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Gold-catalyzed intermolecular [4C+3C] cycloaddition reactions

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ABSTRACT

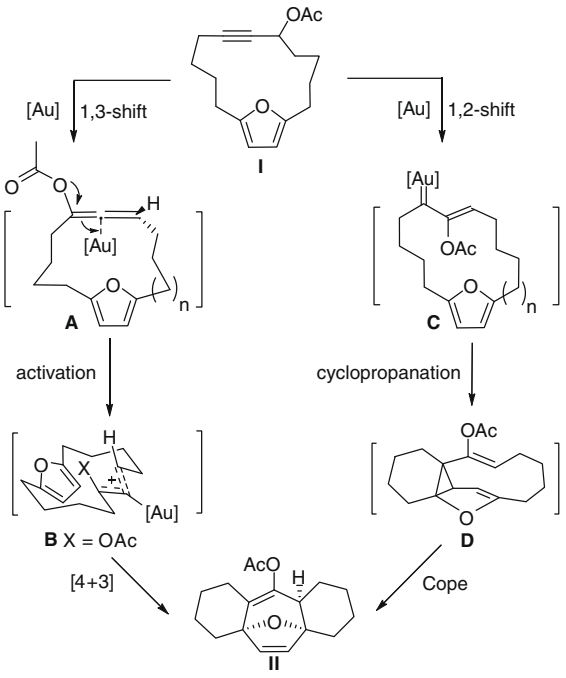
In the presence of the N-heterocyclic carbene gold catalyst (NHC-AuIPr, **7**), propargyl esters **1a–f** and **13** undergo a [4C+3C] cycloaddition reaction with cyclopentadiene and furan under mild conditions. The evidence suggests that the formation of the seven-membered ring occurs by a direct cycloaddition 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] At 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 and Huang reported that 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 Letter, we disclose an intermolecular version of gold-catalyzed formal [4C+3C] cycloaddition reactions. This discovery expands the employment of propargyl esters as precursors in the 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–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 co-workers have studied these reactions extensively.[19,20]

Ohe and co-workers 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 cyclopropanation of olefins using either propargyl esters or enynes as gold(I)-carbene precursors was 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 intramo-



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

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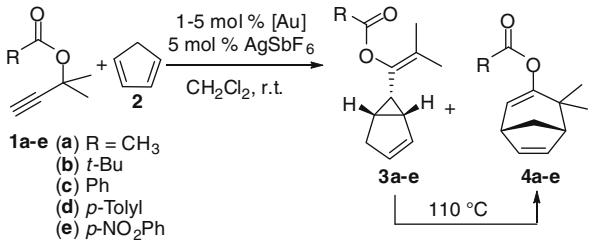
Table 1
Au(III)-catalyzed cyclopropanation/Cope rearrangement reactions



Entry	Gold catalyst[a]	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

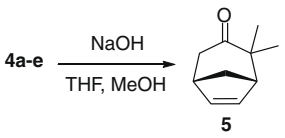
[a] No silver co-catalyst was used for Au(III) catalyst (**6**).
[b] Complex mixtures.

lecular 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-AuIPr **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) gave the vinyl cyclopropane with *endo* stereochemistry, that is, **3a**, along with 3-acetoxy-4,4-dimethylbicyclo[3.2.1]-octa-2,6-diene (**4a**), both compounds are known 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 conversion to the known ketone **5**[26] with base-catalyzed removal of the ester group, Eq. (1).



(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 and 4–1 and 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-AuIPr 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 equiv of furan, Scheme 2. Interestingly, the effect of the gold catalyst **7** parallels the ruthenium catalyst ($[RuCl_2(CO)_3]_2$)[27] and

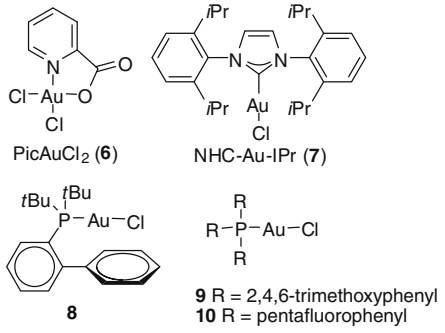
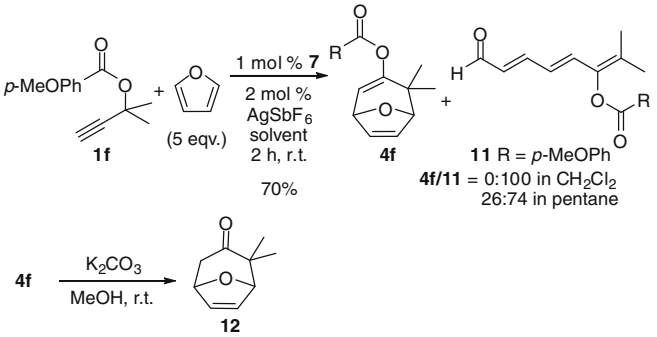
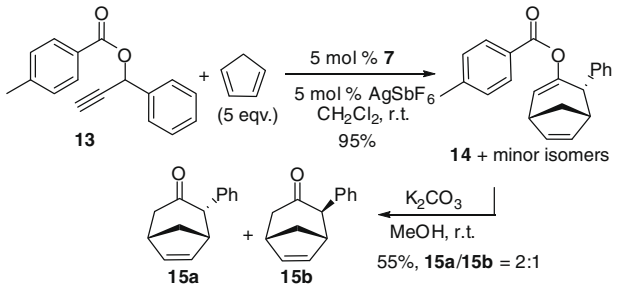


Figure 1. Au(III) catalyst **6** and Au(I) catalysts **7**–**10** were studied for their catalytic activity in the formal [4C+3C] cycloaddition reactions.



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



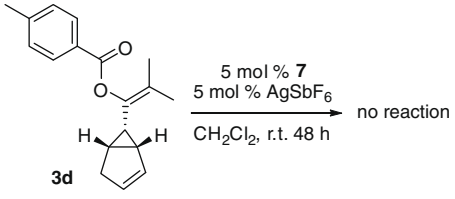
Scheme 3. Reactions of secondary propargyl ester **13** in the presence of catalyst **7**.

the triene aldehyde **11** was obtained as the exclusive product after 2 h 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 dominant 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 2 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.



(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.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures and NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.099.

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