elaborated products. We are also exploring the cycloisomerization of higher homologues of ene vinyl allenes such as ene allyl allenes and others.

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Supporting Information Available: Experimental procedures, crystallographic information files, spectral data, and coordinates of computed structures; complete ref 25. This material is available free of charge via the Internet at http://pubs.acs.org.

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(44) CCDC 706847.

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