Organic **LETTERS**

Letter

Gold(I)-Catalyzed Inter- and Intramolecular Additions of Carbonyl Compounds to Allenenes
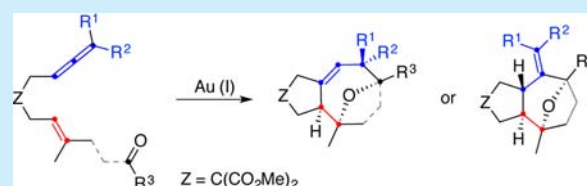
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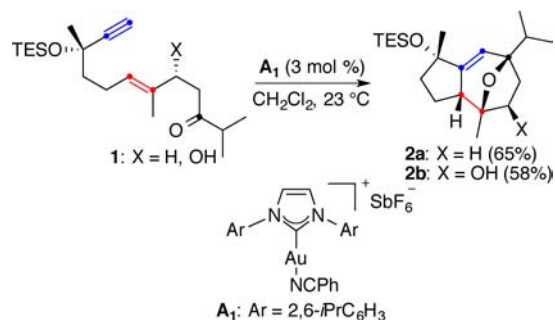
S *Supporting Information*

ABSTRACT: The gold(I)-catalyzed intramolecular reaction of allenes with oxoalkenes leads to bicyclo[6.3.0]undecane ring systems, although in the case of terminally disubstituted allenes, seven-membered rings are formed. The related intermolecular addition of aldehydes to allenes also gives seven-membered rings.

Gold(I)-catalyzed enyne cycloisomerization reactions are powerful tools for the stereoselective construction of complex carbon skeletons.[1] These transformations have been used as the key steps in the total synthesis of diverse natural products.[2,3] We have developed a particularly useful transformation based on the gold(I)-catalyzed [2 + 2 + 2] intramolecular cycloaddition between oxo-1,6-enynes in substrates such as **1**, which leads to oxatricyclic derivatives **2a,b** by a cascade process in which two C−C and one C−O bonds are formed.[4] This methodology was applied in the total syntheses of (+)-orientalol F[3a] and (−)-englerin A[3b,5] (Scheme 1). A mechanistically similar transformation was also developed with oxo-1,5-enynes.[6]

Scheme 1. Gold(I)-Catalyzed [2 + 2 + 2] Intramolecular Cycloaddition between Alkynes and Oxoalkenes

The intermolecular reaction of terminal alkynes with 5-oxoalkenes also gives [3.2.1]oxabicycles.[7] A somewhat analogous intermolecular gold(I)-catalyzed reaction of 5-, 6-, and 7-oxoalkenes with allenamides was developed by the group of Mascareñas to form 7−9-membered rings depending on the length of the tether of the oxoalkenes.[8a] In addition, by use of chiral ligands, this transformation was further developed as an enantioselective process. The same group recently reported the gold(I)-catalyzed [2 + 2 + 2] cycloaddition of allenamides, alkenes, and aldehydes for the synthesis of functionalized tetrahydropyrans.[8b,9] However, similar transformations involving simple oxo-1,7-allenenes have not been described. Herein, as part of a program on the development of new gold(I)-catalyzed cascade reactions for the synthesis of complex sesquiterpenes,[3,10] we report a ready access to the bicyclo[6.3.0]undecane ring system,[11] a motif conspicuously present among sesquiterpenes and higher terpene natural products (Figure 1).[12]
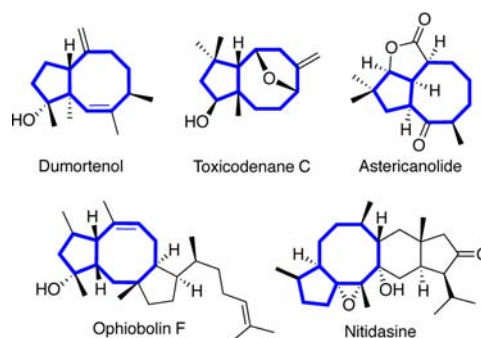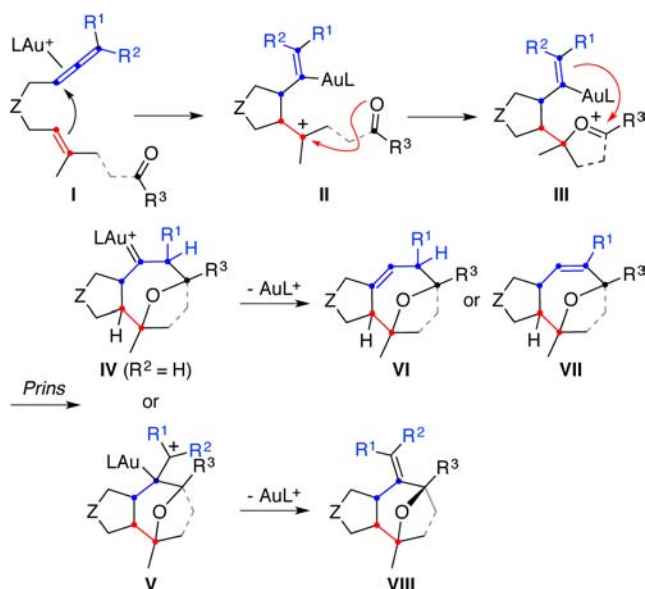

Figure 1. Representative natural terpenoids containing eight-membered rings.

We envisioned that in oxo-1,7-allenenes or 1,7-allenenes reacting intermolecularly with carbonyl compounds the attack of the alkene to a gold(I)-activated allene **I** would generate tertiary carbocation **II**, which would be rapidly trapped by the carbonyl group to form oxonium cation **III** (Scheme 2). Prins cyclization would then form intermediates **IV** or **V** by *endo-* or *exo*-pathways, respectively. Gold(I) carbene **IV** could give rise

Scheme 2. Proposed Mechanism for the Gold-Catalyzed Reaction of 11-Oxo-1,7-allenenes

to eight-membered ring compounds **VI** or **VII** when R^2 = H, whereas **V** would lead to seven-membered ring **VIII**. In addition to the regiochemical uncertainties, control of the final relative configuration was a second matter of concern. It is important to remember that unlike the reaction of the analogous 1,6-enynes **1**, where the cyclization proceeds stereospecifically through cyclopropyl gold(I) carbenes as intermediates,[4,13] reactions of allenes with alkenes are fundamentally different since the configuration of the final products is not mechanistically determined. Thus, the initial cyclization could give *cis*- or *trans*-five-membered rings **II**, and furthermore, new stereocenters are generated in the formation of intermediate **III** from tertiary carbocation **II** as well as in the Prins cyclization leading to **IV**.

Initially, we investigated the intramolecular reactivity of 11-oxo-1,7-allenenes using allene aldehyde **3a** as the substrate in the presence of different catalysts (5 mol %) at room temperature in CH_2Cl_2 (Table 1). In all the cases, we obtained tricyclic derivative **4a** as a result of a cascade reaction proceeding selectively through gold(I) carbene **IV**. The best results were obtained with gold complexes **A₁**, **A₃**, and **D** bearing NHC and phosphite ligands (Table 1, entries 1, 3, and 7). Lower yields were obtained with gold(I) complexes **B** and **C** with bulky biphenyl phosphines[14] (Table 1, entries 4–6). Best results were obtained with IPr–gold(I) cationic complex **A₁** with SbF_6 as the counteranion, leading to the formation of oxatricyclic derivative **4a** in 71% isolated yield as a single diastereomer (Table 1, entry 1). The reaction could also be carried out with $PtCl_2$, although the yield was poor (Table 1, entry 8). The relative configuration was confirmed by determining the X-ray crystal structure of diol **4a′**,[15] prepared by reduction of **4a** with $LiAlH_4$.
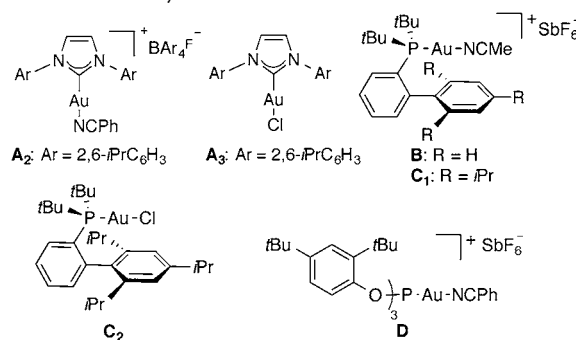
Having the optimal conditions in hands, we sought to evaluate the generality of the reaction, considering the substitution pattern in the allene, the configuration of the alkene, and also the intermolecular reaction between allenenes and aldehydes (Scheme 3). By performing the reaction with the monosubstituted allene **3b**, we observed the same type of reactivity, leading in this case to a mixture of diastereomers.

Table 1. Catalyst Optimization in the Intramolecular Cycloaddition of 11-Oxo-1,7-allenene 3a[a]

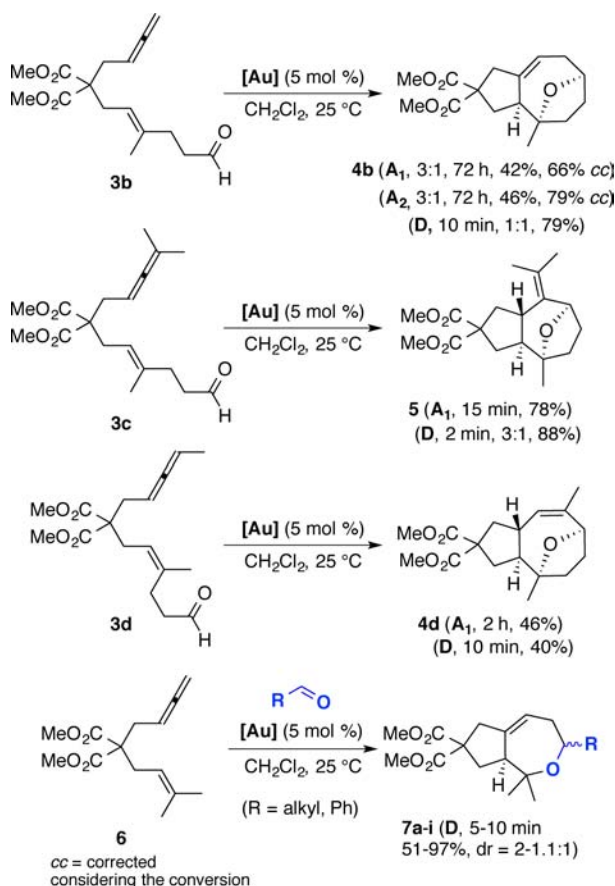| entry	catalyst	time (h)	yield[b] (%)
1	A₁	0.25	78 (71)[c]
2	A₂	0.25	45
3	A₃ + AgSbF₆	0.25	63
4	B	6	37
5	C₁	24	25
6	C₂ + AgSbF₆	24	55
7	D	2 min	67
8	PtCl₂	16	10

[a]Conditions: allenene **3a** and catalyst (5 mol %) in CH_2Cl_2 (0.1 M). [b]Yield of **4a** determined by ¹H NMR; see the Supporting Information for details. [c]Isolated yield.

Catalysts **A₁** or **A₂** led to a 3:1 mixture of diastereomers **4b** in moderate yields (42–46%) after 72 h, whereas more electrophilic catalyst **D** gave **4b** as a 1:1 mixture of diastereomers after just 10 min.[16] Surprisingly, reaction of trisubstituted allene **3c** with catalysts **A₁** gave seven-membered ring **5** in 78% yield instead of an eight-membered cyclic derivative with a *trans* configuration at the fusion between the 5- and the 7-membered rings, which was confirmed by X-ray crystallographic analysis.[15] A similar reaction was observed with phosphite gold complex **D** (88%, 2 min); however, a separable 3:1 mixture of diastereomers was obtained with this catalyst. The lower stereoselectivity observed using catalyst **D** is probably a consequence of the very high electrophilicity of this gold(I) complex, which favors formation of both intermediates *cis*- and *trans*-**II** through early transition states of closely similar energy. Reaction of substrate **3d** with a Z configuration at the alkene led to eight-membered ring **4d** in 40–46% yield using catalysts **A₁** or **D**. Compound **4d**, which was also observed as a minor product in the cyclization of **3a**,[16] could arise by a proton elimination from an intermediate **IV** with a configuration different from that involved in the formation of **4a**.[17] We also investigated the intermolecular version of this reaction using 1,7-allenene **6** and excess aliphatic or aromatic aldehydes (Scheme 3). In the presence of phosphite gold(I) catalyst **D**, fast reactions were observed (5–10 min), yielding hexahydro-1*H*-cyclopenta[*c*]oxepines **7a–i** in moderate to good yields as mixture of diastereomers as a result of a cyclization/*endo*-Prins process. The use of complex **A₁** moderately increased the

Scheme 3. Gold(I)-Catalyzed Intra- and Intermolecular Cycloaddition of 11-Oxo-1,7-allenenes

The cyclization of 11-oxo-1,7-allenenes was extended to ketones instead of aldehydes (Table 2). Under the optimized conditions used for aldehyde **3a**, we were pleased to observe the formation of the tricyclic compounds **4e−k** in 60−87% yields using gold complex **A₁**. X-ray crystallographic analysis of **4g** unambiguously confirmed its relative configuration.[15] Alkyl

Table 2. Gold(I)-Catalyzed Intramolecular Cycloaddition of 11-Oxo-1,7-allenenes 3e−k[a]

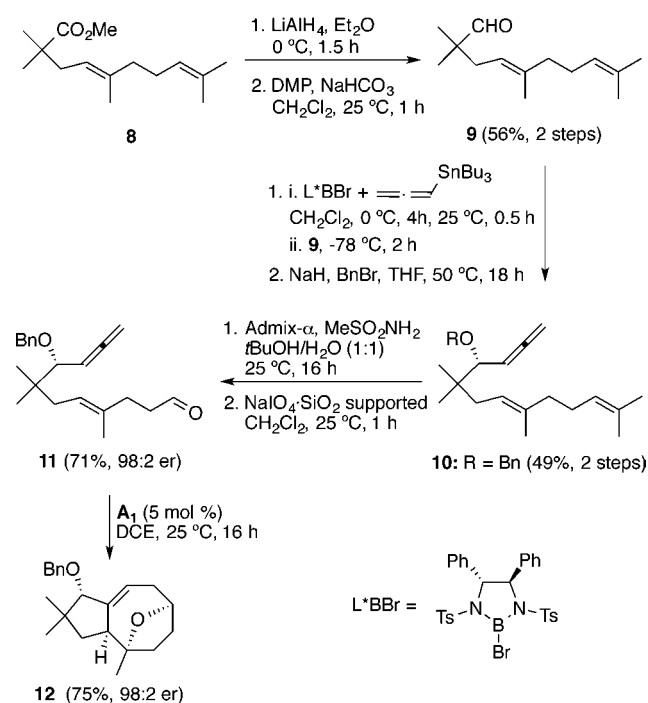| entry	R	time (h)	product (yield, %)[b]
1	Me (**3e**)	6	**4e** (63)
2	*n*-Hex (**3f**)	0.25	**4f** (64)
3	Cy (**3g**)	0.15	**4g** (72)
4	*t*-Bu (**3h**)	3	**4h** (79)
5	Ph (**3i**)	6	**4i** (72)
6	3,5-(CF₃)₂C₆H₃ (**3j**)	2	**4j** (87)
7	CH₂Cl (**3k**)	1	**4k** (60)

^{a}Conditions: allenene **3e−k** and **A₁** (5 mol %) in CH₂Cl₂ (0.1 M). ^{b}Isolated yields.

ketones, including those with bulky groups, and aryl ketones react similarly. Interestingly, oxoenallenenes with electron-withdrawing groups at the ketone, such as **3j** and **3k** (Table 2, entries 6 and 7), reacted smoothly and gave yields similar to those obtained from other ketones, which supports the hypothesis that formation of carbocation **II** is rate-determining and attack of the carbonyl group is, comparatively, a faster process.

Finally, we applied this intramolecular cycloaddition for the enantioselective formation of an oxatricyclic system. The synthesis of the oxoenallene began by alkylation of methyl isobutyrate with geranyl bromide to give ester **8**,[18] which was converted into known aldehyde **9**[19] in two steps by reduction with LiAlH₄ and subsequent oxidation with Dess−Martin periodinone (Scheme 4). Enantioselective allenylation of

Scheme 4. Enantioselective Synthesis of Oxatricyclic Compound 12

aldehyde **9** was performed by applying Corey's method[20] using a chiral bromoborane and propadienyltri-*n*-butylstannane followed by benzylation under standard conditions to yield allene **10**. Treatment of **10** with Admix-α and methylsulfona-mide followed by oxidative cleavage using NaIO₄ on silica[21] led to aldehyde **11**. At this point, the excellent enantioselectivity of the allenylation reaction was confirmed by chiral GC (98:2 er). Exposing **11** to cationic gold(I) complex **A₁** for 16 h at 25 °C gave **12** in 75% yield as the only isolated tricyclic compound. The intermolecular reaction of **11** occurred with complete retention of the configuration.

In summary, we have found that the intramolecular reaction of 11-oxo-1,7-allenenes gives rise to bicyclo[6.3.0]undecane ring systems, usually in good yields and selectivities, which is remarkable for a reaction that most probably proceeds through an open carbocation. Only in the case of 1,1-dialkyl-substituted alkenes are seven-membered ring systems formed as a consequence of an *exo*-selective Prins-type cyclization. This

diastereoselectivity, although the yields were lower and longer reaction times were required.[16]

reaction can also be carried out intermolecularly between 1,7-allenenes with aliphatic or aromatic aldehydes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00342.

> Experimental procedures and characterization data for compounds as well as the X-ray crystal structures of **4a′**, **5**, and **4g** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(15) CCDC 1451024 (**4a′**), CCDC 1451022 (**5**), and CCDC 1451023 (**4g**) contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) See the Supporting Information for more details.

(17) An isomerization of **3a** into **3d** by a gold(I)- or proton-catalyzed process seems unlikely since **3a** was calculated to be 3 kcal·mol^{-1} more stable than **3d** (DFT calculations, B3LYP/6-31G(d), solvent = CH_2Cl_2).

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