Intermolecular Cyclization

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Gold(I)-Catalyzed Intermolecular Cyclopropanation of Enynes with Alkenes: Trapping of Two Different Gold Carbenes**

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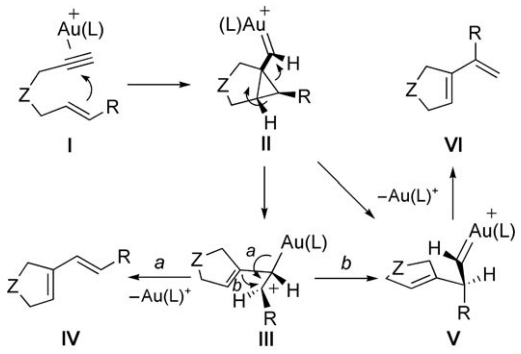
Transition-metal-catalyzed reactions of 1,6-enynes[1,2] that proceed by the selective coordination of the metal center to the alkyne take place through *exo*-cyclopropyl metal carbenes or the related *endo* intermediates.[2,3] In the absence of nucleophiles, enynes undergo skeletal rearrangement (Scheme 1). Based on kinetic data and DFT calculations, we recently proposed that upon coordination of Au^I to the enyne **I**, the resulting *anti*-cyclopropyl gold(I) carbene **II** rearranges to give **III**, which can undergo demetalation (pathway a) to form the single cleavage rearrangement product **IV**. Alternatively, **III** may undergo a 1,2-shift (pathway b) to form a new gold carbene **V**, which gives double cleavage rearrangement diene **VI** after α-hydrogen elimination. The double cleavage rearrangement can also take place directly from intermediate **II** to give **V**.[4]

Strong evidence for the existence of metal carbenes of type **II** has been obtained by intramolecular trapping with alkenes in ruthenium-,[5] platinum-,[6,7] and gold-catalyzed reactions.[4a,8] We have recently shown that the *anti* arrangement of the carbene and the cyclopropane accounts for the configuration observed in all these intramolecular processes.[8]

We now report that carbenes **II** and **V** can be trapped intermolecularly with a variety of alkenes.[9,10] We also found the first examples of a shift of cyclopropyl gold(I) carbenes. These results support the mechanism proposed for the skeletal-rearrangement of enynes.[4]

We first studied the reaction of enyne **1a** with norbornene in the presence of several gold(I) catalysts **A**–**D** (Table 1). In the absence of norbornene, skeletal rearrangement products **3** and **4** were cleanly obtained in overall quantitative yield with catalyst **A** (Table 1, entry 1).[8] However, when the reaction of **1a** was performed in the presence of norbornene (5 equiv),

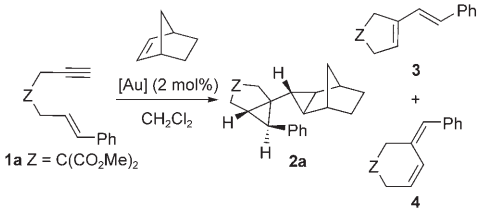


Scheme 1. Skeletal rearrangement of enynes. L = ligand.

biscyclopropane **2a** was obtained as the major product (Table 1, entry 2).[11] The configuration of **2a** was determined by a NOESY experiment.[12] Less satisfactory results were obtained with catalysts **B**[13] and **C**, which led to the formation of **3** and **4** (Table 1, entries 3 and 4). Catalyst **C** presumably forms a highly electrophilic Au^I complex in situ, which has a bulky phosphite moiety as the ligand. Attempts at isolating the corresponding cationic complex in acetonitrile have not been yet successful. The best yields of biscyclopropane **2a** were realized with catalyst **D**[14,15] or AuCl (Table 1, entries 5 and 6, respectively).

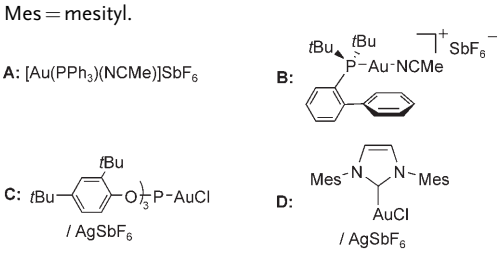
Although catalysts **D** and AuCl gave satisfactory results in the cyclopropanation of enynes, in general cleaner transformations were achieved with **D**. The scope of this reaction is

Table 1: Gold(I)-catalyzed reaction of enyne **1** with norbornene.[a]



Entry	[Au]	Norbornene [equiv]	Yield of **2** [%][b]	**3** + **4** Yield [%]	**3** + **4** Ratio[b]
1	**A**	–	–	99	1:1.4
2	**A**	5	66	29	1:1.2
3	**B**	5	34	62	1.1:1
4	**C**	5	40	52	1:1.6
5	**D**	5	93	3	>10:1
6	AuCl	5	94	0[c]	–

[a] Reactions carried by slow warming from −50 to 23 °C over approximately 15 h with five equivalents of norbornene. [b] Yields and ratios determined by GC for reactions with approximately 100% conversion. [c] Approximately 2% of other uncharacterized products. Mes = mesityl.



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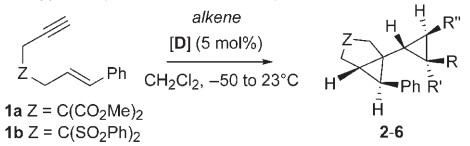
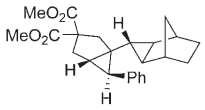
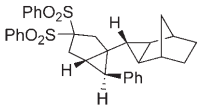
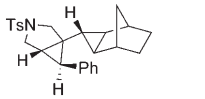
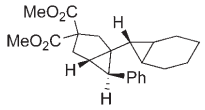
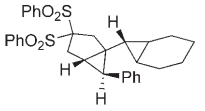
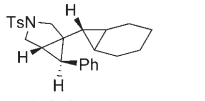
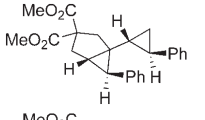
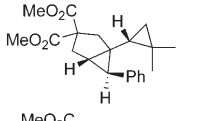
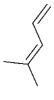
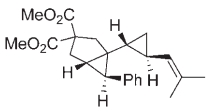
shown in Table 2. A single isomer was obtained in the reactions of **1a–c** with norbornene (Table 2, entries 1–3)[12] and cyclohexene (Table 2, entries 4–6). The yield of the reaction of entry 2 was low as a result of problems encountered in the purification of biscyclopropane **2b**. The reaction of **1a** with styrene provided **4a** in 76% yield (Table 2, entry 7) as a single isomer. Reaction of **1a** with 2-methylpropene and 4-methylpenta-1,3-diene afforded mixtures of two stereoisomers (Table 2, entries 8 and 9, respectively).

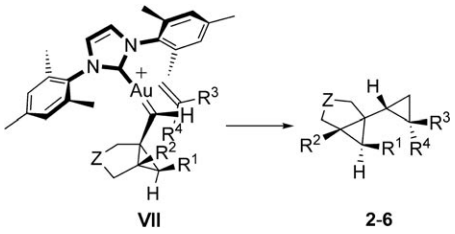
The configurations assigned to the major compounds obtained in the intermolecular cyclopropanations follow those assigned in the intramolecular processes,[8] which correspond to the stereochemical model **VII** for the approach of the alkene to the cyclopropyl gold carbene (Scheme 2).[12] This model also explains the regiochemistry observed in the reaction of 4-methylpenta-1,3-diene (Table 2, entry 9), in which the bulky ligand on the Au center directs the cyclopropanation towards the less sterically hindered alkene.

Table 2: Gold(I)-catalyzed reaction of enynes **1a–c** with alkenes.



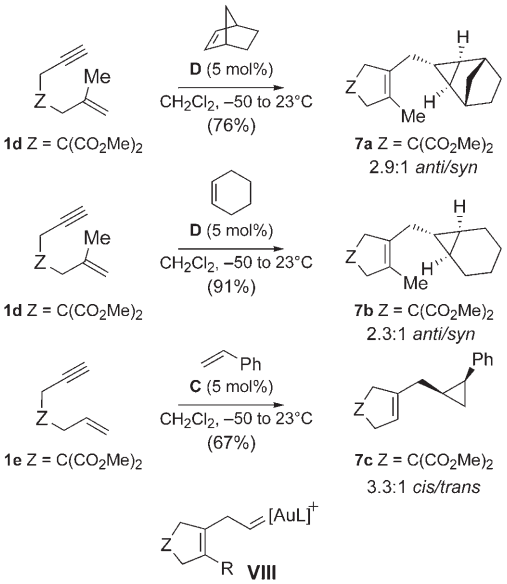
Entry	Alkene	Enyne	Product	Yield [%][a]
1		**1a**	 **2a**	67
2		**1b**	 **2b**	31
3		**1c**	 **2c**	73
4		**1a**	 **3a**	77
5		**1b**	 **3b**	53
6		**1c**	 **3c**	75
7		**1a**	 **4a**	76
8[b,c]		**1a**	 **5a/5a'**	52[d]
9[c]		**1a**	 **6a/6a'**	60[e]

[a] Yields of the isolated products are as the average of at least two reactions; reaction time = 15 h, except for entries 2 and 3 (40 h). [b] Reaction carried out with AuCl (2 mol%). [c] Only the major isomer is shown. [d] Ratio of isomers = 3.7:1. [e] Ratio of isomers = 5:1. Ts = *p*-methylphenylsulfonyl.



Scheme 2. Model for the stereoselective cyclopropanation of alkenes by cyclopropyl gold carbene **VII**.

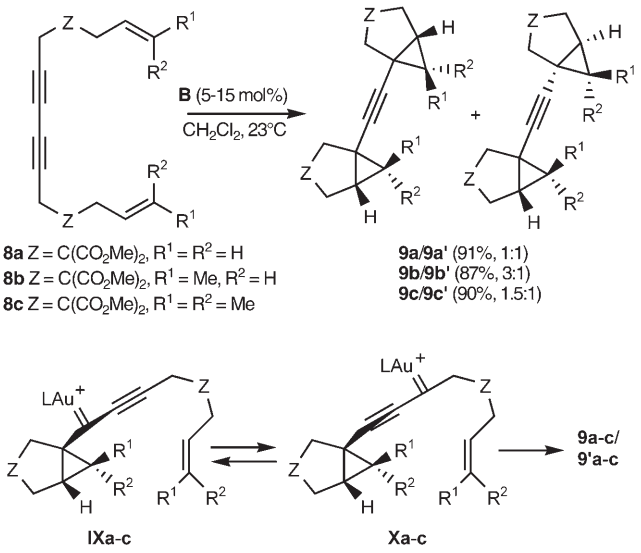
The second Au^I carbene **V** (Scheme 1) can also be trapped intermolecularly with alkenes. Thus, enynes **1d–e** react with different alkenes to form products **7a–c** through a cyclopropanation reaction of intermediates **VIII** (Scheme 3). In the case of **1e**, the best results were obtained with catalyst **C**, which gave **7** as a 3.3:1 mixture of *cis* and *trans* isomers. In the absence of styrene, **1e** reacts with catalyst **C** to give a 2:1 mixture of *exo* and *endo* skeletal rearrangement products in 87% yield. Configuration of the major stereosiomers **7a–c** were based on the analysis of the coupling constants of the cyclopropane hydrogen atoms and NOESY experiments.



Scheme 3. Gold(I)-catalyzed reaction of enynes **1d,e** with alkenes via carbene **VIII**.

Additional evidence for the involvement of metal carbenes in these reactions was obtained in the reaction of dimeric substrates **8a–c** with cationic Au^I catalyst **B**

(Scheme 4). Thus, the reaction of **8a** with **B** (5 mol%) for 5 h furnished **9a** and **9′a** in 91% yield. The ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum showed only 11 signals. However, in C_6D_6



Scheme 4. Cyclopropanation through a [1,3]-metallotropic shift.

(125 MHz), the formation of a 1:1 mixture of *meso*-**9a** and chiral **9a′** was evident by the splitting of three of the carbon signals. On the other hand, **8b** reacted with **B** (15 mol%) for 15 h to give **9b**/**9′b** (90%). Reaction of **8b** with **C** (5 mol%) was completed in 7 h to give **9b**/**9′b** (70%). Similarly, **8c** reacted with **B** (10 mol%) for 24 h to give **9c**/**9′c** (87%). These reactions can be explained by isomerization of the initially formed cyclopropyl gold carbene **IX** to form **X** by a [1,3]-metallotropic shift, followed by intramolecular trapping of the gold carbene by the alkene. This type of [1,3]-metallotropic shift has been observed before for Rh,[16] Cr, Mo, W,[17] and Ru[18,19] carbene complexes.

In summary, we have established the first intermolecular cyclopropanation reactions of enynes with alkenes. This new cyclopropanation[20] allows the synthesis of complex cyclic systems from readily available starting materials with gold(I) catalysts under mild conditions. These results also provide compelling evidence for the existence of metal carbenes of types **II** and **V** in the skeletal rearrangement. We have also provided the first examples of a 1,3-metallotropic shift of d^{10} metal complexes, which further supports the existence of gold carbenes in these reactions.

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