Cyclization

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Prins Cyclizations in Au-Catalyzed Reactions of Enynes**

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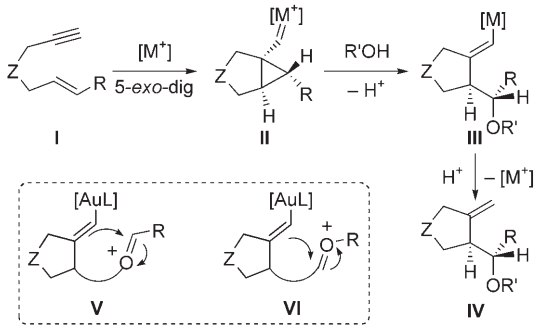
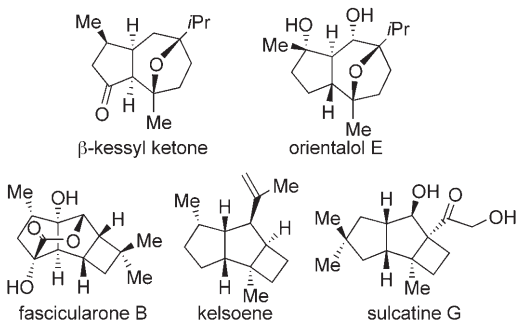
The hydroxy- or alkoxycyclization of enynes **I** catalyzed by electrophilic transition-metal complexes usually takes place through cyclopropyl metal carbenes **II**, which react with nucleophiles R′OH to give intermediates **III** (Scheme 1). The reaction is then terminated by proto-demetalation of the alkenyl metal intermediate **III** to give **IV**.[1,2]



Scheme 1. Different evolution of intermediate **III** by proto-demetalation of the Prins reaction with oxonium cations via **V** or **VI**.

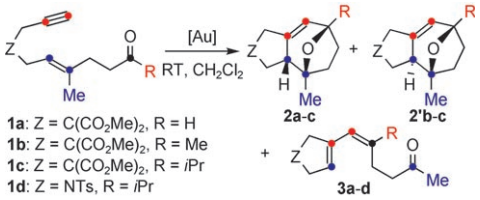
We have now found that in the Au^I-catalyzed cyclization of enynes[3,4] the alkenyl metal intermediate can be trapped with appropriate substituents, as shown in **V** and **VI** in a Prins cyclization. These new cyclizations allow the one-step synthesis of tricyclic skeletons, such as those of β-kessyl ketone[5a] and orientalol E (Scheme 2),[5b] from enynes with carbonyl groups and octahydrocyclobuta[*a*]pentalenes, such as fascicularone B,[6] kelsoene,[7] and sulcatine G,[8] starting from cyclopropyl enynes.

Enynes **1a–c**, bearing a carbonyl group at the alkenyl side chain, are cyclized to give oxatricyclic derivatives **2a–c** and rearranged ketones **3a–c** by using Au^I catalysts (Table 1). The reactions were completed at room temperature in 5–30 min. Aldehyde **1a** gave a mixture of tricycle **2a** (35%) and ketone **3a** (50%) with $[AuCl(PPh_3)]/AgSbF_6$ (catalyst **A**; Table 1, entry 1). Similar results were obtained with $[Au(PPh_3)(MeCN)]SbF_6$ (catalyst **B**) and cationic complex **C**[3] (Table 1, entries 2 and 3). A yield of 58% for **2a** was achieved by using AuCl itself (Table 1, entry 4). In the cyclization of ketones **1b** and **1c**, **2′b**,**c** were obtained as minor isomers, although their formation could be minimized by using Au^I catalysts **B** or **C** (Table 1, entries 6/7 and 10/11). Results with catalysts **A** and **B** were not identical (compare entries 5/6 and 9/10), which suggest that Ag^I may not be innocent in some of these cyclizations.[9] The best yields of **2b–c** were achieved with AuCl (Table 1, entries 8 and 12). Substrate **1d** led only to ketone **3d** (77%; Table 1, entry 13).



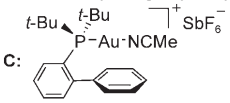
Scheme 2. Representative sesquiterpenes with skeletons accessible by Au-catalyzed cyclizations.

Table 1: Au^I-catalyzed reaction of enynes **1a–d**.[a]



Entry	Enyne	[Au]	2/2′	Yield [%]	2/2′	3	Yield [%]
1	**1a**	**A**	**2a**	35	>50:1	**3a**	50
2	**1a**	**B**	**2a**	36	>50:1	**3a**	34
3	**1a**	**C**	**2a**	29	>50:1	**3a**	50
4	**1a**	AuCl	**2a**	58	>50:1	**3a**	18
5	**1b**	**A**	**2b/2b′**	65	2.3:1	**3b**	9
6	**1b**	**B**	**2b**	47	>50:1	**3b**	44
7	**1b**	**C**	**2b**	47	>50:1	**3b**	52
8	**1b**	AuCl	**2b**	79	>50:1	**3b**	10
9	**1c**	**A**	**2c/2c′**	64	3.4:1	**3c**	22
10	**1c**	**B**	**2c**	49	>50:1	**3c**	45
11	**1c**	**C**	**2c/2c′**	44	26:1	**3c**	39
12	**1c**	AuCl	**2c**	84	>50:1	**3c**	12
13	**1d**	**C**	–	–		**3d**	77

[a] Reactions at 23°C with 3 mol% catalyst for 5–30 min (100% conversion). **A**: $[Au(PPh_3)Cl]/AgSbF_6$, **B**: $[Au(PPh_3)(MeCN)]SbF_6$,



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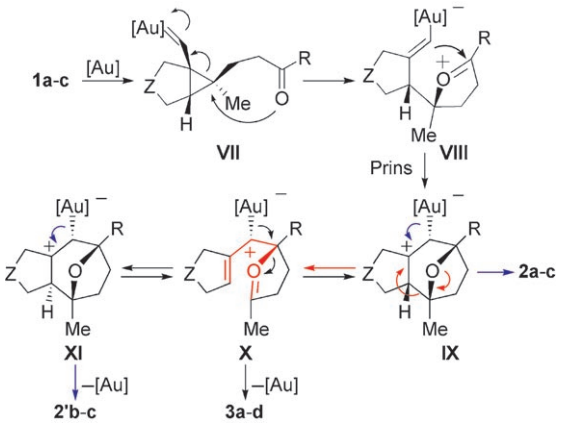
The structures of **2a–d** were assigned by NMR spectroscopic analysis and by the X-ray diffraction determination of **2c**.[10] The *cis* configuration of ketones **3a–d** was based on the coupling constant $^3J = 11.6$ Hz, as observed for **3a** and in NOESY experiments.

The carbonyl group acts as an internal nucleophile in the cyclizations of Table 1, as shown in **VII** (Scheme 3), thus



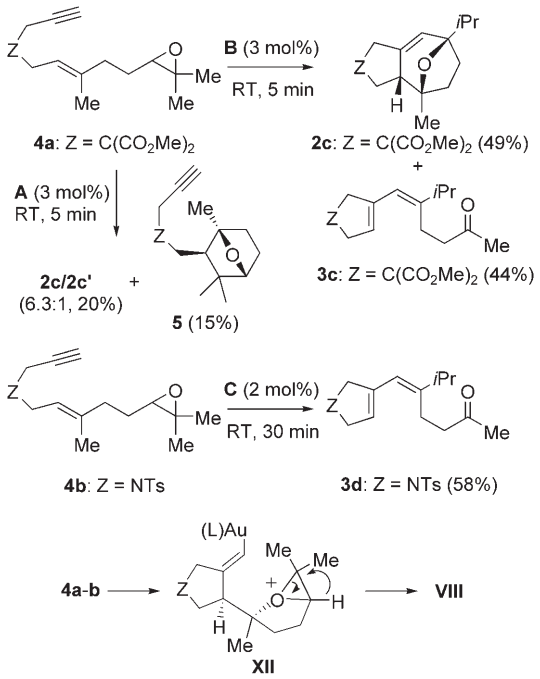
Scheme 3. Proposed mechanism for the cyclization of enynes **1a–c**.

forming oxonium cation **VIII**, which undergoes a Prins reaction[11] to give **IX**. Intermediate **IX** is a substituted 4-tetrahydropyranyl cation, which has been shown to be aromatic.[12] Elimination of the metal fragment forms tricycles **2a–c**. Alternatively, an elimination with fragmentation of the seven-membered ring via **X** leads to carbonyl compounds **3a–d**. Minor epimers **2′b,c** can arise by a competitive 2-oxonia–Cope rearrangement[13] via **X** and **XI**.

The higher selectivity for the formation of tricycles **2a–c** using AuCl as the catalyst (Table 1, entries 4, 8, and 12), relative to the cationic complexes **A–C** could be explained by the faster elimination of the more electron-rich metal center in **IX**, whereas for complexes **A–C** the metal center does not bear a negative charge in intermediates **VIII–XI**.

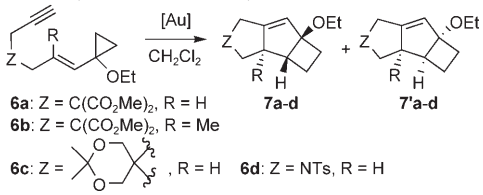
Interestingly, **2c** was also obtained from epoxide **4a** by using catalyst **B** (Scheme 4).[14] On the other hand, the reaction of **4a** with catalyst **A** gave a mixture of **2c/2′c** and oxonorbornane **5**, whose structure was confirmed by X-ray crystallography.[10] Epoxide **4b** reacted with catalyst **C** to give ketone **3d**, a result similar to that from **1d** (Table 1, entry 13). The formation of **2c** and **3c,d** could proceed through intermediates **XII**, which suffer C–O bond cleavage followed by a 1,2-hydrogen shift to form **VIII** (R = *i*Pr). Model epoxides do not isomerize to the corresponding carbonyl compounds under these reaction conditions.[15] We did not observed the direct addition of the ketone or the epoxide to the alkyne in any of these cyclizations.[16]

A related Prins cyclization, which leads to tricycles with an octahydrocyclobuta[*a*]pentalene skeleton (see Scheme 2), was uncovered in the cyclization of cyclopropylenynes **6a–d**[17–19] (Table 2). Thus, the reaction of ethyl ether **6a** with Au^I gave tricycles **7a/7′a** (Table 2, entries 1–3). Interestingly, *syn*-**7′a** was favored with catalyst **C** in the presence of traces of



Scheme 4. Gold-catalyzed reactions of epoxides **4a,b**. Ts = *p*-toluenemethanesulfonate.

Table 2: Au^I-catalyzed reaction of enynes **6a–d**.[a]

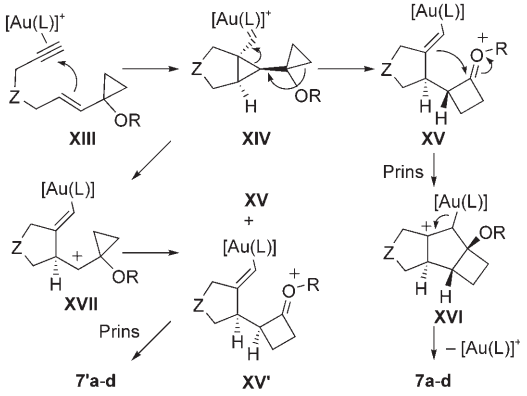


Entry	Enyne	[Au]	*t*	Product (ratio)	Yield [%]
1[a]	**6a**	**C**	5 min	**7a/7′a** (1:1)	88
2[b]	**6a**	**C**	5 min	**7a/7′a** (1:8)	81
3[b,c]	**6a**	**C**	5 min	**7a/7′a** (1:1)	93
4[b,d]	**6a**	AuCl	24 h	**7a/7′a** (30:1)[e]	80[e]
5[a,f]	**6b**	**C**	5 min	**7′b**	44
6[b,f]	**6b**	**C**	5 min	**7b/7′b** (2.5:1)	39
7[b,g]	**6c**	**C**	5 min	**7c/7′c** (3.2:1)	60
8[b,h,d]	**6c**	AuCl	2 h	**7c/7′c** (12:1)	91
9[b,g]	**6d**	**B**	5 min	**7d/7′d** (2:1)	60

[a] Reaction carried out in CH_2Cl_2 ($H_2O \approx 2$ ppm) with 3 mol% catalyst at 23 °C. [b] Reaction with 3–5 mol% water. [c] Reaction with NH_4Cl (2 equiv). [d] Reaction at 0 °C. [e] Average of five runs and determined by ^1H NMR spectroscopic analysis. [f] *E*/*Z* = 1:1. [g] Catalyst = 2 mol%. [h] Catalyst = 12 mol%.

water, whereas the use of AuCl led to the formation of **7a**, although the reaction was relatively slow (Table 2, entries 2 and 4). Low conversions (ca. 20%) were obtained when this reaction was carried out in the presence of 4-Å molecular sieves. Cycloprolylenynes **6b–d** reacted to give tricycles **7b–d** (Table 2, entries 5–9). Cyclobutanones were also formed as minor side products in these reactions.[20,21]

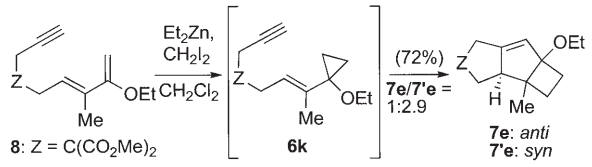
A rationale for the results of Table 2 is provided in Scheme 5. Accordingly, **XIII** forms cyclopropyl metal carbene



Scheme 5. Proposed mechanism for the gold-catalyzed reaction of enynes **6a–d**.

XIV, which undergoes ring expansion to form **XV**. The alkenyl gold complex of **XV** could react with the oxonium cation to form **XVI**, which upon demetalation forms tricycles **7a–d** by a Prins reaction.[11] The concerted pathway (**XIV**→**XV**) is favored with AuCl as the catalyst, whereas cationic Au^I complexes apparently favor a nonconcerted reaction via cyclopropyl-stabilized cation **XVII**,[22] which undergoes a non-stereospecific ring expansion to give mixtures of **7a–d**/**7′a–d**.[23] However, as suggested by the dependence of the stereochemical outcome on the amount of water, we cannot exclude a pathway in which water opens intermediate **XIV** to form an alcohol, followed by a pinacol-type expansion. This process would result in an overall retention of configuration to form **XV′**.

Tricycles **7e**/**7′e** were directly obtained when the synthesis of **6k** was attempted by the cyclopropanation of dienyne **8** with the Furukawa reagent[24] (−65→23 °C; Scheme 6). This result is consistent with the mechanistic hypothesis of Scheme 5, in which the nonconcerted pathway is favored with Zn^{II} through intermediates **XV′**, thus leading to *syn*,*cis* diastereomer **7′e** as the major tricycle.



Scheme 6. Direct Zn^{II}-promoted cyclopropanation/cyclization of enyne **8**.

In summary, the alkenyl gold intermediate formed in the cyclization of enynes can be trapped in 5-*exo*-*dig* or 6-*endo*-*dig* Prins reactions to form an additional C–C bond. These Au^I-catalyzed cyclizations of functionalized enynes led to the ready assemblage of tricyclic carbon skeletons that are present in a number of naturally occurring compounds. Thus, for example, tricycle **2c**, which possesses the same skeleton and relative configuration of β-kessyl ketone and orientalol E (Scheme 2), can be obtained in high yield in a single step. The transformation of **1a–d** into ketones **3a–d** represents a new type of skeletal rearrangement of enynes.

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