Gold Catalysis

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Gold(I)-Catalyzed Cycloisomerization of Enynes Containing Cyclopropenes**

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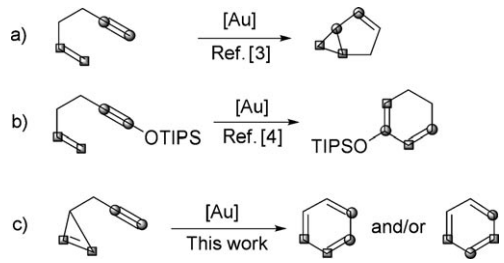
Transition-metal-catalyzed cycloisomerizations of enynes have recently been extensively studied. In particular, gold catalysts have been shown to be highly efficient in this type of reactions, which provide rapid and atom economical access to a variety of cyclic structural motifs.[1,2] Previous investigations have demonstrated that the reaction pathway is highly substrate-dependent. In the absence of external nucleophiles, the alkene moiety usually acts as a nucleophile to attack the gold-activated alkyne moiety and trigger skeletal rearrangement. In the case of 1,5-enyne systems, gold-catalyzed reactions lead to the formation of [3.1.0] bicyclic compounds, presumably through a cyclopropylcarbene intermediate (Scheme 1a).[3] When there is a siloxy substituent at the terminal position of the alkyne moiety, the gold-catalyzed reaction gives cyclohexadienes through a mechanism involving a series of alkyl migrations (Scheme 1b).[4]

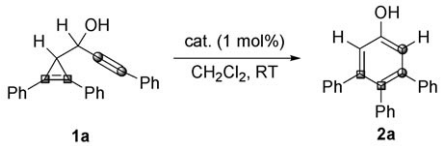


Scheme 1. Gold-catalyzed cycloisomerizations of 1,5-enynes. TIPS = triisopropylsilyl.

On the other hand, cyclopropenes have attracted considerable attention from the synthetic community as a result of their diverse reactivity.[5] The high steric ring strain of cyclopropenes give them a comparable character to alkynes;[6] in particular, the high π-density of the double bond in cyclopropene makes it highly reactive toward transition metal catalysis. Recently, gold-catalyzed reactions of cyclopropenes have been reported.[7] These reports show that gold complexes can efficiently interact with the double bond of cyclopropene to trigger ring-opening of the cyclopropene. Inspired by these findings, we became interested in the gold-catalyzed reaction of a system that contained both triple-bond and cyclopropene moieties, such as the propargyl cyclopropene shown in Scheme 1c. As triple bonds and cyclopropenes are supposed to have similar reactivities toward gold complexes, an intriguing question would be which unsaturated bond is preferentially activated by a gold catalyst. Furthermore, the propargyl cyclopropene can be considered as a 1,5-enyne system. Thus, we were also intrigued as to whether it reacts in a similar manner to conventional 1,5-enynes. Herein, we report a highly efficient gold-catalyzed rearrangement of propargyl cyclopropenes, which affords benzene derivatives. The triple bond is preferentially activated by gold catalyst and the reaction may proceed through a novel mechanism involving multiple alkyl migrations.

At the outset, we examined the reactivity of 3-hydroxy substituted propargyl cyclopropene **1a** with transition metal catalysts (Table 1). To our delight, with 1 mol% of AuCl or $AuCl_3$, an efficient reaction occurred in 5 minutes to afford phenol derivative **2a** in high yield (Table 1, entries 1 and 2). AgOTf also catalyzed this transformation, but the reaction took much longer to complete (Table 1, entry 3). The yield was improved by using [Au(PPh_3)Cl]/AgOTf (Table 1, entry 4). $PtCl_2$ also gave high yield of **2a**, but it took 6 hours for the reaction to complete (Table 1, entry 5). We also examined $In(OTf)_3$ and HOTf; the former afforded trace amount of product and the latter gave no desired product.

Table 1: Catalytic cycloisomerization of **1a**.[a]



1a **2a**

Entry	Catalyst	Reaction time [min]	Yield [%][b]
1	AuCl	5	88
2	$AuCl_3$	5	82
3	AgOTf	120	86
4	[Au(PPh_3)Cl]/AgOTf	5	96
5	$PtCl_2$	360	94
6	$In(OTf)_3$	120	< 5
7	HOTf	120	0

[a] All reactions were carried out using 50 mg of **1a** in 3 mL CH_2Cl_2. [b] Yield of isolated product. Tf = trifluoromethanesulfonyl.

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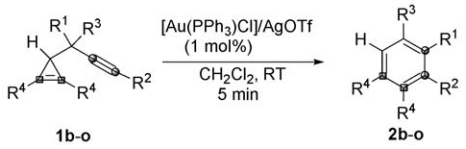
Next, we prepared a series of secondary and tertiary propargyl alcohols that bear cyclopropene moieties (**1b–o**). All of these substrates underwent the cycloisomerization reaction to give high yields of phenol derivatives (Table 2).

Table 2: Gold(I)-catalyzed cycloisomerization of **1b–o**.[a]

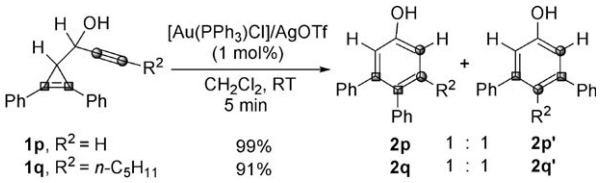


Entry	R^1	R^2	R^3	R^4	Yield [%][b]
1	Me	Ph	OH	Ph	**2b**, 97
2	*n*Bu	Ph	OH	Ph	**2c**, 96
3	CH_2=CH	Ph	OH	Ph	**2d**, 95
4	PhC≡C	Ph	OH	Ph	**2e**, 82
5	Ph	Ph	OH	Ph	**2f**, 90
6	CN	Ph	OTMS	Ph	**2g**, 89[c]
7	H	Ph	OAc	Ph	**2h**, 96
8	H	CO_2Et	OH	Ph	**2i**, 97
9	H	*p*-$O_2NC_6H_4$	OH	Ph	**2j**, 96
10	H	*p*-$F_3CC_6H_4$	OH	Ph	**2k**, 95
11	H	*p*-$MeOC_6H_4$	OH	Ph	**2l**, 91
12	H	*p*-$Me_2NC_6H_4$	OH	Ph	**2m**, 71
13	*n*BuC≡C	*n*Bu	OH	*n*Bu	**2n**, 74
14[d]	H	H	H	Ph	**2o**, 97

[a] All reactions were carried out using 100 mg of **1b–o** and 3 mL of CH_2Cl_2. [b] Yield of isolated product. [c] Phenol was isolated after column chromatography. [d] Reaction was carried out with 2 mol% of the catalyst.

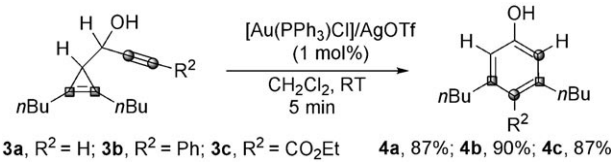
For the tertiary propargyl alcohols, the products were isolated with an R^1 migration onto the adjacent alkyne carbon. Alkyl, alkenyl, alkynyl, aryl, and cyano groups all migrated successfully (Table 2, entries 1–6, 13).[8] The products were fully characterized by spectroscopy and for one of the products (**2b**), the structure was further confirmed by single-crystal X-ray analysis.[9] Interestingly, for the acetate ester **1h**, the 1,2-acetoxy migration product was not observed (Table 2, entry 7).[2,10] As the siloxy substituent in the alkyne dramatically altered the reaction pathway in the 1,5-enyne system reported by Kozmin and co-workers,[4] we then examined substrates with substituents other than a phenyl group at the terminal position of the alkyne moiety. Introducing either electron-withdrawing or electron-donating groups onto the phenyl substituent of R^2 did not affect the reactions (Table 2, entries 9–12). With an electron-withdrawing ester substituent, **2i** was isolated in high yield (Table 2, entry 8). In the case of **1n**, in which R^1 was alkynyl group and R^2 was alkyl group, the reaction also afforded the expected cycloisomerization product **2n** as the main product, together with small amount of furan side-product, which was derived from the secondary gold-catalyzed reaction of product **2n**. Finally, it is worthy of note that the reaction occurs with equally high efficiency when both R^1 and R^3 are H, to give 1,2-diphenylbenzene **2o** (Table 2, entry 14).

To our surprise, when propargyl alcohols **1p** and **1q** were subjected to the same reaction conditions, a mixture of symmetrical (**2p′** and **2q′**) and unsymmetrical benzene derivatives (**2p** and **2q**) were isolated in high yields (Scheme 2). The generation of products **2p′** and **2q′** indicates a complete cleavage of the cyclopropene double bond and the alkyne triple bond similar to the siloxy-substituted 1,5-enyne system reported by Kozmin and co-workers.[4]



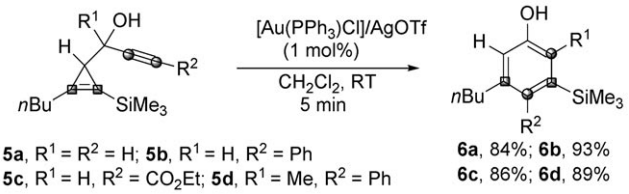
Scheme 2. Gold-catalyzed reaction of **1p** and **1q**.

We further observed that substituents in the cyclopropene moiety have a crucial effect on the reaction pathway. As shown in Scheme 3, the gold-catalyzed reaction of **3a–c**, in which the substituents on cyclopropene were *n*-butyl groups, afforded exclusively symmetric phenol derivatives **4a–c**, which were formed through a double-cleavage process. A comparison of these results with those in Table 2 suggests that the R^2 substituent at the terminal position of alkyne has a less significant effect on the switch of reaction pathway.



Scheme 3. Gold-catalyzed reaction of **3a–c**.

The importance of the cyclopropene substituents on the reaction pathway is further demonstrated by the reaction of **5a–d** (Scheme 4). In substrates **5a–d**, the substituents on the double bond of the cyclopropene moiety are unsymmetrical, with one being *n*Bu and other being TMS (trimethylsilyl). The gold-catalyzed reactions of **5a–d** all afforded the double-cleavage products exclusively. The two diastereoisomers in the substrates were both converted into the same phenol derivatives. It is worthy of note that the TMS group was positioned between R^1 and R^2 in all of those cases. This result is consistent with the β-cation-stabilizing effect of silicon for



Scheme 4. Gold-catalyzed reaction of **5a–d**.

carbon cations (see **A**, Scheme 5). The structures of **6b–d** were confirmed by NOESY experiments.

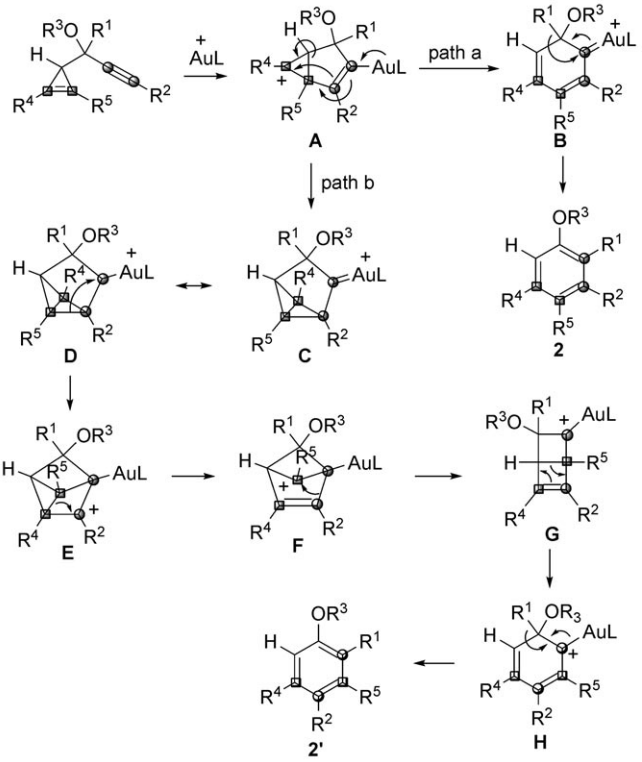
A possible mechanism to account for the above experiment results is shown in Scheme 5. We assumed that the triple bond in the propargyl cyclopropene was preferentially complexed to the gold catalyst. The π-electron of the cyclopropene then attacks the gold-activated alkyne as a nucleophile in a 5-*endo-dig* manner to form a bicyclo-[3.1.0]hexene intermediate **A**, from which two pathways are possible, thus leading to two regioisomeric products. For path a, back-donation of the electron from the gold center leads to ring enlargement and the formation of six-membered gold carbene intermediate **B**,[11] which undergoes 1,2-shift of an R^1 group to afford the phenol product. In this pathway, there is no complete disconnection of double bond and triple bond. In path b, back-donation of the electron from the gold center leads to the formation of bicyclo[1.1.0]butane intermediate **C**.[12] From intermediate **C**, three consecutive 1,2-alkyl shifts via carbocation species **D**, **E**, and **F** occur, thus affording Dewar-benzene-type intermediate **G**.[13] Through the three consecutive 1,2-alkyl shifts, the cleavage of both double and triple bonds are complete.[14] Subsequently, ring opening of intermediate **G** leads to the formation of intermediate **H**,[15,16] from which a 1,2-shift generates the final product **2′**.

The dramatic effect of substituents on the switch of reaction pathway may be due to steric effects of the substituent. When there are two phenyl groups on the double bond and one aryl group in the terminal alkyne, the reactive sites would be too crowded to form the intermediates **C**, **D**, **E**, and **G**. As a result, the reaction will follow path a. In contrast, when smaller hydrogen or alkyl groups were on the terminal alkyne, the reaction partially followed path b, as shown in the reaction of **1p** and **1q**. When the cyclopropene double bond was substituted by relatively smaller *n*-butyl groups, path b was favored, regardless of the substituents on the alkyne.

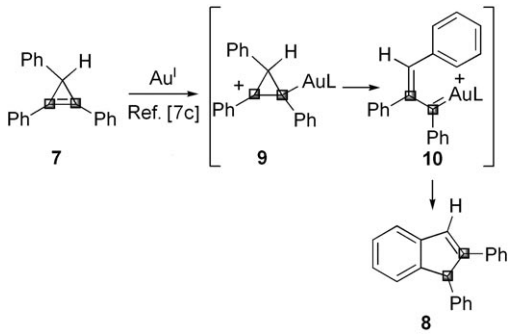
An intriguing question in the mechanism is the reactivity of cyclopropene toward gold complexes as compared with that of an alkyne. We have previously reported that cyclopropene **7** rearranges to indene **8** when catalyzed by [Au(PPh$_3$)Cl]/AgOTf (2 mol%) in dichloromethane at room temperature (Scheme 6);[7c] vinyl gold carbene species **10** was suggested as the intermediate. The reaction conditions were identical to the gold-catalyzed reaction of propargyl cyclopropene, but it took longer (30 min) with slightly higher catalyst loading.

To gain further insights into the substituent effects, we synthesized cyclopropene derivatives **11**–**18** and investigated their reactions under gold catalysis. Compounds **11**–**13** showed no reaction under identical conditions, which suggests that the cyclopropene moiety has a relatively low reactivity toward gold complex. These results are in agreement with the mechanism proposed in Scheme 5, in which the activation of a triple bond triggers the cycloisomerization process.[17]

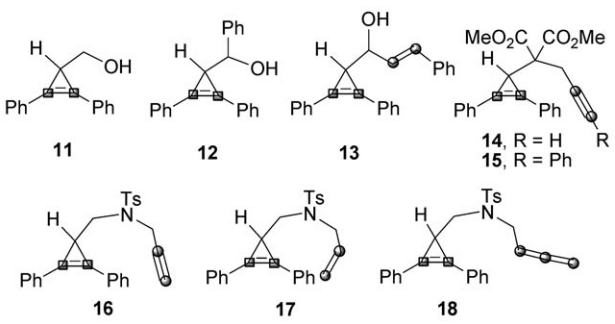
Cyclopropene derivatives **14** and **15** are 1,6-enyne systems. We observed that the gold-catalyzed reactions of **14** and **15** proceeded through similar mechanisms, initiated by the 5-*exo-dig* attack of the gold-catalyzed triple bond by a cyclo-



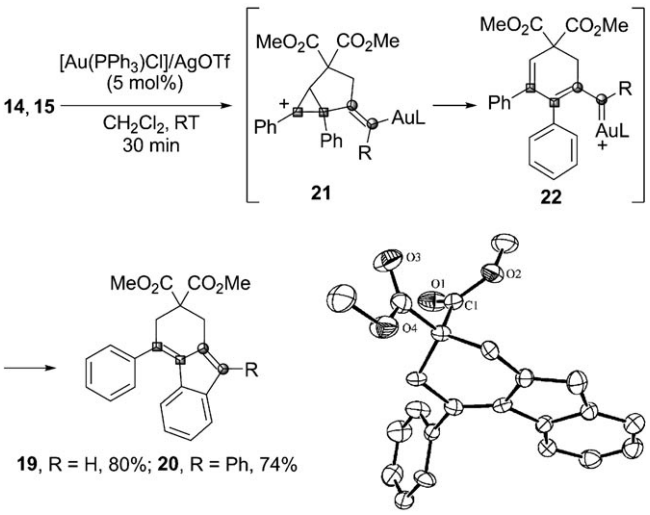
Scheme 5. Mechanistic rationale.



Scheme 6. Gold-catalyzed reaction of cyclopropene.

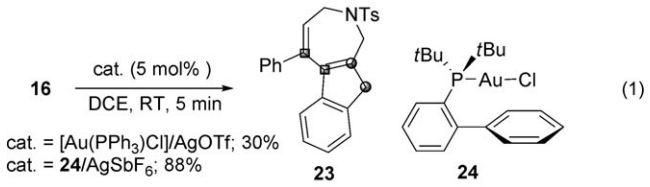


propene to generate gold–carbene **22** (Scheme 7). The reaction affords tricyclic products **19** and **20**. The structure of **19** was confirmed by X-ray crystallographic analysis.[9]



Scheme 7. Gold-catalyzed reaction of 1,6-enyne systems.

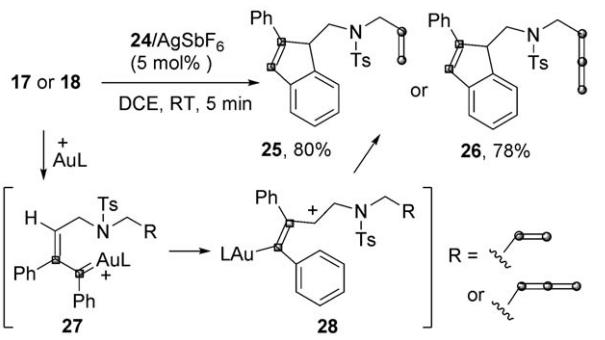
Cyclopropene derivative **16** is a 1,7-enyne system; its gold-catalyzed reaction proceeded in a similar manner to conventional 1,7-enyne systems, that is, through 1,6-*exo-dig* attack to afford **23** in 30% yield with catalytic $[Au(PPh_3)Cl]/AgOTf$ [Eq. (1)]. Interestingly, gold(I) complex **24** was highly efficient for this reaction, which afforded **23** in 88% yield.



(1)

Finally, it was observed that the gold(I)-catalyzed reaction of **17** and **18** with **24**/$AgSbF_6$ gave **25** and **26**, respectively (Scheme 8). The formation of **25** and **26** can be rationalized by a mechanism involving gold–carbene **27** and intermediate **28**, of which Friedel–Crafts reaction afforded the cyclization products.

In conclusion, we have reported the first gold-catalyzed reaction of propargyl cyclopropene systems. The reaction is highly efficient, affording benzene derivatives in high yields. Depending on the substituents, the reaction may occur through a mechanism involving cleavage of both double and triple bonds. From a synthetic point of view, this novel cycloisomerization reaction may serve as an efficient access to multisubstituted phenol derivatives.[18] Moreover, the systematic study on the gold-catalyzed reaction of a series of unsaturated system bearing a cyclopropenyl moiety provides insight into the relative reactivity of various unsaturated bonds toward gold catalysts. Based on the current study and



Scheme 8. Gold-catalyzed reaction of 1,7-ene-cyclopropene. DCE = dichloroethane, Ts = 4-toluenesulfonyl.

those reported in the literature, it can be concluded that alkyne groups is more effectively activated by gold catalyst than cyclopropenes.

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[9] CCDC 774056 (**2b**) and CCDC 774055 (**19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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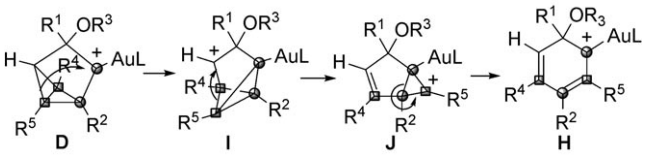
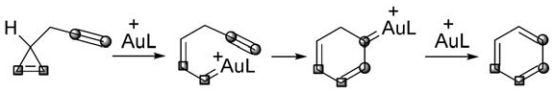
[15] For investigations on the ring-opening of Dewar benzene and related structures, see: a) T. R. Boussie, A. Streitwieser, *J. Org. Chem.* **1993**, *58*, 2377 – 2380; b) F. L. Cozens, A. L. Pincock, J. A. Pincock, R. Smith, *J. Org. Chem.* **1998**, *63*, 434 – 435; c) M. J. Goldstein, R. S. Leight, *J. Am. Chem. Soc.* **1977**, *99*, 8112 – 8114; d) R. P. Johnson, K. J. Daoust, *J. Am. Chem. Soc.* **1996**, *118*, 7381 – 7385.

[16] Alternatively, **H** might be formed from **D** through **I** and **J** involving one 1,3- and two 1,2-alkyl shifts, as suggested by one of the referees.



[17] These experiments can preclude the following mechanism for the generation of gold–carbene species.



[18] For a recent example on the synthesis of multi-substituted benzene derivatives, see: P. García-García, M. A. Fernández-Rodríguez, E. Aguilar, *Angew. Chem.* **2009**, *121*, 5642 – 5645; *Angew. Chem. Int. Ed.* **2009**, *48*, 5534 – 5537.

