Gold-Catalyzed Cyclization of Oxo-1,5-enynes

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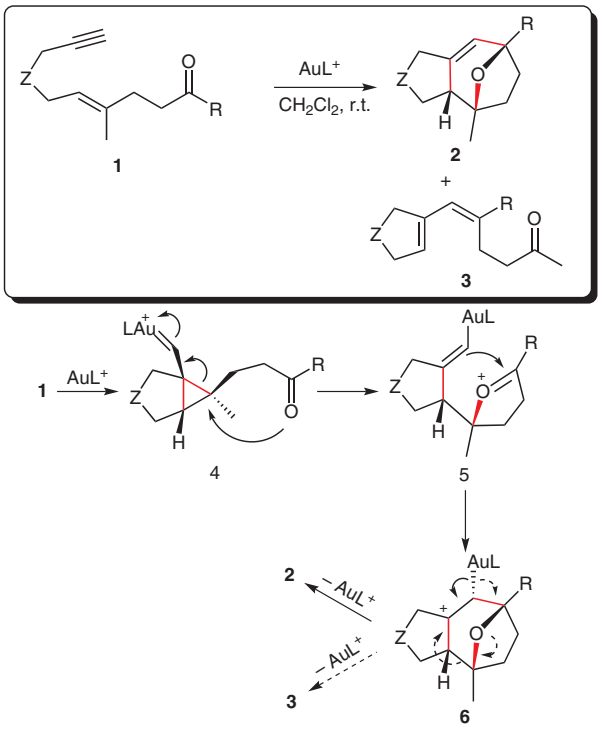
Abstract: Cationic gold(I) complexes catalyze the cycloisomerization of oxo-1,5-enynes to form oxatricyclic derivatives through an intramolecular Prins reaction.

Key words: gold, enynes, alkynes, cycloisomerization

Functionalized 1,n-enynes undergo cycloisomerization reactions with gold(I) catalysts to form a wide variety of complex carbon architectures.[1] 1,6-Enynes **1** bearing a carbonyl group at the alkenyl side chain react with gold(I) catalysts to form oxatricyclic derivatives **2** (Scheme 1).[2] In this tandem [2+2+2] alkyne/alkene/carbonyl cycloaddition process, two C–C and one C–O bonds are assembled stereospecifically. In addition, monocyclic derivatives **3** are also formed as minor products by a competitive fragmentation.[2]

The gold(I)-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition reaction was proposed to take place by opening of the cyclopropyl gold(I) carbenes **4** by the carbonyl group to form oxonium cation **5**, which undergoes an intramolecular Prins reaction to form a tricyclic intermediate **6**, which leads to oxatricyclic derivatives **2** or fragmentation derivatives **3** (Scheme 1). The fragmentation process can be the predominant pathway in the analogous gold(I)-catalyzed intermolecular reaction of 1,6-enynes with aldehydes.[3] Other 1,6-enynes with a terminally unsubstituted alkene react differently in intermolecular processes with carbonyl compounds to give other types of tricyclic derivatives.[4]



Scheme 1

We have used the gold(I)-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition for the total synthesis of orientalol F (**7**), pubinernoid B (**8**),[5] and englerin A (**9**)[6] (Figure 1). A very similar approach was developed independently for the synthesis of **9** using gold catalysis.[7]

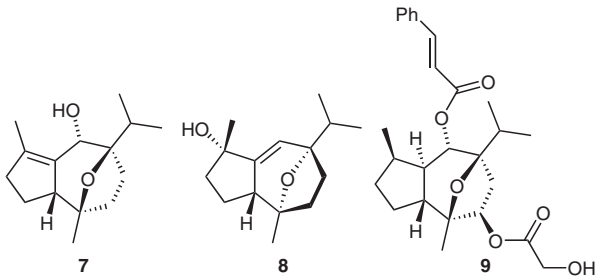


Figure 1

We decided to examine the gold(I)-catalyzed cyclization of oxo-1,5-enynes **10** for the synthesis of oxatricyclic derivatives **11**, via intermediates **12**,[8,9] to form **13** by a similar intramolecular ring-opening by the carbonyl group (Scheme 2). Intermediate **13** could form a second C–C bond by a Prins reaction that, in this case, would give rise to a carbene-like intermediate **14**. We expected that **14** would evolve by 1,2-H migration followed by demetalation to form **11**.

The required substrates **10a–e** (Z = $CHSO_2Ph$) for the cyclization were readily prepared in four to six steps from geranyl bromide via dienylenyne **17** as shown in Scheme 3.[10]

We first examined the cyclization of (*E*)-enynal **10a** with cationic gold(I) catalysts **A–G** (Figure 2), which allow the cycloisomerization reactions to be performed under silver(I)-free conditions (Table 1).[11] The cyclization proceeded satisfactorily using gold complexes **A–C**, bearing bulky dialkylbiphenylphosphine ligands[12] (Table 1, entries 1–9) or NHC-Au(I) complex **E**[13,14] (Table 1, entries 11 and 12), whereas poorer yields were obtained with cat-

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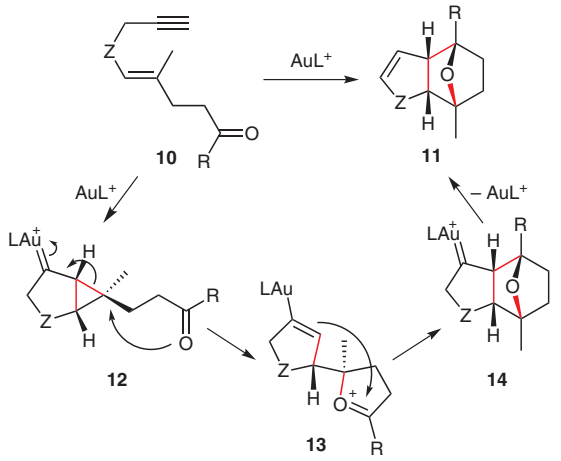
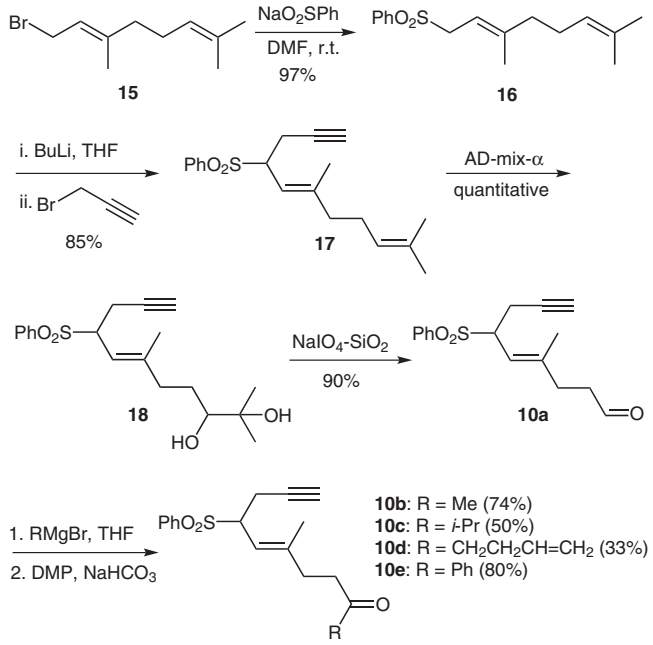


Scheme 2



Scheme 3

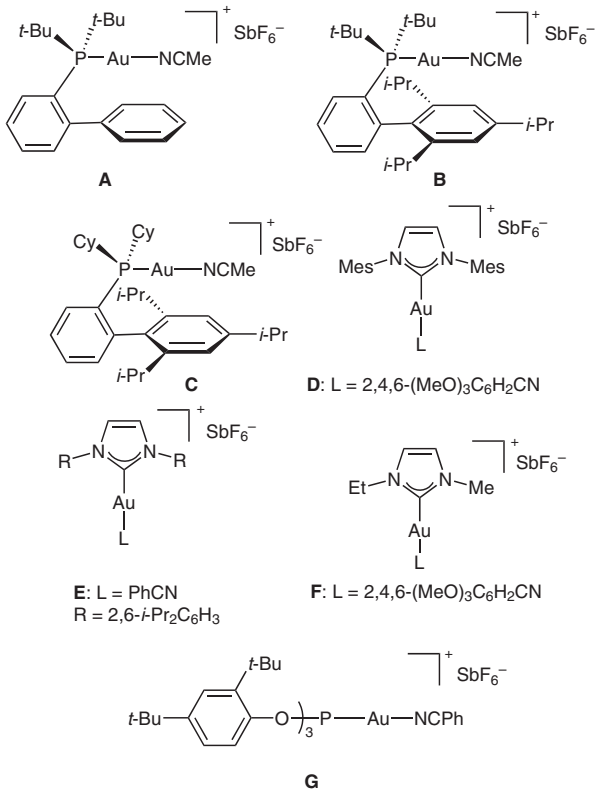


Figure 2

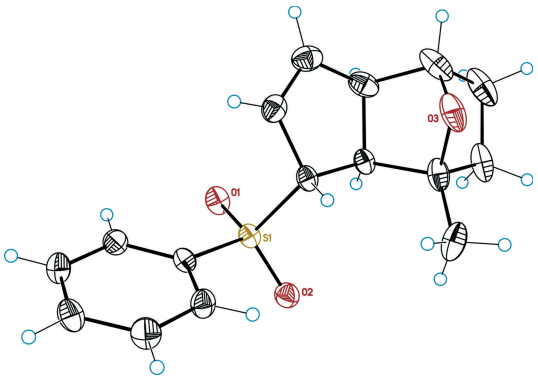


Figure 3 X-ray crystal structure of **11a′**

alysts **D**, **F**, **G**, AuCl, or $AuCl_3$ (Table 1, entries 10 and 13–16). No cycloisomerization was observed with $NaAuCl_4$, $PtCl_2$, $PtCl_4$, $AgSbF_6$, $GaCl_3$, or $PdCl_2$ (Table 1, entries 18–22).

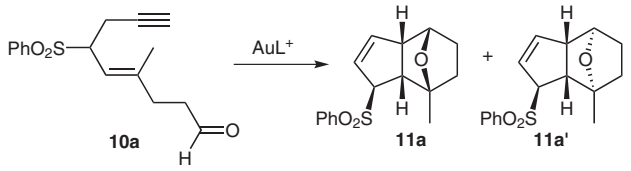
In all cases, besides the expected cyclized derivative **11a**, its stereoisomer **11a′** was also obtained as a minor product, with the exception of the reaction using catalyst **G**, which led to the formation of **11a** and **11a′** in a 1:1.5 ratio (Table 1, entry 14). Their configuration was determined by NOESY experiments and further confirmed by the determination of the X-ray structure of **11a′** (Figure 3), which was obtained as a major product in the cycloisomerization of **19** (see below).

The best results in the cyclization of **10a** were obtained using catalyst **A**, which is commercially available, in CH_2Cl_2 at room temperature. This cationic gold(I) complex was also the best catalyst for the cyclization of oxo-1,5-enynes **10b–e** to form **11b–e** and **11b–e′** with moderate stereoselectivities (Table 2).

Interestingly, the cyclization of **19** (the Z isomer of **10a**), proceeded with excellent stereoselectivity to give **11a′** (Table 3). Although the best result was obtained using 2 mol% catalysts **A** (Table 3, entry 2) good results were also obtained with catalysts **B**, **E**, and **G** (Table 3, entries 3–5).

When gold(I) complexes bearing donating ligands are used as catalysts, the major cycloisomerization pathway is stereospecific leading to **13a** and **13a'** from *trans*- and *cis*-substrates, respectively (Scheme 4). However, the overall stereoselectivity is not complete, which is consistent with the existence of two competitive processes. In analogy with the Stork–Eschenmoser model,[15,16] some gold(I)-catalyzed cascade reactions have been proposed to be con-

Table 1 Gold-Catalyzed Cyclization of (*E*)-Enynal **10a**[a]



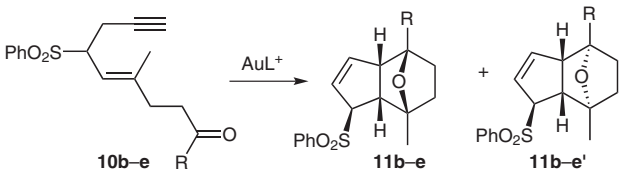
Entry	Catalyst	Solvent	Time (h)	Yield (%)	Ratio **11a/11a′**
1	**A**	CH_2Cl_2	13	54	4.2:1
2[b]	**A**	CH_2Cl_2	2	74	4.5:1
3[c]	**A**	CH_2Cl_2	0.2	65	5.6:1
4	**A**	toluene	15	57[d]	4.6:1
5	**A**	EtOAc	15	[e]	1:1.4
6	**B**	CH_2Cl_2	14	75	3.6:1
7 [b]	**B**	CH_2Cl_2	2	78	3.3:1
8	**C**	CH_2Cl_2	2	72	3.6:1
9[b]	**C**	CH_2Cl_2	2	71	3.1:1
10	**D**	CH_2Cl_2	72	6	2:1
11	**E**	CH_2Cl_2	13	64	4:1
12[b]	**E**	CH_2Cl_2	2.5	60	4:1
13	**F**	CH_2Cl_2	72	16	2:1
14	**G**	CH_2Cl_2	7	47	1:1.5
15	AuCl	CH_2Cl_2	14	5	4:1[f]
16	$AuCl_3$	CH_2Cl_2	14	9	3.5:1[f]
17	$NaAuCl_4$	CH_2Cl_2	24	–	–[g]
18	$PtCl_2$	CH_2Cl_2	14	–	–[g]
19	$PtCl_4$	CH_2Cl_2	14	–	–[g]
20	$AgSbF_6$	CH_2Cl_2	14	–	–[g]
21	$GaCl_3$	CH_2Cl_2	14	–	–[g]
22	$PdCl_2$	CH_2Cl_2	24	–	–[g]

[a] 5 mol% catalyst, 23 °C. Conversion ≥ 93%.
[b] 2 mol% catalyst.
[c] Reaction at 80 °C (microwave irradiation).
[d] Determined by ^{1}H NMR (1,4-diacetylbenzene as internal standard).
[e] Yield not determined (quantitative conversion).
[f] Conversion: 57–61%
[g] **11a/11a′** were not detected. The starting material was partially recovered.

certed.[17] However, the formation of minor stereoisomers **11a′** and **11a** in the cyclization reactions of **10a** and **19**, respectively, is more consistent with a stepwise process occurring through discrete intermediates such as **12a** and **12a′**, which is in line with other theoretical and experimental results.[18]

In summary, these results show that the gold(I)-catalyzed cyclization of oxo-1,5-enynes also occurs efficiently in the 1,5-enyne series by a tandem process that involves a Prins reaction. Extension of these results for the synthesis of other ring systems is under way.

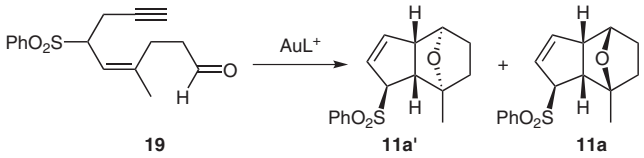
Table 2 Gold-Catalyzed Cyclization of Oxo-1,5-enynes **10b–e**[a]



Entry	**10b–e**	Catalyst	Time (h)	Yield (%)	Ratio **11a/11a′**
1	**10b**	**A**	14	98	3.7:1
2[b]	**10b**	**A**	4	93	3.1:1
3	**10b**	**E**	14	97	3.2:1
4[b]	**10b**	**E**	4	91	3.2:1
5	**10b**	**G**	7	12	1:2.5
6	**10c**	**A**	4	51	4:1
7	**10c**	**E**	7	32	1.7:1
8	**10d**	**A**	2	64	4:1
9[b]	**10d**	**A**	2	89	4:1
10	**10e**	**A**	14	62	4:1

[a] 5 mol% catalyst, 23 °C. Conversion ≥ 99%.
[b] 2 mol% catalyst.

Table 3 Gold-Catalyzed Cyclization of *Z*-Enynal **19**[a]



Entry	Catalyst	Time (h)	Yield (%)	Ratio **11a′/11a**
1	**A**	2	77	20:1
2[b]	**A**	2	97	30:1
3	**B**	4	88	20:1
4	**E**	15	85	20:1
5	**G**	12	65	25:1

[a] 5 mol% catalyst, 23 °C. Conversion ≥ 99%.
[b] 2 mol% catalyst.

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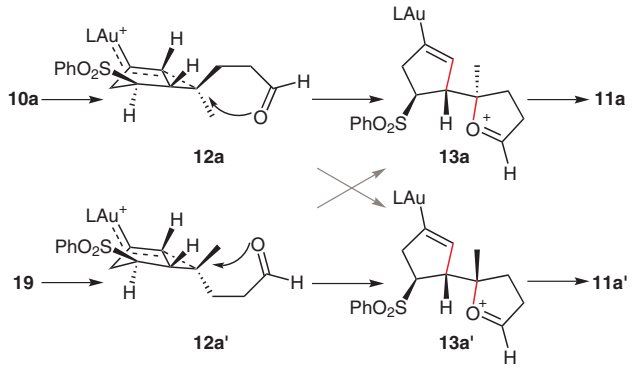

Scheme 4

Adán (ICIQ X-ray Diffraction unit), and the ICIQ Foundation for financial support

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(10) **(*E*)-4-Methyl-6-(phenylsulfonyl)non-4-en-8-ynal (10a)**: Yellow solid; mp 52–54 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (t, *J* = 1.5 Hz, 1 H), 7.97–7.73 (m, 2 H), 7.69–7.60 (m, 1 H), 7.56–7.52 (m, 3 H), 5.08 (ddd, *J* = 10.3, 2.6, 1.3 Hz, 1 H), 3.95 (td, *J* = 10.2, 3.8 Hz, 1 H), 2.98 (ddd, *J* = 16.7, 3.8, 2.8 Hz, 1 H), 2.60 (ddd, *J* = 16.7, 10.2, 2.7 Hz, 2 H), 2.47 (tm, *J* = 7.5 Hz, 2 H), 2.32 (t, *J* = 7.4 Hz, 2 H), 1.94 (t, *J* = 2.7 Hz, 1 H), 1.32 (d, *J* = 1.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 201.27 (CHO), 144.80 (C), 137.37 (C), 134.02 (C), 129.33 (CH), 129.28 (CH), 129.13 (CH), 116.85 (CH), 71.11 (CH), 63.03 (CH), 41.66 (CH_2), 31.8 (CH_2), 18.86 (CH_2), 16.83 (CH_3). IR (thin film): 3244 (CH terminal alkyne), 1712 (C=O) cm^{-1}. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{18}O_3SNa$: 313.0874; found: 313.0867. **(*E*)-5-Methyl-7-(phenylsulfonyl)dec-5-en-9-yn-2-one (10b)**: Yellow solid; mp 53–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.82 (m, 2 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 7.56–7.52 (m, 2 H), 5.06 (dd, *J* = 10.3, 1.2 Hz, 1 H), 3.95 (td, *J* = 10.2, 3.8 Hz, 1 H), 2.99 (ddd, *J* = 16.7, 3.5, 2.9 Hz, 1 H), 2.61 (ddd, *J* = 16.7, 10.1, 2.6 Hz, 1 H), 2.48 (dd, *J* = 8.6, 6.6 Hz, 2 H), 2.27 (t, *J* = 7.8 Hz, 2 H), 2.15 (s, 3 H), 1.94 (t, *J* = 2.6 Hz, 1 H), 1.31 (d, *J* = 1.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 207.58 (C), 145.43 (C), 137.36 (C), 133.93 (CH), 129.25 (CH), 129.05 (CH), 116.17 (CH), 79.00 (C), 71.02 (CH), 62.99 (CH), 41.52 (CH_2), 33.25 (CH_2), 30.05 (CH_3), 18.82 (CH_2), 16.86 (CH_3). IR (thin film): 3295 (CH terminal alkyne), 1704 (C=O) cm^{-1}. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{20}O_3SNa$: 327.1031; found: 327.1030

(11) **General procedure for the cyclization of oxo-1,5-enynes**: 1,5-Oxoenyne and the gold(I) complex **A**–**G** (2–5 mol%) were dissolved in CH_2Cl_2 (0.5–1.2 mL) and stirred at room temperature until full conversion was observed (reaction monitored by TLC). One drop of Et_3N was added and the crude reaction was filtered through Celite and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the cyclized product. **(1*S*,3a*S*,4*S*,7*R*,7a*R*)-7-Methyl-1-[(phenylperoxy)thio]-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (11a)**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89–7.85 (m, 2 H), 7.75–7.62 (m, 1 H), 7.61–7.51 (m, 2 H), 5.99 (dt, *J* = 5.7, 2.0 Hz, 1 H), 5.77 (dt, *J* = 4.3, 1.9 Hz, 1 H), 4.48 (t, *J* = 5.6 Hz, 1 H), 4.00–3.98 (m, 1 H), 3.34–3.01 (m, 1 H), 2.74 (dt, *J* = 9.5, 2.0 Hz, 1 H), 1.73–1.51 (m, 1 H), 1.51–1.33 (m, 2 H), 1.27–1.25 (m, 1 H), 1.21 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 141.36 (CH), 136.91 (C), 133.97 (CH), 129.49 (CH), 129.12 (CH), 125.04 (CH), 86.01 (C), 79.03 (CH), 72.35 (CH), 56.03 (CH), 52.88 (CH), 30.32 (CH_2), 28.58 (CH_2), 20.18 (CH_3). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{18}O_3SNa$: 313.0874; found: 313.0869. **(1*S*,3a*S*,4*R*,7*S*,7a*R*)-7-Methyl-1-[(phenylperoxy)thio]-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (11a′)**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88–7.85 (m, 2 H), 7.73–7.60 (m, 1 H), 7.63–7.49 (m, 2 H), 5.92 (dt, *J* = 5.7, 2.2 Hz, 1 H), 5.62 (dt, *J* = 5.7, 2.1 Hz, 1 H), 4.26–4.18 (m, 1 H), 4.14 (d, *J* = 5.1 Hz, 1 H), 2.96 (ddd, *J* = 7.0, 4.6, 2.3 Hz, 1 H), 2.72 (dd, *J* = 7.2, 3.1 Hz, 1 H), 1.82–1.74 (m, 1 H), 1.62–1.58 (m, 1 H), 1.56–1.48 (m, 2 H), 1.32 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 139.30 (CH), 137.71 (C), 133.90 (CH), 129.23 (CH), 129.17 (CH), 126.02 (CH), 84.58 (C), 78.97 (CH), 74.25 (CH), 58.21 (CH), 50.34 (CH), 36.31 (CH_2), 30.75 (CH_2), 17.99 (CH_3). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{18}O_3SNa$: 313.0874; found: 313.0882

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