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Gold(I)-Catalyzed Intermolecular [2+2] Cycloaddition of Alkynes with Alkenes

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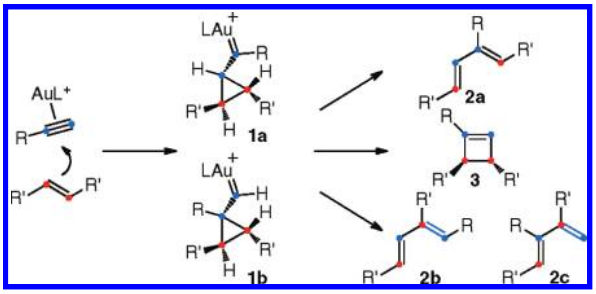
Abstract: The gold(I)-catalyzed intermolecular reaction of terminal alkynes with alkenes leads to cyclobutenes. The use of sterically hindered cationic Au(I) complexes as catalysts is key for the success of this reaction.

Cyclizations of 1,n-enynes have been the benchmark for the development of gold-catalyzed reactions.[1,2] Although much has been advanced in the understanding of the reactivity of alkynes with electrophilic catalysts, the intermolecular reaction of alkynes with alkenes using these catalysts is still unknown.[3] Based on the general reactivity of 1,n-enynes with Au(I),[1,2] the intermolecular reaction of alkynes with alkenes would be expected to proceed via regioisomeric cyclopropyl gold(I) carbenes **1a** and/or **1b** to give dienes **2a**−**c**[1,2,4] or cyclobutenes **3**[5,6] (Scheme 1).

Scheme 1



One of the potential problems facing the development of this transformation is the competitive coordination of the alkene to the catalyst forming Au(I)−alkene complexes.[7] Moreover, the resulting products could react further with the starting alkyne leading to complex reaction mixtures or suffer polymerization in the presence of Au(I) complexes.[8] We reasoned that inactivation of the catalyst by the alkenes and competitive pathways could be minimized by using sterically hindered cationic Au(I) complexes that could selectively activate alkynes in the presence of alkenes. Here we report the intermolecular gold(I)-catalyzed reaction of terminal alkynes with alkenes that results in a [2+2] cycloaddition. This reaction gives regioselectively substituted cyclobutenes, which are useful building blocks in synthesis.[9,10]

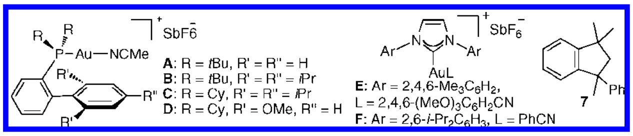
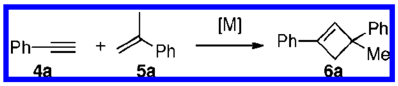


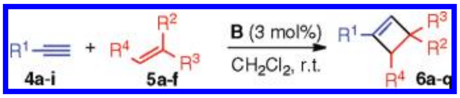
Table 1. Gold(I)-Catalyzed Reaction of **4a** with **5a**[a]

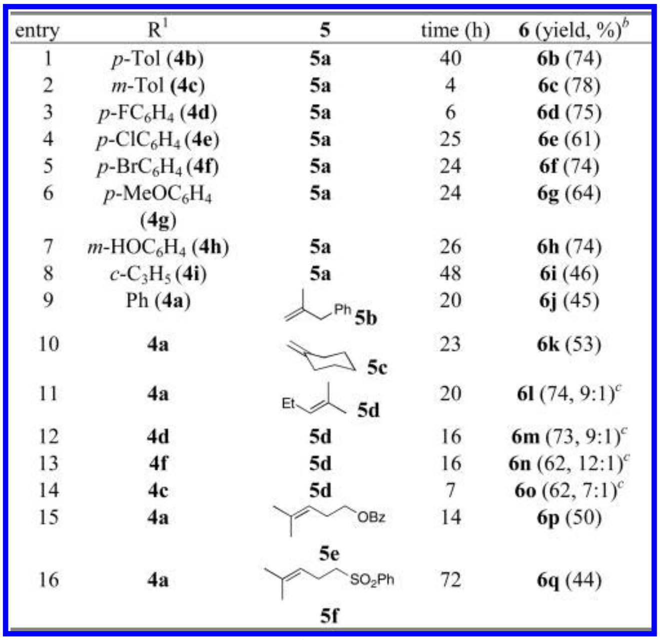


entry	[M]	**4a/5a**	time (h)	**6a** (yield, %)[b]
1	AuCl	2:1	72	–
2	$Ph_3PAuCl/AgSbF_6$	2:1	16	–[c]
3	**A**	2:1	18	42
4	**A**	1:2	18	67 (60)
5	**B**	1:2	16	81 (80)
6	**C**	1:2	16	70
7	**D**	1:2	16	19
8	**E**	3:1	4	–[d]
9	**F**	3:1	4	58

[a] 3 mol % catalyst, in CH_2Cl_2 at room temperature. [b] ^1H NMR yields. Isolated yields in parentheses. [c] **7** was obtained (43%). [d] Complex mixture.

Table 2. Gold(I)-Catalyzed Reaction of Alkynes **4a**−**h** with Alkenes **5a**−**f**[a]





entry	R[1]	**5**	time (h)	**6** (yield, %)[b]
1	*p*-Tol (**4b**)	**5a**	40	**6b** (74)
2	*m*-Tol (**4c**)	**5a**	4	**6c** (78)
3	*p*-FC_6H_4 (**4d**)	**5a**	6	**6d** (75)
4	*p*-ClC_6H_4 (**4e**)	**5a**	25	**6e** (61)
5	*p*-BrC_6H_4 (**4f**)	**5a**	24	**6f** (74)
6	*p*-$MeOC_6H_4$ (**4g**)	**5a**	24	**6g** (64)
7	*m*-HOC_6H_4 (**4h**)	**5a**	26	**6h** (74)
8	*c*-C_3H_5 (**4i**)	**5a**	48	**6i** (46)
9	Ph (**4a**)	Ph **5b**	20	**6j** (45)
10	**4a**	**5c**	23	**6k** (53)
11	**4a**	Et **5d**	20	**6l** (74, 9:1)[c]
12	**4d**	**5d**	16	**6m** (73, 9:1)[c]
13	**4f**	**5d**	16	**6n** (62, 12:1)[c]
14	**4c**	**5d**	7	**6o** (62, 7:1)[c]
15	**4a**	OBz **5e**	14	**6p** (50)
16	**4a**	SO_2Ph **5f**	72	**6q** (44)

[a] 2:1 Alkyne/alkene ratio. [b] Isolated yields, regioisomeric ratio. [c] Minor regioisomers are 1,3,4,4-tetrasubstituted cyclobutenes.

No reaction was observed between phenylacetylene (**4a**) and α-methylstyrene (**5a**) with AuCl, whereas $Ph_3PAuCl/AgSbF_6$ led only to dimerization of **5a** to form **7**[11] (Table 1, entries 1 and 2). In contrast, cyclobutene **6a** was obtained as a single regioisomer with catalysts **A**−**C** bearing bulky dialkylbiarylphosphine ligands (Table 1, entries 3−6).[6e,12,13] The best results were obtained using more sterically crowded complex **B** (Table 1, entry 5). Less hindered complex **D** led to lower yields (Table 1, entry 7). NHC−gold(I)

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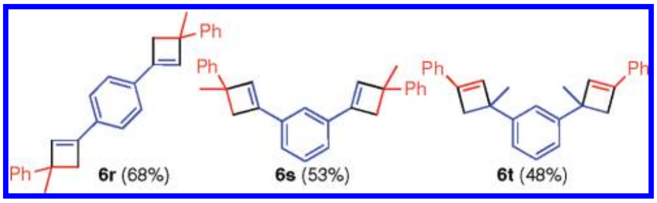
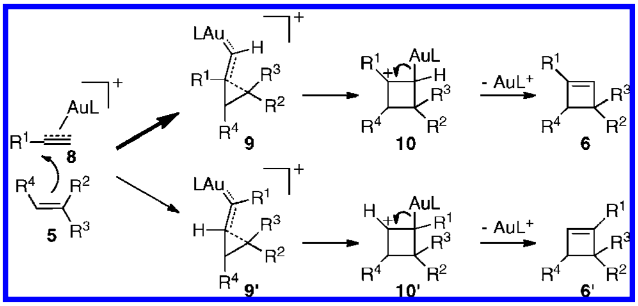


Figure 1

Scheme 2



complex **E** was not effective, whereas **F** led to **6a** in 58% yield after 4 h (Table 1, entries 8 and 9). In this case, longer reaction times led to lower yields.[14]

Reaction of terminal alkynes **4a**−**i** with alkenes **5a**−**f** led regioselectively to cyclobutenes **6a**−**q** in moderate to good yields using catalysts **B** (Table 2). The reaction proceeds satisfactorily with alkynes with both electron-rich and electron-poor substituents, including a free OH group (Table 2, entry 7).[15]

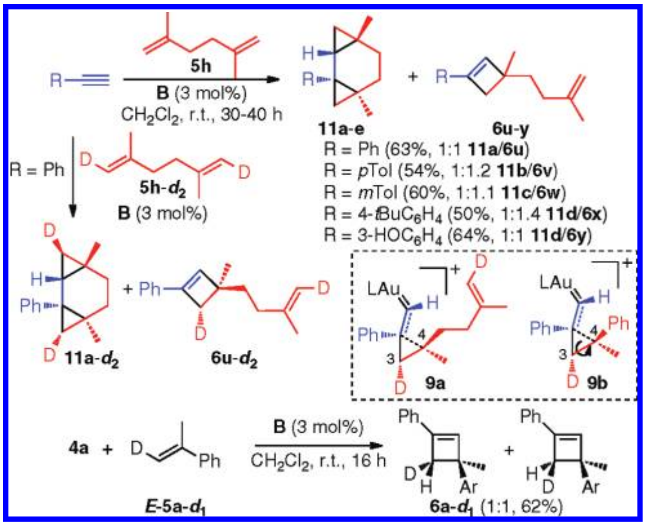
Biscyclobutenes **6r** and **6s** were also obtained from *p*- and *m*-diethynylbenzene, respectively (Figure 1). Similarly, reaction of *m*-di(prop-1-en-2-yl)benzene (**5g**) with **4a** gave biscyclobutene **6t**.

These results are consistent with a reaction of cationic Au(I)−alkyne complexes **8** with the alkenes **5** to form intermediates **9**/**9′**,[16] which give cyclobutenes **6**/**6′** via carbocations **10**/**10′** (Scheme 2). Selective formation of regioisomers **6** is probably due to the faster formation of intermediate **9**, which is an analogue of the *exo*-type intermediates in the gold(I)-catalyzed cyclization of 1,n-enynes.[2]

Gold(I)-catalyzed reaction of terminal alkynes with 1,5-diene **5h** gave biscyclopropyl derivatives **11a**−**e** with an *anti*-relative configuration, in addition to cyclobutenes **6u**−**y** (Scheme 3). Formation of **11a**−**e** and **6u**−**y** could be explained by the different evolution of stereoisomeric intermediates **9** by intramolecular cyclopropanation[17] or ring expansion. Reaction of **4a** with **5h-d_2** gave stereospecifically **11a-d_2** and **6u-d_2** (1:1 ratio), which suggests that the reaction proceeds through intermediate **9a** in which no free rotation occurs around the C3−C4 bond. However, reaction **4a** with (*E*)-**5a-d_1** gave cycloadduct **6a-d_1** as a 1:1 mixture of diastereomers. These results are consistent with a [2+2] cycloaddition proceeding stepwise through intermediates **9**[18] in which rotation around the C3−C4 bond can occur if the alkene bears electron-donating substituents.[19]

In summary, this work shows that in the absence of the constrains imposed by the tethers in intramolecular processes, the gold(I)-catalyzed reaction of alkynes with alkenes leads to cyclobutenes. Key for the success of this [2+2] cycloaddition is the use of gold(I) complexes with bulky ligands that selectively activate alkynes in the presence of alkenes, which opens new opportunities for the invention of related intermolecular gold(I)-catalyzed processes.

Scheme 3



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Supporting Information Available: Additional data, experimental details, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A rapid equilibrium was immediately established between catalyst **A** and $[AuL(alkene)]SbF_6$ (L = phosphine) in CD_2Cl_2 (^1H and ^{31}P NMR analysis).[7] However, even at 23 °C, this equilibrium was slow with catalyst **B** (K_{eq} = 0.02 (**5a**) and 0.17 (**5d**)). Isomerization of the alkenes (i.e., **5e** to 1-methylcyclohexene) was observed with complex **A** at 23 °C, whereas this isomerization was very slow with **B**.

(14) See Supporting Information for additional details.

(15) Internal alkynes such as 1-phenyl-1-propyne and 1-phenyl-1-hexyne were recovered unchanged under these conditions.

(16) Ph_2SO inhibited the [2+2]-cycloaddition with catalyst **B**. For the trapping of gold(I) carbenes with Ph_2SO in reactions of 1,6-enynes, see: Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.

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(18) Calculations [M06 6-31G* (C,H,P), LANL2DZ (Au) (Spartan 08); L = PMe_3] of intermediate **9a** show a distorted cyclopropyl gold carbene structure with cyclopropane bond distances of 1.44−1.71 Å. The calculated structure for **9b** is closer to an open carbocation (longest cyclopropane bond distance of 2.16 Å), whereas for **9b′** (Scheme 2) it corresponds to a cyclopropyl gold(I) carbene (cyclopropane bond distances 1.47−1.64 Å).

(19) This is reminiscent of that found in the cyclizations of 1,6-enynes with strongly electron-donating substituents at C1 of the alkene: Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7892–7895.

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