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Gold-catalyzed Intermolecular [4C + 3C] Cycloaddition Reactions

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Abstract

In the presence of the *N*-heterocyclic carbene gold catalyst (NHC-AuIPr, **7**), propargyl esters **1a–f** and **13** undergo a [4C + 3C] cycloaddition reaction with cyclopentadiene and furan under mild conditions. The evidence suggests the formation of the seven-membered ring occurs by a direct cycloaddition process, rather than a stepwise cyclopropanation/Cope rearrangement sequence.

The potent antiangiogenesis natural product family of cortistatins contain a center seven-membered ring flanked by two six-membered rings.[1,2] Our initial attempt to construct the tetracyclic ring system using a transannular [4C+3C] cycloaddition strategy was met with mixed results.[3,4] In the same time, Mascarenas and co-workers reported an intramolecular [4C +3C] cycloaddition reaction, in which an allene functional group was selectively activated by Pt or Au catalyst.[5] This type of allene-diene intramolecular [4C+3C] cycloaddition reactions was further improved to occur under milder conditions.[6–8] Other reports using propargyl esters as reactants involved stepwise [4+3] cycloaddition reactions to prepare benzonorcaradienes and azepines.[9,10] More recently, Harmata reported the treatment of 5-silyloxydioxins with 5 mol % $AuCl_3/AgSbF_6$ in the presence of cyclopentadiene or furan resulted in the formation of [4C+3C]-cycloadducts.[11] In this report, we disclose an intermolecular version of gold-catalyzed formal [4C+3C] cycloaddition reactions. This discovery expands the employment of propargyl esters as precursors in gold-catalyzed [4+3] cycloaddition reactions.[12]

The likely mechanism for our recently reported gold-catalyzed transannular [4+3] cycloaddition could involve two possible pathways based on known examples in the literature.[13–15] The first pathway involves a gold-stabilized allyl cation and the second involves a gold carbene intermediate. As shown in Scheme 1, the first pathway (**I** to **II** through **A** and **B**) includes (1) a 3,3-rearrangement of the propargyl ester to give an allenyl ester (**A**),[16,17] (2) in situ activation by the same gold catalyst to generate an allyl cation **B**,[18] and (3) a [4+3] cycloaddition followed by a 1,2-acetoxy migration and deauration to produce the tetracyclic ring system **II**. The second mechanism through intermediates **C** and **D** is depicted on the right side in Scheme 1. This pathway involves a 1,2-acetoxy migration followed by a cyclopropanation/Cope rearrangement to produce the same product. Diazoesters undergo cyclopropanation/Cope rearrangement reactions in the presence of rhodium catalysts and Davies and coworkers have studied these reactions extensively.[19,20]

Ohe and coworkers reported cyclopropanation of alkenes using propargylic carboxylates as vinylcarbene precursors and $[RuCl_2(CO)_3]_2$ as the catalyst.[21] More recently, Au(I)-catalyzed

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Supplementary data
Supplementary data associated with this article (experimental procedures, NMR spectra) can be found in the online version at

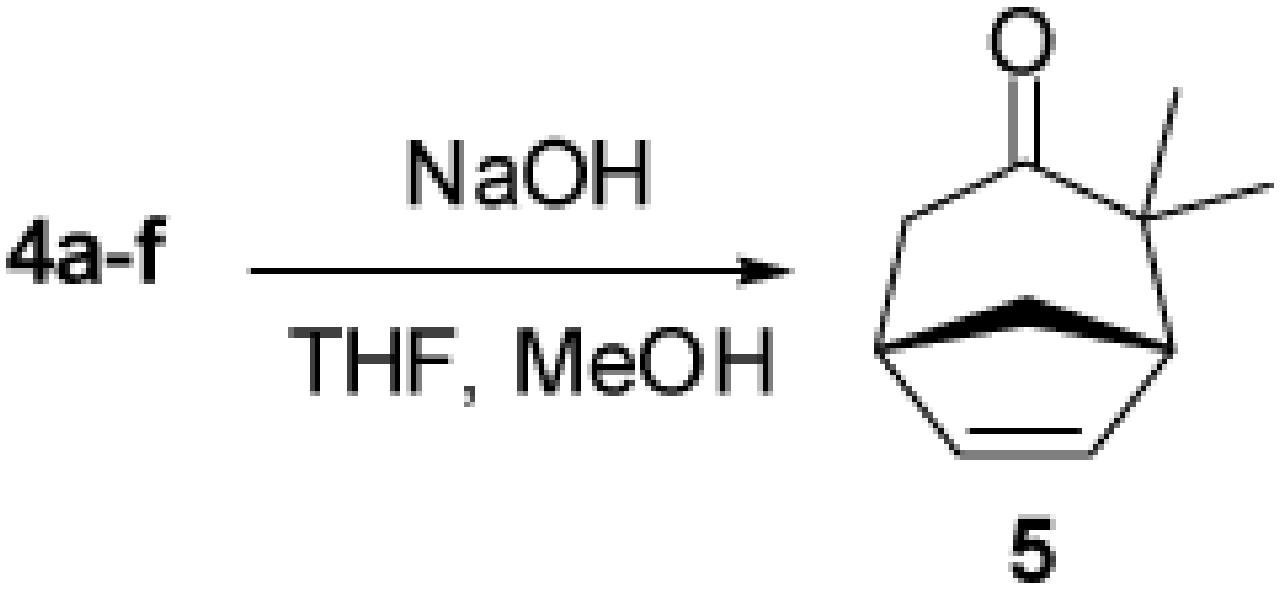
cyclopropanation of olefins using either propargyl esters or enynes as gold-(I)-carbene precursors were reported.[22,23]

Because of their easy preparation, propargyl esters are convenient synthetic precursors. We are interested in expanding the usage of propargyl esters from transannular to inter- and intramolecular versions as the substrates in gold-catalyzed [4+3] cycloaddition reactions. The initial experiments were carried out using propargyl esters **1a–e** and Au(III) catalyst $PicAuCl_2$ **6** (Table 1 and Fig. 1)[24] which we have successfully employed in transannular [4+3] cycloaddition reactions.[12] Other gold catalysts screened include the NHC-Au-IPr **7** and the $R_3PAu(I)Cl$ **8–10**.

The reactions of propargylic carboxylates **1a**–**e** with cyclopentadiene were studied in CH_2Cl_2 at room temperature in the presence of gold catalysts **6–10**. In the presence of the Au (III) catalyst **6**, a cyclopropanation and a formal [4C + 3C] cycloaddition reaction occurred smoothly to afford a mixture of products **3** and **4**. Although other Au(I) catalysts (**8–10**) were not effective (entries 8–10), we are pleased to find the gold catalyst with an *N*-heterocyclic carbene (NHC)[25] ligand to be a highly effective catalyst for this transformation. With only 1% of the NHC-Au(I) catalyst **7**, the reaction proceeded smoothly to give the corresponding products **3d** and **4d** (entry 7, Table 1). This reaction is very similar to the report by Ohe using $[RuCl_2(CO)_3]_2$ as the catalyst,[21] although a higher reaction temperature was required previously.

The reaction of **1a** (R = Me) give the vinyl cyclopropane with *endo* stereochemistry, i.e., **3a**, along with 3-acetoxy-4,4-dimethylbicyclo[3.2.1]-octa-2,6-diene (**4a**), both are known compounds from the previously reported study with Ru catalyst.[21] The ^1H and ^{13}C NMR spectra of **3a** and **4a** are consistent with the reported data.[21] No vinyl cyclopropane with *exo* configuration was observed.

The vinyl cyclopropanes *endo*-**3** can be converted to the corresponding bicyclo[3.2.1]octa-2,6-dienes (**4**) through a Cope rearrangement reaction by heating a solution of *endo*-**3** in toluene at reflux for 12 h. The structure of the bicyclic enol esters **4** was further confirmed by convertion to the known ketone **5**[26] with base catalyzed removal of the ester group, Eq (1).



Eq. (1)

With 5 mol% of the gold catalyst **6**, several propargyl esters (**1a–e**) with different R group were compared for their reactivity (Table 1). The benzoate esters gave higher yields than the alkanoate esters (comparing entries 3 & 4 to 1 & 2). However, the low yields of **4a** and **4b** were most likely due to the volatility of the products.

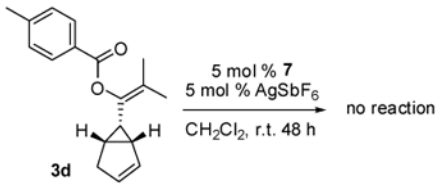
Encouraged by the catalytic efficiency of the NHC-Au-IPr catalyst **7**, the study was expanded to include furan as a diene substrate. In the presence of 1% of **7**, propargyl ester **1f** was allowed to react with 5 eqv. of furan, Scheme 2. Interestingly, the effect of the gold catalyst **7** parallels the ruthenium catalyst ($[RuCl_2(CO)_3]_2$)[27] and the triene aldehyde **11** was obtained as the exclusive product after 2 hours at room temperature in the solvent of CH_2Cl_2. However, when the same reaction was conducted in pentane a significant amount of the formal [4+3] cycloaddition product **4f** was also isolated.

The structure of **4f** was confirmed by converting to the known ketone **12**.[28] The structure of the propargyl ester was examined by using **13** as a reactant in the presence of catalyst **7**, Scheme 3.

To our delight, the reaction proceeded smoothly to afford a mixture in 95% yield with one diminant product. The major product, tentatively assigned as **14**, was isolated along with minor isomers that have similar polarity and are difficult to separate. To expedite the isolation and structure identification, this mixture was subjected to the usual base-catalyzed removal of the ester group. This led to a clean separation of the major product **15a** and its diastereomer **15b** along with small amount of unidentified isomers. Product **15a** is a known compound which was previously prepared using a classical oxyallyl cation addition to cyclopentadiene.[29,30]

Under catalysis of the NHC-AuIPr catalyst **7**, the results are dramatically different for propargyl esters **1a–f** and **13**. The former gave a nearly 1:1 mixture of cyclopropanation product **3** and the formal [4+3] cycloaddition product **4**, while the latter produced predominantly the [4+3] cycloaddition product **14**. It is likely that compound **14** is produced directly from an

intermolecular [4+3] cycloaddition process. Evidence in support of a direct [4+3] cycloaddition lies in the mild conditions of the reaction. High temperature (refluxing in toluene for 12 h) was required for converting the cyclopropanation products **3a–e** to **4a–e** while compound **14** was obtained at room temperature from an overnight reaction. To further explore the pathways for the formation of the [4C+3C] cycloaddition products, isolated compound **3d** was recommitted to the reaction conditions with fresh gold catalyst **7** for two days at rt, Eq (2). No reaction was observed. This strongly suggests that the formation of the products **4a–e** came from a direct [4C+3C] cycloaddition mechanism.



Eq. (2)

We have shown that gold catalyst **7** is capable of initiating an intermolecular [4+3] cycloaddition reaction. Based on the evidence, the formation of the seven-membered rings occurs by a direct [4+3] cycloaddition mechanism, rather than a stepwise cyclopropanation/ Cope rearrangement sequence. Further study on ligand effects on the product ratio is underway in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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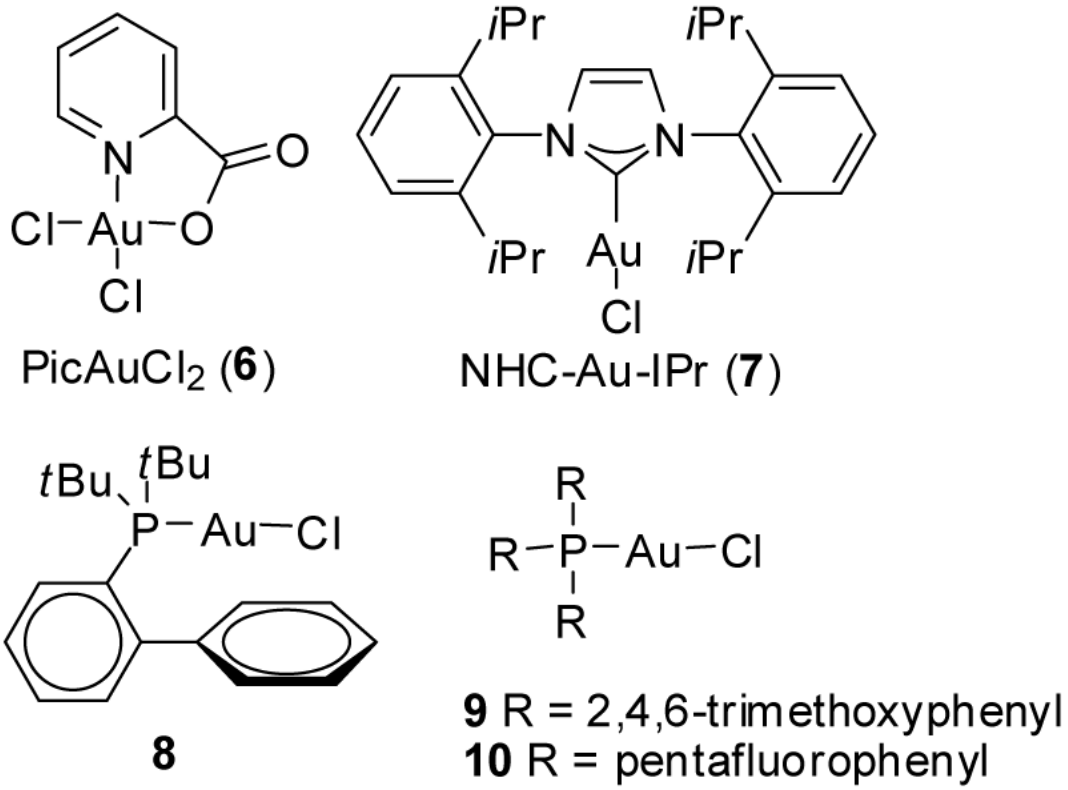
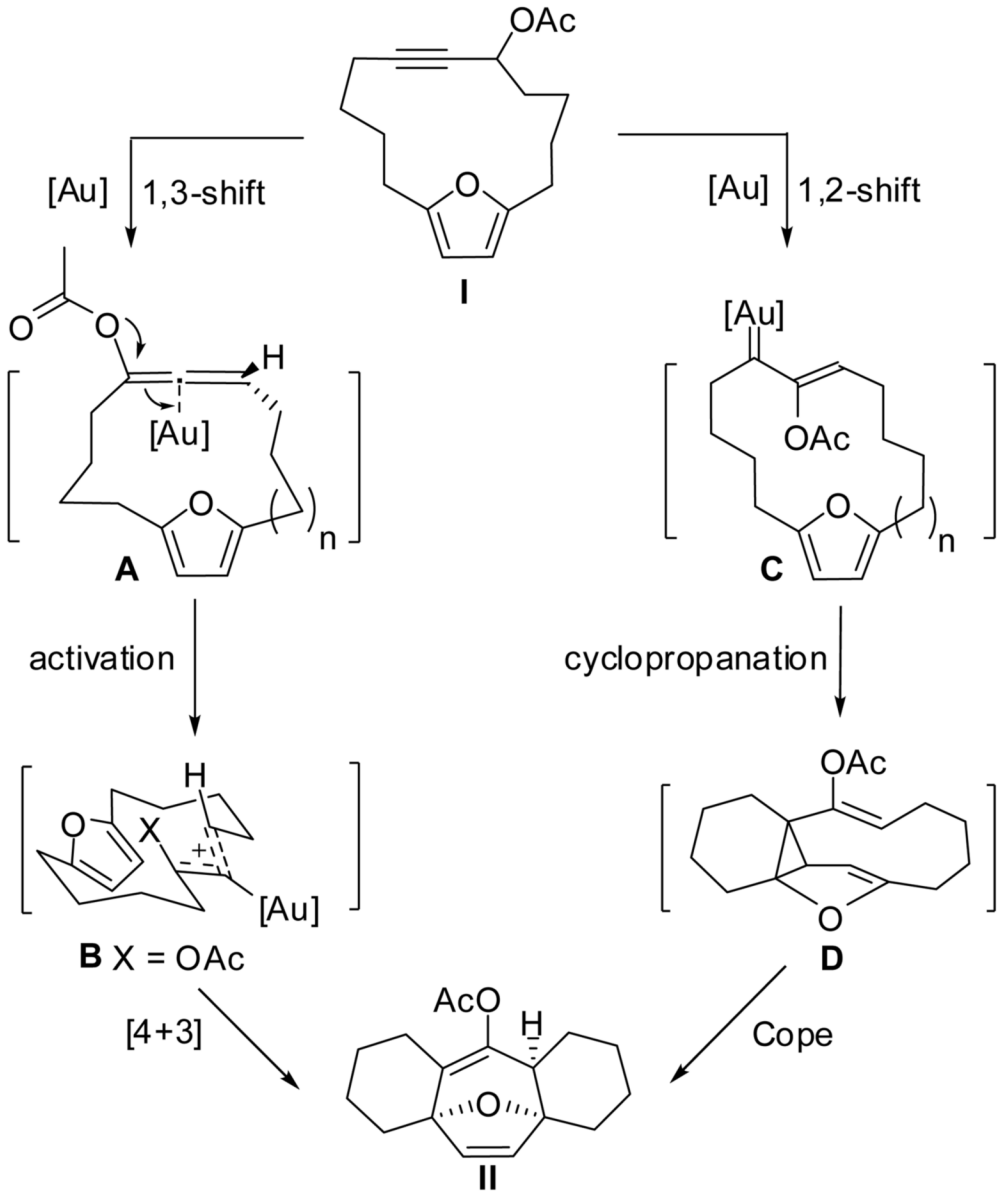
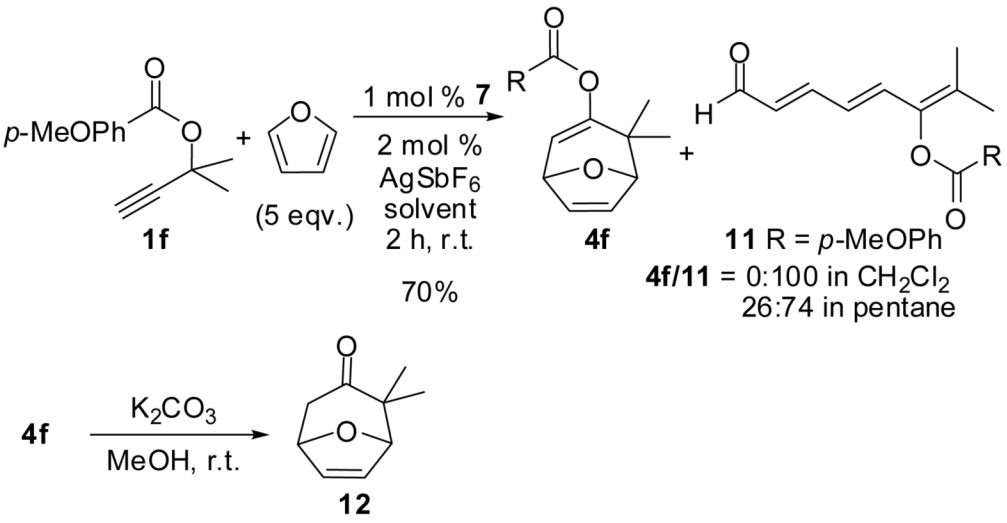


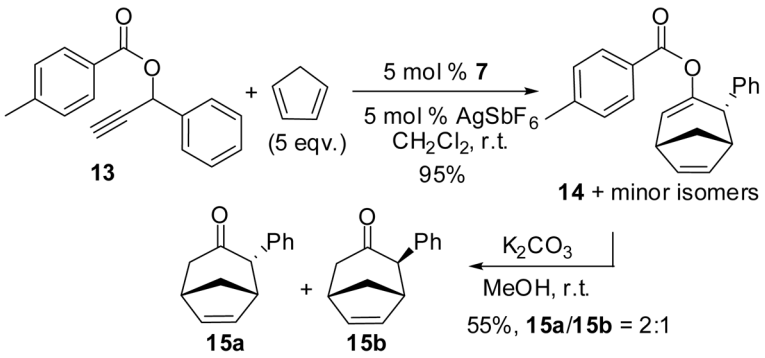
Fig. 1.
Au(III) catalyst **6** and Au(I) catalysts **7–10** were studied for their catalytic activity in the formal [4C + 3C] cycloaddition reactions.



Scheme 1.
Gold-catalyzed transannular [4+3] cycloaddition reaction: two possible pathways



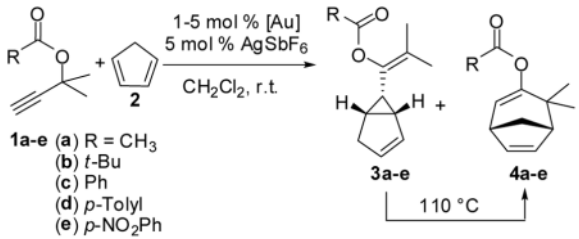
Scheme 2.
Reactions of furan with 1f in the presence of catalyst **7**



Scheme 3.
Reactions of secondary propargyl ester **13** in the presence of catalyst **7**.

Table 1

Au(III)-catalyzed cyclopropanation/Cope rearrangement reactions



Entry	Gold[a] catalyst	mol%	R	Time (h)	%Yield	Ratio (3 : 4)
1	**6**	5	Methyl (**a**)	24	57	1 : 1.6
2	**6**	5	*t*-Butyl (**b**)	24	57	1 : 2.8
3	**6**	5	Phenyl (**c**)	24	90	1 : 2.1
4	**6**	5	*p*-Tolyl (**d**)	24	92	1 : 2.1
5	**6**	5	*p*-nitrophenyl (**e**)	24	63	1 : 1.3
6	**7**	5	*p*-Tolyl (**d**)	1	82	1 : 1.2
7	**7**	1	*p*-Tolyl (**d**)	23	92	1 : 1.6
8[b]	**8**	5	*p*-Tolyl (**d**)	3	n/a	n/a
9[b]	**9**	5	*p*-Tolyl (**d**)	2	n/a	n/a
10[b]	**10**	5	*p*-Tolyl (**d**)	0.25	n/a	n/a

[a] No silver co-catalyst was used for Au(III) catalyst (**6**).

[b] Complex mixtures.