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Gold(I)-Catalyzed Intramolecular Cyclopropanation of Dienynes

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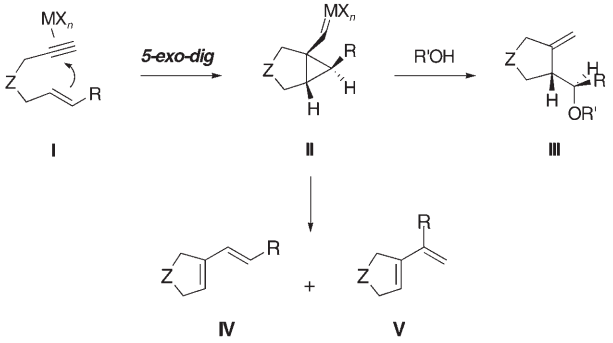
Abstract: Gold(I) complexes are the most active catalysts for the biscyclopropanation of dienynes to form tetracyclic compounds. Pt^{II} and Zn^{II} are also able to promote the biscyclopropanation, although less efficiently. The configurations obtained in all cases with the use of gold(I) catalysts can be explained by the pathway proceeding through *anti* cyclopropyl gold carbenes. Similar intermediates are most probably involved in reactions catalyzed by Ru^{II} and Pt^{II}. Two different cyclopropanation pathways have been found; they depend on the structures of the cyclopropyl gold carbenes (*anti* or *syn*) and the relative arrangements of the metal carbenes and the alkenes.

Keywords: alkynes · cyclization · density functional calculations · gold · platinum · zinc

Introduction

Transition-metal-catalyzed reactions of 1,6-enynes[1,2] that proceed through the selective coordination of the metal to the alkyne (**I**) take place through *exo*-cyclopropyl metal carbenes **II** or the related *endo* intermediates (Scheme 1).[2,3] Reactions between **II** and alcohols or water gives products of alkoxy- or hydroxycyclization **III**. In the absence of nucleophiles, enynes undergo skeletal rearrangements to form dienes **IV** (*single cleavage*) and/or **V** (*double cleavage*).[4,5]

We proposed the involvement of intermediates **II** in Pt^{II}-catalyzed cyclization of enynes on the basis of DFT calculations[2a,b] and the isolation of cyclopropanecarbaldehyde in Pt^{II}-[2b] or Pd^{II}-mediated hydroxycyclization[6] of certain enynes. Recently, we have also proposed similar intermediates in Au^{I}-catalyzed hydroxy- and alkoxycyclization[3,7] and the skeletal rearrangements of 1,6-enynes.[8] Cyclopropyl derivatives were also obtained by Trost et al. in intermolecular reactions between dienynes and alkenes.[9] Other theoretical work has also supported the involvement of intermediates **II** in these reactions.[2,3,10]



Scheme 1. *exo*-Cyclization of enynes through cyclopropyl metal carbenes **II**.

Strong evidence for the existence of intermediates such as **II** was also obtained in the reactions of dienynes such as **1** catalyzed by electrophilic metal complexes described by Murai's group (Scheme 2).[11] The ruthenium carbene intermediate is trapped intramolecularly by the terminal alkene yielding tetracycle **2** containing two cyclopropanes.

Malacria's group has described related examples in the $PtCl_2$-catalyzed reactions of substrates **3,** containing propargyl alcohol or ether units in their structures, to form tetra-

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Supporting information (atomic coordinates for structures) for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

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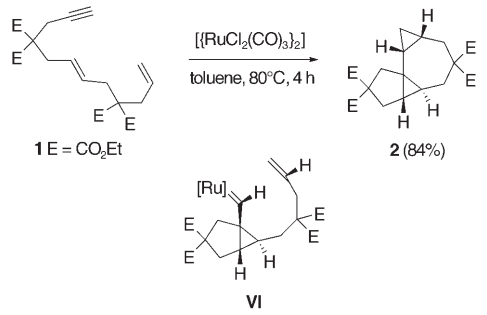
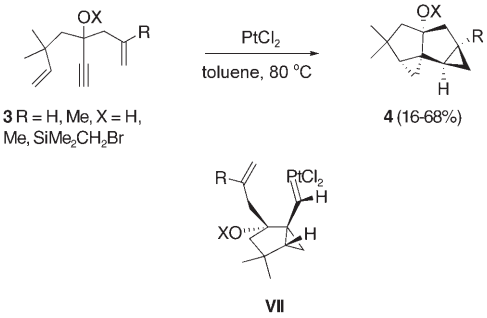


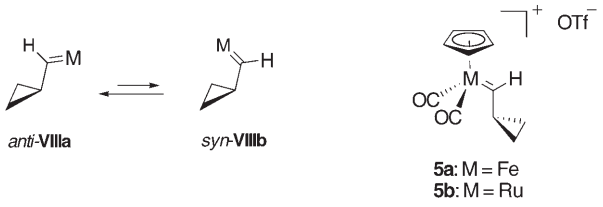
Scheme 2. Ru^{II}-catalyzed biscyclopropanation of dienyne **1**.[11]

cycles **4** (Scheme 3).[12] In this reaction, the cyclopropyl platinum carbene **VII** is probably formed as an intermediate.[10]



Scheme 3. Pt^{II}-catalyzed biscyclopropanation of dienynes **3**.[12]

In a cyclization of this kind, the relative configuration of the second cyclopropane is determined by the conformation of the cyclopropyl metal carbene around the single C–C bond. The observed stereochemistry of the last cyclopropanation can be interpreted by assuming a more favored antiperiplanar arrangement of the cyclopropane and the metal carbene (*anti*-**VIIIa**) (Scheme 4), which is in full agreement



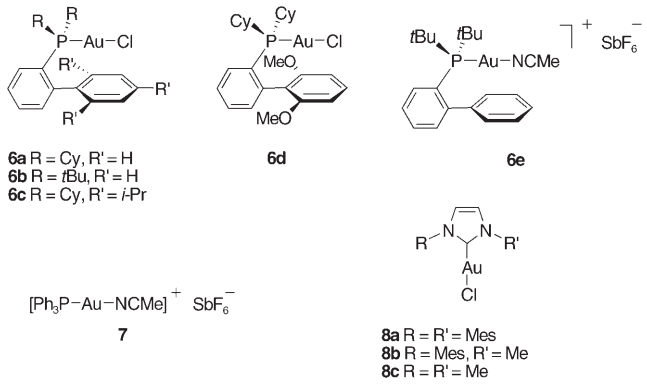
Scheme 4. *syn*- and *anti*-Cyclopropyl metal carbenes.

with the results of the calculations.[2b,c,3] Such an arrangement is also consistent with the results of Brookhart et al.,[13] which show preferred antiperiplanar conformations for iron (**5a**) and ruthenium (**5b**) cyclopropyl carbene complexes.

Using cationic gold(I) complexes $[Au(PPh_3)]^+ X^-$ (X = BF_4, SbF_6), we have recently reported examples of biscyclopropanation reactions occurring at temperatures much lower that those required with Ru^{II} and Pt^{II} catalysts.[3,14] Here we report details of this work, including a theoretical study of the Au^I-catalyzed intramolecular cyclopropanation.

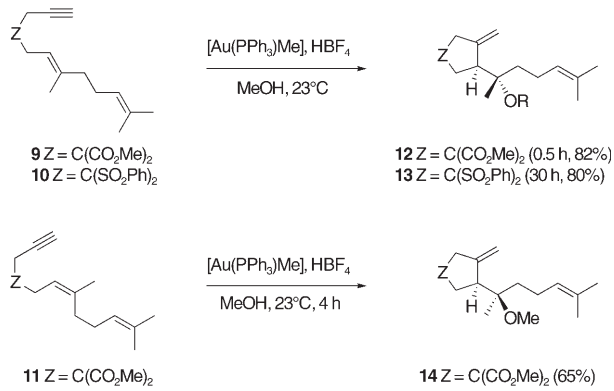
Results and Discussion

Scope of the intramolecular cyclopropanation: In addition to readily available $[Au(PPh_3)Cl]$,[15] we also assayed as catalysts the new Au^I complexes **6a-e**,[16] with bulky, biphenyl-



based phosphanes.[17] Cationic complex **7** was prepared by chloride abstraction of $[Au(PPh_3)Cl]$ with $AgSbF_6$ in acetonitrile. Complexes with *N*-heterocyclic donor ligands **8a–c**[18] were also tested as catalysts. Complex **8a** and several related complexes have been independently prepared by Nolan et al.[19]

We had found that dienynes **9–11** react with a catalyst formed from $[Au(PPh_3)Me]$ and protic acid in MeOH to give methoxycyclization products **12–14** exclusively (Scheme 5).[3,7]



Scheme 5. Methoxycyclization of dienynes **9–11**.

In the absence of MeOH, dienyne **9** reacts with a variety of Au^I complexes to give tetracycle **15** as the major or exclusive product under very mild conditions (Table 1). An active catalyst could also be generated by treatment of $[Au(PPh_3)Me]$ with trifluoroacetic acid (TFA). No reaction was observed in DMF or in the presence of additional PPh_3

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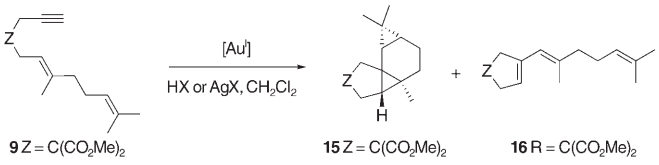
Table 1. Intramolecular cyclopropanation of dienyne **15** with [Au^{I}] (2 mol%).



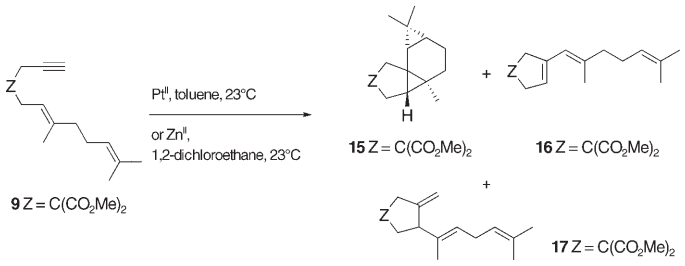
Entry	Catalyst[a]	T [°C]	t [h]	Product(s) (yield [%])
	AuCl	23	1	**15** (60) + **16** (2%)
1	AuCl/$AgSbF_6$	−40	3	**15** (13)
2	[Au(SMe_2)Cl]/$AgSbF_6$	−40	3	**15** (22)
3	[Au(PPh_3)Cl]/$AgSbF_6$	−40	3	**15** (47)
4	[Au(PCy_3)Cl]/$AgSbF_6$	−40	3	**15** (55)
5	[Au{P(C_6F_5)$_3$}Cl]/$AgSbF_6$	−40	3	**15** (24)
6	[Au{P(o-Tol)$_3$}Cl]/$AgSbF_6$	−40	3	**15** (64)
7	[Au($AsPh_3$)Cl]/$AgSbF_6$	−40	3	**15** (50)
8	[Au(PPh_3)Cl]/$AgBF_4$	−30	0.3	**15** (78) + **16** (7)
9	[Au(PPh_3)Me]/TFA[b]	23	240	**15** (63)
10	**6a**	−40	3	**15** (78)
11	**6c**	−40	3	**15** (49) + **16** (30)
12	**7**	23	0.1	**15** (98)
13	**8a**	−40	3	**15** (71)
14	**8b**	−40	3	**15** (71)
15	**8c**	−40	3	**15** (79)

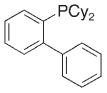
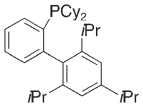
[a] 2 mol% Au^{I} complex and (for reactions in entries 1–8, 10, 11, 13–15) 2 mol% Ag^{I} salt. [b] 3 mol% gold(I) and 6 mol% TFA.

(1 equiv). The tetracyclization was usually complete with quantitative conversion in less than 3 h at −40 °C with most Au^{I} catalysts, the exceptions being catalysts generated from AuCl, [Au(SMe_2)Cl], and [Au{P(C_6F_5)$_3$}Cl]/(Table 1, entries 1, 2, and 5), which gave lower yields. For preparative purposes, the best conversion was achieved by use of cationic catalyst **7**, which resulted in almost quantitative formation of tetracycle **15** in just 5 min at room temperature (Table 1, entry 12). Whilst skeletal rearrangement derivative **16** could also be detected as a minor product in some of the reactions, a substantial amount of **16** was formed with complex **6c** (Table 1, entry 11), which bears a rather bulky phosphane as ligand.

The use of Pt^{II} and Zn^{II} as catalysts in the tetracyclization of **9** was also examined (Table 2). In all cases, reactions catalyzed by Pt^{II} were slower than those catalyzed by Au^{I} (Table 1). The reaction proceeded more satisfactorily with complexes prepared in situ from $PtCl_2$ and 1 equivalent of PCy_3 as ligand, which gave the best selectivity and yield of **15** (ca. 37%) (Table 2, entry 2). With other bulky phosphanes, in addition to tetracycle **15**, the skeletal rearrangement product **16** was obtained as the major compound, along with Alder-ene cycloisomerization derivative **17**[2a,b] (Table 2, entries 3–5). Interestingly, although Zn^{II} has seldom been used in enyne cyclizations,[20] we found that **9** reacted in the presence of [$ZnCl_2$(PPh_3)][21] and $AgSbF_6$ (50 mol% each) in 1,2-dichloroethane at room temperature to afford a mixture of tetracycle **15** and skeletal rearrangement product **16**, although the yield of isolated product was low (Table 2, entry 6). With [$ZnCl_2$(PPh_3)] or Zn(OTf)$_2$ in the absence of Ag^{I}, **16** was obtained along with other uncharacterized compounds (Table 2, entries 7–9).

Table 2. Intramolecular cyclopropanation of dienyne **9** in the presence of Pt^{II} (5 mol%) or Zn^{II}.



Entry	MX_n [mol%]	L[a]	t [h]	Product(s) (yield, [%]; ratio)[b]
1	$PtCl_2$ (5)	–	17	**15** (30)
2	$PtCl_2$ (5)	PCy_3	17	**15** + **16** + **17** (70; 3:1.6:1)
3	$PtCl_2$ (5)	P(oTol)$_3$	17	**15** + **16** + **17** (89; 6:8:1)
4	$PtCl_2$ (5)		17	**15** + **16** + **17** (74; 2:2.6:1)
5	$PtCl_2$ (5)		17	**15** + **16** + **17** (77; 1.7:2.6:1)
6	[$ZnCl_2$(PPh_3)]/$AgSbF_6$ (50)	-	0.5	**15** (9) + **16** (21)[c]
7	[$ZnCl_2$(PPh_3)]	-	7[d]	**16** (11)[e]
8	Zn(OTf)$_2$ (50)	-	15[d]	**16** (10)[f]
9	Zn(OTf)$_2$ (50)	PPh_3	24[d]	**16** (7)[g]

[a] An equimolar amount of L was used. [b] Yield of isolated product; product ratios determined by GC and/or ^{1}H NMR spectroscopy. [c] 88% conversion; yield of **16** determined by ^{1}H NMR spectroscopy. [d] Reaction performed at 70 °C. [e] 71% conversion; yield of **16** determined by ^{1}H NMR spectroscopy. [f] 65% conversion; yield of **16** determined by ^{1}H NMR spectroscopy. [g] 74% conversion; yield of **16** determined by ^{1}H NMR spectroscopy.

Tetracycles were also obtained in the reactions of other dienynes (Scheme 6). The disulfone **10** and the diacetate **19** cyclized in excellent yields in the presence of catalyst **7** in 5 min at room temperature to give the tetracycles **18** and **20**, respectively. In the case of the *N*-toluene-4-sulfonyl derivative **21**, use of the cationic Au^{I} complex **7** gave a 50% yield, whereas a better yield was obtained with [Au(PPh_3)Cl] and $AgSbF_6$ in CH_2Cl_2 at 0 °C. The propargyl ester **23** afforded **24** as a single isomer in the presence of the neutral Au^{I} complex **8c**. The cyclization of **25**, an analogue of substrate **1** (Scheme 2) with three additional methyl groups on the alkenes, provided the tetracycle **26** in good yield under very mild conditions. On the other hand, the reaction of **27** in the presence of catalyst **7** was relatively slower and provided a mixture of the tetracycle **28** and the skeletal rearrangement product **29**.

In all cases single diastereomers were obtained. The configurations of the tetracyclic compounds were determined by NOESY experiments. In the case of the bissulfone **18**, the configuration was confirmed by an X-ray structure determination (Figure 1).

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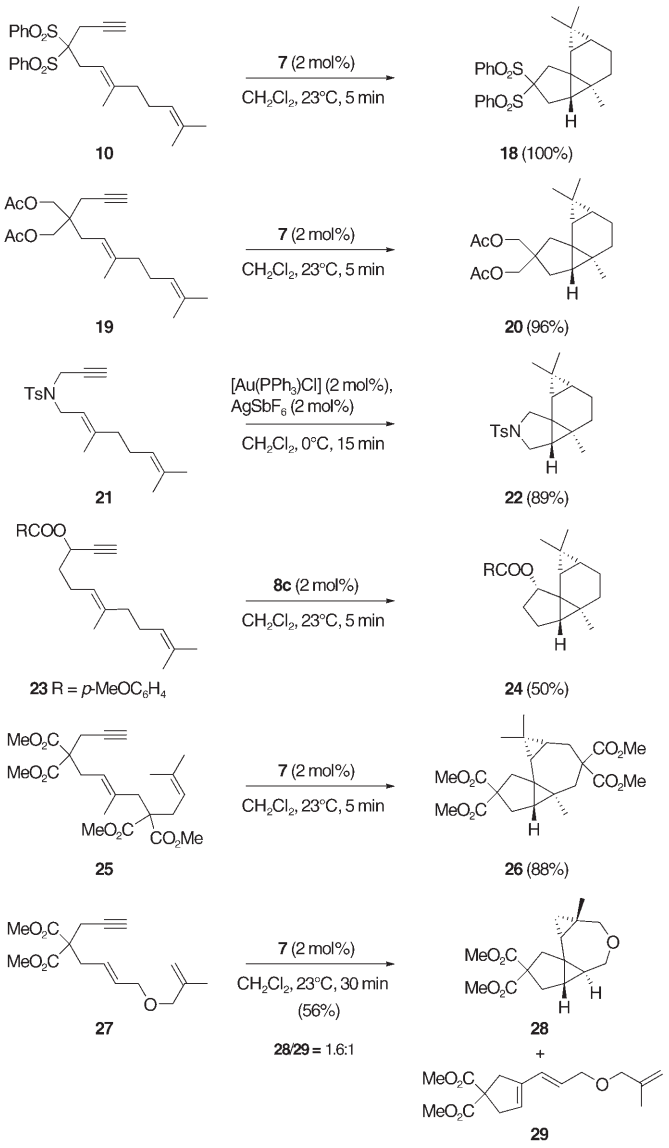


Scheme 6. Cyclization of dienynes **10**, **19**, **21**, **23**, **25**, and **27**.

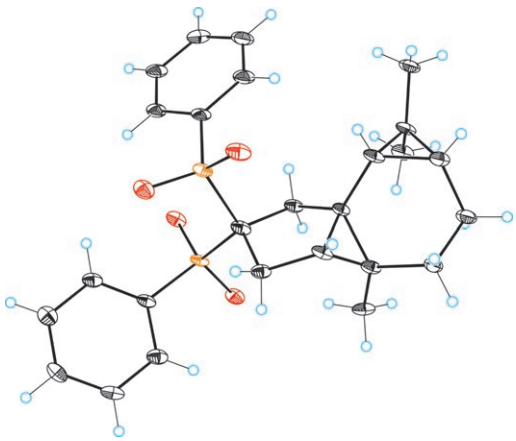
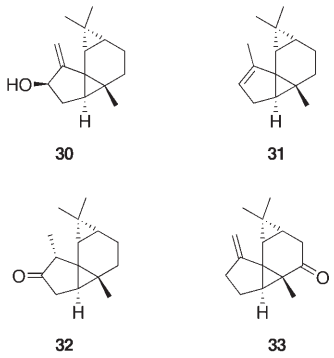
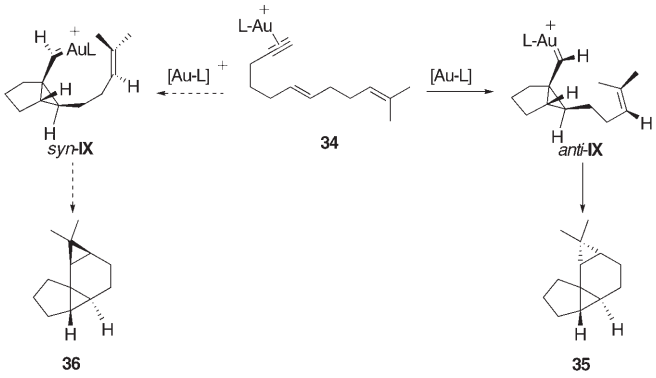


Figure 1. Structure of the tetracycle **18** (ORTEP diagram with thermal ellipsoids at 50% probability).

It is interesting to note that tetracycles **15**, **18**, **20**, **22**, and **24** possess the same carbon skeleton as myliol (**30**), an unusual sesquiterpene that was isolated as the major component of pentane extracts of the liverwort (Hepaticae) *Mylia taylorii*.[22,23] Other members of this family of sesquiterpene are anastreptene (**31**),[24] dihydromylione A (**32**),[25] and myli-4(15)-en-9-one (**33**).[26]



Stereoselectivity and the mechanism of the double cyclopropanation: The relative configuration between the two cyclopropane rings common to the natural products **30**–**33** is the opposite of that obtained in the cyclization of the dienynes. An explanation of the formation of products **35** and **36**, with opposite configurations at the dimethylcyclopropane, is presented in Scheme 7. Thus, a simplified dienyne such as **34**



Scheme 7. Mechanistic proposal for the stereoselective formation of tetracycles **32** via *anti*-**IX**.

could form either *anti*-**IX** or *syn*-**IX** cyclopropyl gold(I) carbenes, which would undergo intramolecular cyclopropanation to give **35** (unnatural configuration) or **36** (*ent*-myliol-type configuration).

The stereoselectivity of the last cyclopropanation appears to be a result of the kinetically controlled trapping of *anti*-**IX**. To gain insight into the mechanism of this process we carried out DFT calculations starting from model complex **34**, which shows the metal coordinated in an η^1 fashion to the alkyne (Figure 2). As also observed with a simpler 1,6-

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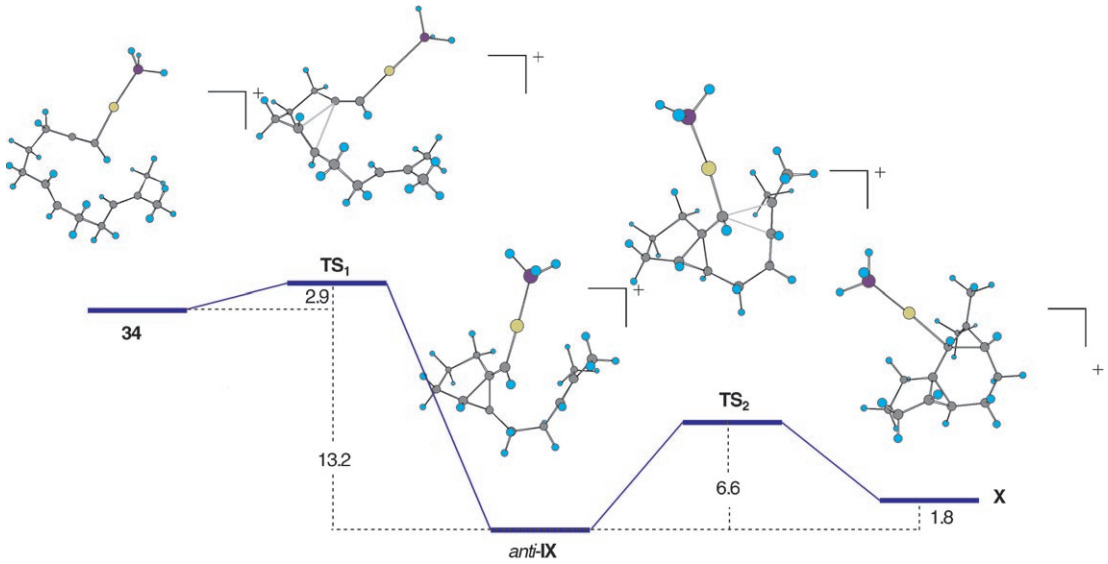

Figure 2. Reaction pathway for the biscyclopropanation from complex **34** calculated at the B3LYP/6–31G(d) (C,H,P), LANL2DZ (Au) level (ZPE-corrected energies are given in kcal mol^{-1}). Color code: Au: yellow; C: gray; P: purple; H: turquoise.

enyne,[3] complex **34** evolves exothermically through *anti* attack of the alkene to the (η^1-alkyne)gold moiety to form *anti*-**IX** through an early transition state $\mathbf{TS_1}$. Remarkably, the second cyclopropanation takes place via transition state $\mathbf{TS_2}$ in a single step to form a corner-metalated cyclopropane **X** in a slightly endothermic process. However, this reaction is kinetically reasonable and much more favorable than the possible isomerization of *anti*-**IX** to *syn*-**IX** (see Figure 3), a process for which an activation energy as high as 24.7 kcal mol^{-1} has been estimated in a model system.[8] Corner metalation of the cyclopropane would be expected to be more favorable for a poor back-donor such as Au^I.[27,28] A concerted cyclopropanation by a platinum carbene has also been identified as the most favorable pathway for the cyclopropanation of a model system in which a propargylic hydroxyl group could act as an additional coordination site for the metal.[10]

Complex *syn*-**IX** can be formed directly by *syn* attack of the alkene on the (η^1-alkyne)gold moiety in complex **34′**, a slightly more stable conformer of **34** (Figure 3). However, the activation energy required to reach $\mathbf{TS_3}$ in this *syn* process is much higher than that required in the *anti* attack of the alkene to form *anti*-**IX** (10.3 vs. 2.9 kcal mol^{-1}). Complex *syn*-**IX** shows a weak stabilizing interaction between the electrophilic gold(I) carbene and the alkene that might explain why **34′** does not evolve to form a cyclobutene intermediate. Intermediate *syn*-**IX** evolves by a complex two-step process to form firstly a C–C bond in intermediate **XI** and finally an edge-metalated cyclopropane **XII**. A subsequent demetalation would furnish **36** (Scheme 7), with the relative configuration fond in myliol (**30**) and related sesquiterpenes. Overall, however, this alternative biscyclopropanation proceeding via *syn*-**IX** is kinetically and thermodynamically much less favorable than that proceeding via *anti*-**IX**.

It is interesting to note that, whereas in the cyclopropanation of *anti*-**IX** the gold carbene behaves as a two-electron electrophile (such as in the formation of bromonium ions from alkenes), the gold carbene of *syn*-**IX** behaves as a proton or a carbenium ion, producing an open carbocation-type species **XI**. In either case, both processes appear to be electrophilic cyclopropanations of alkenes.[29]

Conclusion

Highly alkynophilic gold(I) complexes are the most active catalysts for the biscyclopropanation of dienynes to form complex tetracyclic compounds. These reactions are remarkably clean in most cases and take place at room temperature in a few minutes. Pt^{II} and Zn^{II} are also able to promote the biscyclopropanation, although less efficiently. The common configuration obtained in all cases can be explained by the pathway shown in Figure 2, proceeding through intermediates such as *anti*-**IX**. Similar intermediates are most probably involved in reactions catalyzed by Ru^{II} and Pt^{II}. Interestingly, two different cyclopropanation pathways have been uncovered, depending on the structures of cyclopropyl gold carbenes (*anti* or *syn*) and the relative arrangements of the carbenes and the alkenes. Similar mechanisms might be operative in the recently developed intermolecular Au^I-catalyzed cyclopropanation of alkenes with diazo compounds.[30,31]

Experimental Section

Computational methods: Calculations were performed with Gaussian 98.[32] The geometries of all complexes were optimized by application

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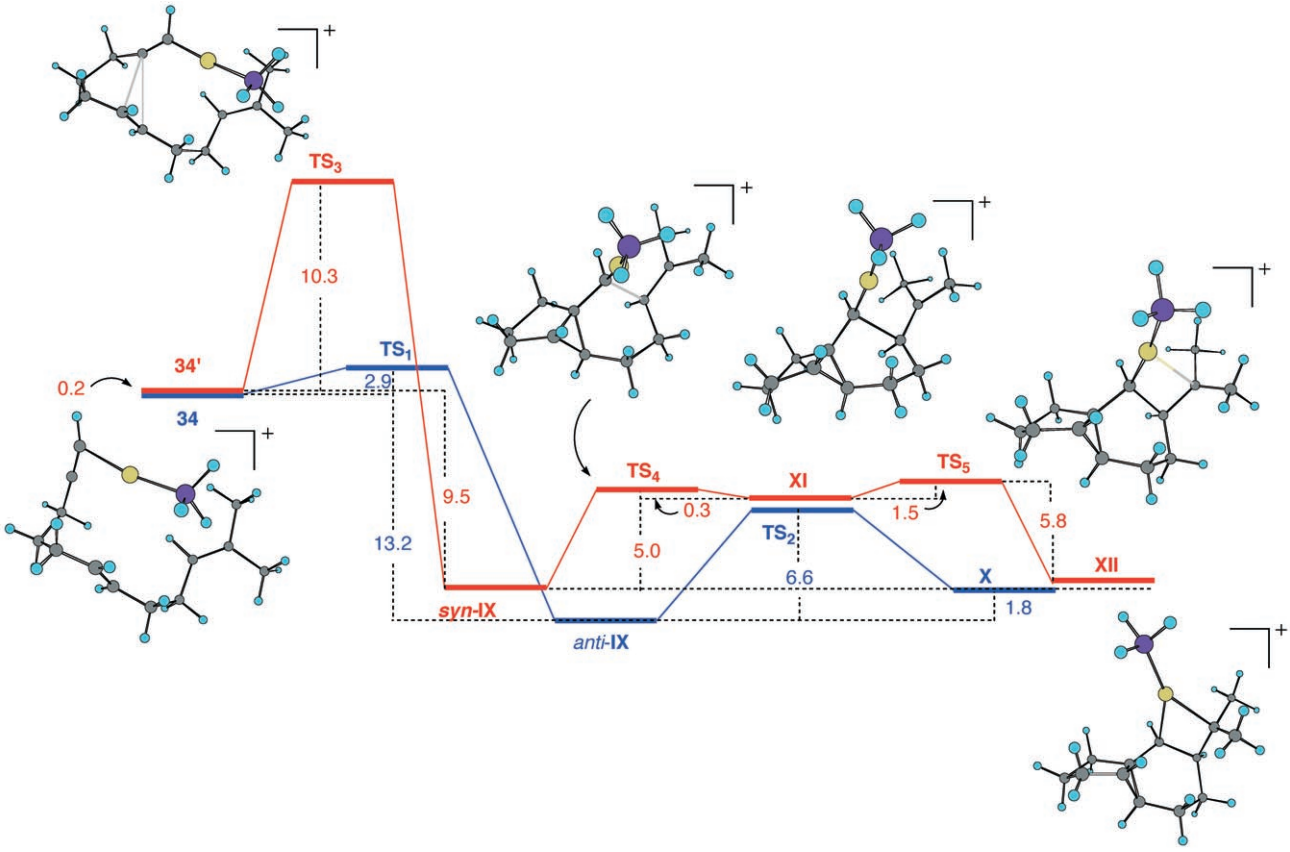

Figure 3. Reaction pathway for the biscyclopropanation from complex **34′** calculated at the B3LYP/6–31G(d) (C,H,P), LANL2DZ (Au) level (ZPE-corrected energies are given in kcal mol^{-1}). The biscyclopropanation pathway from complex **34** (blue) is included for comparison. Color code: Au: yellow; C: gray; P: purple; H: turquoise.

of density functional theory (DFT) at the generalized gradient approximation through the use of the B3LYP hybrid functional.[33] The standard 6–31G(d) basis set was used for C, H, and P. The LANL2DZ basis set, which includes the relativistic effective core potential (ECP) of Hay and Wadt[34] and employs a split-valence (double-ξ) basis set, was used for Au. Energies include zero-point energy (ZPE) correction. Harmonic frequencies were calculated at the same level to characterize the stationary points and to determine the zero-point energies. The starting approximate geometries for the transition states (TSs) were located graphically. Intrinsic reaction coordinate calculations were used to confirm the actual reagent and products for all transition states.

Chemical: All reactions were carried out under Ar or N_2 in dry solvents. Chromatography purifications were carried out with flash grade silica gel (SDS Chromatogel 60 ACC, 40–60 μm).

Compounds **9** and **17** have been described.[2a,b] The synthesis of the Au^{I} complexes **6a–e**, **7**, and **8a–c** is described in the accompanying paper.[7]

Synthesis of dienynes

(*E*)-7,11-Dimethyl-4,4-bis(phenylsulfonyl)dodeca-6,10-dien-1-yne (10): (*E*)-4,8-Dimethyl-1,1-bis(phenylsulfonyl)nona-3,7-diene[7] (500 mg, 1.15 mmol) was added at 0 °C to a suspension of NaH (55 mg, 1.38 mmol, 60% mineral oil) in DMF (15 mL). After 20 min, propargyl bromide (138 mg, 1.15 mmol) was added, and the resulting mixture was stirred at 23 °C for 12 h. After extractive workup (Et_2O/10% HCl) and chromatography (hexane/EtOAc 4:1), **10** (245 mg, 45%) was obtained as a pale yellow solid: mp 78–79.5°; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16–8.14 (m, 2H), 8.13–8.11 (m, 2H), 7.73–7.68 (m, 2H), 7.59–7.55 (m, 4H), 5.42 (t, J = 6.5 Hz, 1H), 5.12–5.10 (m, 1H), 3.18 (d, J = 2.8 Hz, 2H), 3.04 (d, J = 6.5 Hz, 2H), 2.16–2.02 (m, 5H), 1.69 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.44, 136.48, 134.64, 131.52, 128.45, 123.91, 114.87, 89.27, 76.11, 73.99, 39.88, 27.69, 26.18, 25.68, 20.36, 17.74, 16.59 (one carbon signal overlaps) ppm; HMRS-CI m/z calcd for $C_{26}H_{30}O_4S_2$: 471.1664; found 471.1675 $[M+1]^+$.

2-((*E*)-3,7-Dimethylocta-2,6-dienyl)-2-(prop-2-ynyl)propane-1,3-diol: A solution of dimethyl geranylpropargylmalonate (**9**) (2.000 g, 6.53 mmol) in THF (8 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (496 mg, 13.06 mmol) in THF (8 mL). The reaction mixture was stirred at 23 °C for 3 h, and was then cooled to 0 °C and quenched with a saturated solution of tartaric acid. After extractive workup (Et_2O) and chromatography the diol was obtained as a colorless oil. Yield 70% (1055.4 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.14 (m, 1H), 5.04 (m, 1H), 3.64 (m, 4H), 2.31 (br s, 2H), 2.25 (d, J = 2.0 Hz, 2H), 2.08–2.00 (m, 7H), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 8 s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.72, 131.64, 124.12, 118.60, 81.35, 70.65, 67.72, 42.86, 40.04, 30.05, 26.47, 25.71, 21.43, 17.69, 16.09 ppm; HMRS-ESI m/z calcd for $C_{16}H_{27}O_2$ 251.2011; found 251.2014 $[M+1]^+$.

Tetramethyl (*E*)-7,12-dimethyltrideca-6,11-dien-1-yne-4,4,9,9-tetracarboxylate (25): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.20 (t, J = 7.5 Hz, 1H), 4.91 (t, J = 7.5 Hz, 1H), 3.72 (s, 6H), 3.69 (s, 6H), 2.80 (s, 2H), 2.75 (d, J = 2.6 Hz, 2H), 2.60 (s, 2H), 2.58 (s, 2H), 2.02 (t, J = 2.7 Hz, 1H), 1.68 (s, 3H), 1.59 (s, 3H), 1.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.70, 170.60, 135.82, 133.00, 124.67, 117.69, 76.69, 71.76, 57.56, 52.72, 52.34, 41.67, 31.07, 31.00, 26.04, 22.43, 17.91, 16.82 ppm; HRMS-ESI m/z calcd for $C_{23}H_{32}O_8Na$: 459.1995; found 459.1999 $[M+Na]^+$.

2-((*E*)-3,7-Dimethylocta-2,6-dienyl)-2-(prop-2-ynyl)propane-1,3-diyl diacetate (19): A solution of the above diol (1.000 g, 4.0 mmol) in CH_2Cl_2 (4 mL) was added to a solution of DMAP (48.8 mg, 0.4 mmol) and pyridine (650 μl, 8.0 mmol). Ac_2O (1.5 mL, 16 mmol) was then added dropwise. The mixture was stirred at 23 °C overnight, and after extractive workup (CH_2Cl_2) and chromatography, **19** was obtained as a colorless oil.

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Yield 92% (1230 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (m, 2H), 4.05 (m, 4H), 2.25 (d, J = 2.4 Hz, 2H), 2.18 (d, J = 8.0 Hz, 2H), 2.13–2.02 (m, 4H), 2.06 (s, 6H), 2.00 (t, J = 2.7 Hz, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$; DEPT): δ = 170.71 (2 C), 139.57 (C) 131.64 (C) 124.07 (CH), 117.47 (CH), 71.90 (CH), 71.10 (C) 65.49 (2×CH_2), 40.67 (C), 40.03 (CH_2), 29.70 (CH_2), 26.47 (CH_2), 25.67 (2×CH_3), 22.02 (CH_2), 20.82 (CH_3), 17.67 (CH_3), 16.04 (CH_3) ppm; HMRS-ESI m/z calcd for $C_{20}H_{29}O_4$: 333.2071; found 333.2072 $[M-1]^+$.

***N*-((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)-*N*-(prop-2-ynyl)-*N*-(toluene-4-sulfonyl)amine (21)**

i: A solution of toluene-4-sulfonamide (863 mg, 5.04 mmol) in DMF (10 mL) was added at 0°C to a suspension of NaH (60% in mineral oil, 202 mg, 5.04 mmol) in DMF (5 mL), followed by geranyl bromide (1.00 mL, 5.04 mmol). The mixture was stirred for 4 h at 23°C and was then quenched with H_2O. After extractive workup (EtOAc/HCl (10%)) and chromatography (hexane/EtOAc 20:1 to 10:1), *N*-((2*E*)-3,7-dimethylocta-2,6-dienyl)toluene-4-sulfonamide[35] was obtained as a vitreous solid (203 mg, 13%): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 5.04 (m, 2H), 4.27 (t, J = 5.3 Hz, 1H), 3.55 (t, J = 6.5 Hz, 2H), 2.42 (s, 3H), 1.98–1.91 (m, 4H), 1.66 (s, 3H), 1.56 (s, 3H), 1.53 (s, 3H) ppm.

ii: *N*-((2*E*)-3,7-Dimethyl-octa-2,6-dienyl)toluene-4-sulfonamide (170 mg, 0.55 mmol) was added at 0°C to a suspension of NaH (60% mineral oil, 22 mg, 0.55 mmol) in DMF (10 mL). After 10 min, propargyl bromide (80% in toluene, 82 mg, 0.55 mmol,) was added, and the resulting mixture was stirred at 23°C overnight. After the usual workup (EtOAc/HCl (10%)) and chromatography (hexane/EtOAc 30:1), **21** was obtained as a colorless oil (133 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 5.05 (m, 2H), 4.05 (d, J = 2.4 Hz, 2H), 3.82 (d, J = 7.3 Hz, 2H), 2.42 (s, 3H), 2.05–1.96 (m, 4H), 1.67 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$; DEPT): δ = 143.35 (C), 142.48 (C), 136.17 (C), 131.88 (C), 129.38 (CH), 127.80 (CH), 123.71 (CH), 117.77 (CH), 77.08 (CH), 73.29 (C), 43.84 (CH_2), 39.60 (CH_2), 35.22 (CH_2), 26.14 (CH_2), 25.67 (CH_3), 21.51 (CH_3), 17.65 (CH_3), 16.11 (CH_3) ppm; EI-MS m/z (%): 69.00 (71), 91.00 (100), 155.00 (11), 190.15 (9), 222.00 (21), 276.10 (1).

(*E*)-7,11-Dimethyldodeca-6,10-dien-1-yn-3-yl 4-methoxybenzoate (23)

i: A solution of (4*E*)-5,9-dimethyl-4,8-deca-4,8-dienal[36] (353 mg, 1.96 mmol) in THF (5 mL) was added at 0°C to a solution of propargylmagnesium bromide (0.5 M in THF, 5.88 mL, 2.94 mmol) and the mixture was stirred at 23°C for 2 h. After extractive workup (Et_2O) and chromatography (hexane/EtOAc 30:1), (*E*)-7,11-dimethyldodeca-6,10-dien-1-yn-3-ol was obtained as a yellow oil (218 mg, 54%): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.16–5.04 (m, 2H), 4.35 (m, 1H), 2.47 (t, J = 2.0 Hz, 1H), 2.13–2.08 (m, 2H), 1.98–1.91 (m, 5H), 1.72–1.65 (m, 1H), 1.61 (s, 3H), 1.55 (s, 3H), 1.52 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$; DEPT): δ = 136.33 (C), 131.38 (C), 124.17 (CH), 122.97 (CH), 84.99 (C), 72.84 (CH), 61.78 (CH), 39.63 (CH_2), 37.51 (CH_2), 31.83 (CH_2), 26.53 (CH_2), 17.59 (CH_3), 15.92 (CH_3) ppm; HRMS-EI m/z calcd for $C_{14}H_{22}O$: 205.1592; found 205.1589 $[M-1]^+$.

ii: A solution of (*E*)-7,11-dimethyldodeca-6,10-dien-1-yn-3-ol (50 mg, 0.24 mmol) in CH_2Cl_2 (1.5 mL) was added to a mixture of pyridine (0.078 mL, 0.97 mmol) and *p*-anisoyl chloride (83 mg, 0.48 mmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred for 24 h at 23°C and was then heated at reflux in CH_2Cl_2 for 1 h. The solvent was evaporated and the resulting oil was purified by chromatography (hexane/EtOAc 9:1) to give **23** as a colorless oil (75 mg, 86%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.41 (td, J = 6.6, 2.1 Hz, 1H), 5.18–5.05 (m, 2H), 3.86 (s, 3H), 2.48 (d, J = 2.3 Hz, 1H), 2.23 (q, J = 7.3 Hz, 2H), 2.11–1.91 (m, 6H), 1.68 (s, 3H), 1.60 (m, 3H), 1.56 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.19, 163.55, 136.69, 131.81, 131.47, 124.19, 122.42, 113.6, 81.64, 73.48, 63.60, 55.43, 53.20, 39.66, 34.86, 26.62, 25.66, 23.52, 17.67, 16.00 ppm; HMRS-ESI m/z calcd for $C_{23}H_{33}O_8$: 437.2175; found 437.2168 $[M+H]^+$.

Dimethyl 2-[(*E*)-4-(2-methylallyloxy)but-2-enyl]-2-(prop-2-ynyl)malonate (27)

i: Butadiene monoxide (0.946 mL, 11.75 mmol) and dimethyl propargylmalonate (1.78 mL, 11.75 mmol) were added to a mixture of [Pd_2(dba)$_3$·dba] (338.7 mg, 0.589 mmol) and dppe (245.5 mg, 0.616 mmol) in dry THF (10 mL). The mixture was stirred for 3 h at 23°C, the volatiles were evaporated, and the residue was dissolved in Et_2O and filtered through a plug of Celite. After chromatography (hexane/EtOAc 4:1 to 2:1), dimethyl 2-(4-hydroxybut-2-enyl)-2-(prop-2-ynyl)malonate was obtained as a colorless oil (1.64 g, 58%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (dtt, J = 15.5, 5.6, 1.2 Hz, 1H), 5.51 (dtt, J = 15.1, 7.5, 1.5 Hz, 1H), 4.09 (d, J = 5.6 Hz, 2H), 3.74 (s, 6H), 2.82–2.80 (m, 2H), 2.79 (d, J = 2.9 Hz, 2H), 2.02 (t, J = 2.6 Hz, 1H), 1.5 (brs, 1H).

ii: A solution of the dimethyl 2-(4-hydroxybut-2-enyl)-2-(prop-2-ynyl)-malonate (554 mg, 2.3 mmol) in DMF (2 mL) was added at 0°C to a suspension of NaH (101 mg, 2.5 mmol, 60% mineral oil) in DMF (3 mL). After 30 min, neryl bromide was added and the mixture was stirred overnight. After extractive workup (water/Et_2O) and chromatography (hexane/EtOAc 95:5), **27** (373 mg, 55%) was obtained: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (dt, J = 15.2, 5.9 Hz, 1H), 5.48 (dt, J = 15.2, 7.6 Hz, 1H), 4.92 (s, 1H), 4.86 (s, 1H), 3.87 (d, J = 6.5 Hz, 2H), 3.82 (s, 2H), 3.72, (s, 6H), 2.79 (d, J = 7.3 Hz, 2H), 2.77 (d, J = 2.6 Hz, 2H), 2.00 (t, J = 2.6 Hz, 1H), 1.70 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.10, 142.18, 132.05, 126.25, 112.02, 73.72, 71.51, 69.85, 56.87, 52.69, 35.04, 22.69, 19.40 ppm; HMRS-CI m/z calcd for $C_{16}H_{22}O_5$: 295.1545; found 295.1551 $[M+1]^+$.

Cyclization reactions: The enyne (0.10–0.50 mmol) in CH_2Cl_2 (1 mL) was added to a mixture of gold(I) complex (2 mol%) in CH_2Cl_2 (2 mL) and the mixture was stirred for the time and at the temperature indicated in Scheme 6. The resulting mixture was filtered through SiO_2 and the solvent was evaporated to give the corresponding product, which was purified by column chromatography (EtOAc/hexane mixtures).

Tetracycle 15: Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.43 (s, 3H), 3.34 (s, 3H), 2.87 (qd, J = 7.3, 1.8 Hz, 1H), 2.80 (dd, J = 14.5, 1.8 Hz, 1H), 2.49 (d, J = 14.5 Hz, 1H), 2.28 (dd, J = 14.5, 2.8 Hz, 1H), 1.57 (m, 2H), 1.13 (dd, J = 7.3, 2.9 Hz, 1H), 1.09 (d, J = 8.9 Hz, 1H), 1.06 (s, 3H), 1.03–0.96 (m, 4H), 0.92 (s, 3H), 0.78 (td, J = 13.0, 4.4 Hz, 1H), 0.64 (td, J = 8.6, 6.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.77, 171.67, 68.18, 52.74, 52.41, 40.14, 38.21, 34.92, 34.30, 33.07, 28.96, 28.23, 23,96, 20.24, 17.56, 16.59, 14.40 (one carbon signal overlaps) ppm; HMRS-FAB m/z calcd for $C_{18}H_{26}O_4$: 306.1813; found 306.1818. The structure of **15** was confirmed by COSY and NOESY experiments.

Dimethyl 3-((*E*)-2,6-Dimethylhepta-1,5-dienyl)cyclopent-3-ene-1,1-dicarboxylate (16): Yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.73 (brs, 1H), 5.41 (brs, 1H), 5.09 (m, 1H), 3.74 (s, 6H), 3.20 (d, J = 1.8 Hz, 2H), 3.06 (s, 2H), 2.2–2.0 (m, 4H), 1.82 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.66, 139.26, 138.74, 131.74, 124.62, 123.92, 120.29, 59.29, 52.81, 43.45, 41.15, 40.39, 26.76, 25.66, 18.28, 17.67 ppm; HMRS-CI m/z calcd for $C_{18}H_{26}O_4$: 306.1831; found 306.1833.

Tetracycle 18: White solid: mp 72.5–74°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, J = 7.3 Hz, 2H), 8.05 (d, J = 7.4 Hz, 2H), 7.73–7.68 (m, 2H), 7.63–7.57 (m, 4H), 2.85 (d, J = 16.2 Hz, 1H), 2.76 (ddd, J = 15.8, 7.3, 2.2 Hz, 1H), 2.45 (dd, J = 15.8, 2.8 Hz, 1H), 2.38 (dd, J = 16.4, 2.2 Hz, 1H), 1.73 (dt, J = 13.1, 3.2 Hz, 1H), 1.67–1.61 (m, 1H), 1.26 (dd, J = 7.1, 2.8 Hz, 1H), 1.18 (s, 3H), 1.11 (s, 3H), 0.97 (d, J = 8.8 Hz, 1H), 0.93–0.85 (m, 1H), 0.83 (s, 3H), 0.77–0.69 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): δ = 173.95 (C), 135.91 (C), 134.46 (CH), 134.33 (CH), 132.14 (CH), 130.84 (CH), 128.56 (CH), 128.51 (CH), 100.68 (C), 39.96 (CH), 36.78 (CH_2), 36.27 (CH_2), 33.24 (C), 32.74 (CH_2), 31.54 (C), 27.91 (CH_3), 24.69 (CH), 23.97 (CH), 20.58 (C), 17.67 (CH_3), 16.16 (CH_2), 13.66 (CH_3) ppm; HMRS-EI m/z calcd for $C_{26}H_{30}O_4S_2$: 470.1586; found 470.1577. The structure of **18** was confirmed by COSY, NOESY, HMBC, and HMQC experiments and by X-ray diffraction.

Tetracycle 20: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (s, 2H), 3.90 (dd, J = 15.2, 11.1 Hz, 2H), 2.09 (s, 3H), 2.04 (s, 3H), 1.75 (ddd, J = 14.4, 7.4, 1.7 Hz, 1H), 1.73–1.57 (m, 2H), 1.55 (q, J = 14.4 Hz, 2H), 1.27 (dd, J = 14.4, 2.4, Hz, 1H), 1.05–0.94 (m with a s at 1.01, 5H), 0.94 (s, 3H), 0.89–0.76 (m with a s at 0.87, 5H), 0.66 (td, J = 8.5, 6.2 Hz, 1H) ppm;

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^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.35, 66.92, 66.21, 54.92, 38.02, 37.18, 35.14, 31.75, 31.21, 28.34, 28.20, 25.95, 24.06, 20.90, 20.83, 20.20, 17.47, 16.55, 14.38 ppm; HMRS-ESI m/z calcd for $C_{20}H_{30}O_4Na$ $[M+Na]^+$: 357.2042; found 357.2033. This structure was confirmed by COSY, NOESY, HMBC, and HMQC experiments.

Tetracycle 22: Vitreous solid: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 3.37–3.34 (m, 3H), 3.31 (d, J = 9.6 Hz, 1H), 2.42 (s, 3H), 1.66–1.64 (m, 1H), 1.63–1.60 (m, 1H), 1.03 (d, J = 4.7 Hz, 1H), 1.02–0.96 (m, 1H), 0.98 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.85 (m, 1H), 0.67 (m, 1H), 0.69 (d, J = 8.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): δ = 143.18 (C), 134.42 (C), 129.61 (CH), 127.41 (CH), 51.78 (CH_2), 48.03 (CH_2), 35.10 (CH), 34.63 (CH_2), 29.80 (C), 28.07 (CH_3), 24.48 (C), 23.83 (CH), 22.28 (CH), 21.56 (CH_3), 20.46 (C), 17.57 (CH_3), 16.46 (CH_2), 12.49 (CH_3) ppm; HMRS-CI *m/z* calcd for $C_{20}H_{27}NO_2S$: 345.1762; found 345.1766. The structure of **22** was confirmed by COSY, NOESY, HMBC, and HMQC experiments.

Tetracycle 24: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.9 Hz, 2H), 6.84 (d, J = 9.7 Hz, 2H), 5.70 (dd, J = 10.5, 6.7 Hz, 1H), 3.78 (s, 3H), 2.56–2.44 (m, 1H), 2.06–1.97 (m, 1H), 1.79–1.69 (m, 1H), 1.62–1.48 (m, 1H), 1.46–1.34 (m, 2H), 1.46–1.34 (m, 2H), 1.21 (s, 3H), 1.15 (d, J = 6.3 Hz, 1H), 0.97 (s, 3H), 0.87 (s, 3H), 0.81 (d, J = 9.2 Hz, 1H), 0.53 (ddd, J = 9.4, 5.0, 3.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.47, 131.54, 123.57, 113.50, 84.66, 55.42, 35.13, 34.05, 33.53, 31.93, 29.45, 25.78, 25.59, 23.66, 22.16, 18.35, 17.93, 17.88 ppm; HRMS-EI *m/z* calcd for $C_{22}H_{28}O_3Na$: 363.1936; found 363.1944 $[M+Na]^+$. The structure of **24** was confirmed by COSY, NOESY, HMBC, and HMQC experiments.

Tetracycle 26: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 2.68 (d, J = 13.6 Hz, 1H), 2.64 (d, J = 13.6 Hz, 1H), 2.41 (d, J = 13.6 Hz, 1H), 2.29 (d, J = 13.6 Hz, 1H), 2.29–2.20 (m, 1H), 2.14 (d, J = 14.6, 4.1 Hz, 1H), 1.80–1.55 (m, 2H), 1.21 (s, 3H), 1.13 (s, 3H), 1.04 (s, 3H), 0.57–0.52 (m, 2H), 0.34 (dd, J = 11.8, 3.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.10, 172.82, 172.70, 172.36, 58.73, 55.81, 52.94, 52.35, 43.90, 42.95, 31.41, 30.03, 29.55, 28.59, 28.27, 24.02, 23.60, 22.06, 19.60, 17.75, 13.96 ppm; HRMS-EI *m/z* calcd for $C_{23}H_{33}O_8$: 437.2175; found 437.2168 $[M+H]^+$. The structure of **26** was confirmed by COSY, NOESY, HMBC, and HMQC experiments.

Tetracycle 28: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.07 (dd, J = 12.0, 4.7 Hz, 1H), 3.84 (dd, J = 11.8, 1.1 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.31 (d, J = 12 Hz, 1H), 3.13 (t, J = 11.5 Hz, 1H), 2.60 (d, J = 2.9 Hz, 2H), 2.50 (d, J = 14.2 Hz, 1H), 2.46 (d, J = 14.1 Hz, 1H), 1.10 (td, J = 5.9, 2.9 Hz, 1H), 1.08–1.03 (m with a s at 1.06, 4H), 0.60–0.55 (m, 1H), 0.53 (dd, J = 8.7, 5.0 Hz, 1H), 0.39 (t, J = 5.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.89, 172.32, 71.8, 71.81, 67.35, 59.58, 53.03, 41.59, 36.55, 32.16, 31.08, 25.47, 24.53, 20.94, 17.91, 17.48 ppm; HRMS-EI *m/z* calcd for $C_{16}H_{22}O_5Na$: 317.1365; found 317.1365 $[M+Na]^+$. The structure of **28** was confirmed by COSY, NOESY, HMBC, and HMQC experiments.

Dimethyl 3-[(*E*)-3-(2-methylallyloxy)prop-1-enyl]cyclopent-3-ene-1,1-dicarboxylate (29): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (d, J = 16.2 Hz, 1H), 5.64 (dt, J = 15.8, 6.1 Hz, 1H), 5.56 (s, 1H), 4.96 (s, 1H), 4.90 (s, 1H), 4.02 (s, 1H), 4.00 (s, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 3.13 (s, 1H), 3.10 (1H), 1.74 (3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 166.18, 127.90, 127.58, 126.69, 119.88, 112.19, 74.17, 70.23, 52.90, 40.94, 39.77, 19.54 (two carbons signals overlap) ppm; HRMS-EI *m/z* calcd. for $C_{16}H_{22}O_5Na$: 317.1365; found 317.1362 $[M+Na]^+$.

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