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Gold(I)-Catalyzed Macrocyclization of 1,*n*-Enynes

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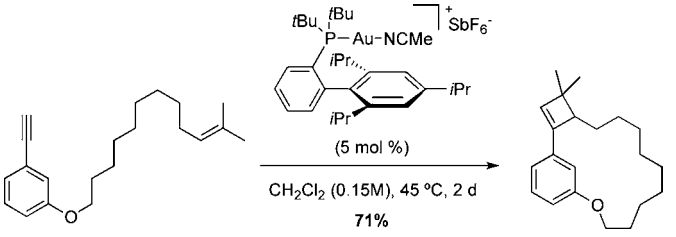
ABSTRACT



The gold(I)-catalyzed [2 + 2] cycloaddition of large 1,*n*-enynes (*n* = 10−16) provides access to 9- to 15-membered ring macrocycles incorporating a cyclobutene moiety. The reaction requires the use of a gold(I) catalyst bearing a sterically hindered biphenylphosphine ligand.

Macrocycles are present in a multitude of important natural products that display a wide variety of biological activities.[1] Macrocycles are also commonly exploited in the fields of material science[2] and in supramolecular chemistry.[3] The most common methods for gaining access to macrocycles involve macrolactonizations,[4] ring-closing metathesis,[5] or cross-couplings.[6,7] Gold-catalyzed cycloisomerization has emerged as a powerful tool for the creation of new carbon−carbon bonds due to the remarkable carbophilic properties of gold.[8] Among the possible cyclizations of 1,*n*-enynes, the formation of cyclobutenes has been only reported in a few intramolecular processes.[9] We recently reported the first example of an intermolecular gold(I)-catalyzed [2 + 2] cycloaddition of terminal alkynes with alkenes that occurred under mild conditions (Scheme 1).[10,11] The reaction proceeds regioselectively to afford cyclobutenes using gold(I) complex **A** bearing a sterically hindered biphenylphosphine ligand, presumably through a distorted cyclopropyl gold(I) carbene intermediate **I**.

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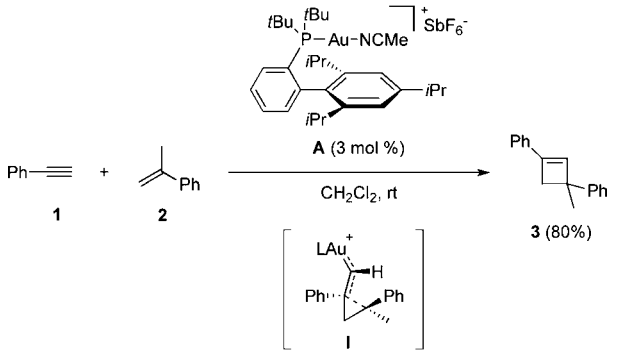
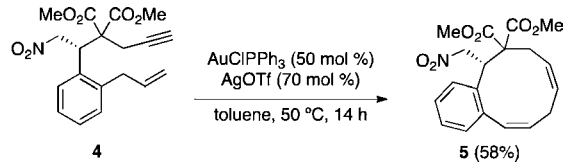
Scheme 1. Intermolecular Gold(I)-Catalyzed [2 + 2] Cycloaddition of Terminal Alkynes with Alkenes



Whereas the reactivity of 1,*n*-enynes (n = 5–8) in the presence of gold complexes has been documented,[12] examples involving larger 1,*n*-enynes (n > 8) are scarcer. The largest 1,*n*-enyne involved in a gold-catalyzed cycloisomerization is a 1,9-enyne, which leads to a 10-membered ring (Scheme 2).[13] However, this cyclization required a large amount of gold(I) catalyst (50 mol %) and leads to the cyclic product in moderate yield.

Scheme 2. Gold(I)-Catalyzed Cyclization of 1,9-Enyne **4** To Form 10-Membered Ring **5**



Here we report the first examples of macrocyclization of large 1,*n*-enynes (n = 10–16) using gold(I) catalysts by a click-type alkyne/alkene cycloaddition.

In contrast to the transformations involving small 1,*n*-enynes (n = 5–8) that are entropically favored, obtaining macrocycles from the largest 1,*n*-enynes (n > 9) is more challenging. Preferably, the reactive partners must be close in a stable conformation to perform the reaction under mild conditions. For example, substrate **6** does not lead to the formation of the corresponding macrocycle with cationic catalyst **A**, and only the starting material is recovered (Scheme 3).

To circumvent this problem, we decided to add a phenyl ring in the spacer to favor the reactivity, focusing our attention first on 1,14-enyne **8** (Table 1). We observed that the reaction outcome was highly dependent on the

Scheme 3. Attempted Gold(I)-Catalyzed Cyclization of 1,10-Enyne **6**

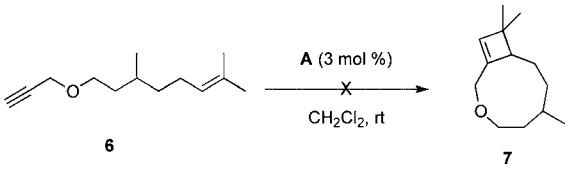
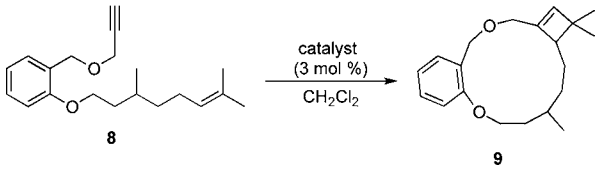
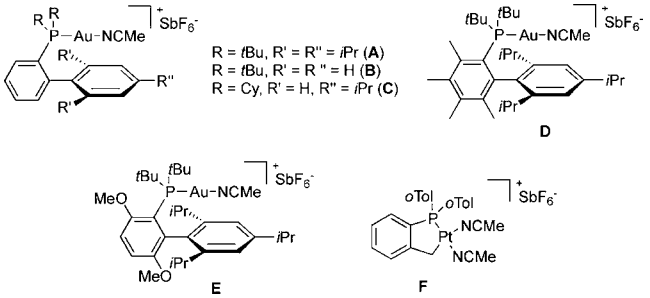


Table 1. Gold(I)-Catalyzed Macrocyclization of 1,14-Enyne **6** To Form 13-Membered Ring Macrocycle **7**



entry	catalyst	molarity (M)	temp (°C)	time (h)	yield[a] (%)
1	**A**	0.25	23	3	23
2	**A**	0.07	23	6	53
3	**A**	0.07	45	3	24
4	**A**	0.007	23	12	71 (57)
5	**A**	0.007	45	3	56
6	**B**	0.007	23	1	26
7	**C**	0.007	23	12	47
8	**D**	0.007	23	12	73 (58)
9	**E**	0.007	23	12	55
10	$AuClPPh_3$/$AgSbF_6$	0.007	23	2	10
11	$PtCl_2$	0.007	45	14	–
12	$PtCl_4$	0.007	45	14	–
13	**F**	0.007	45	14	–
14	$AgSbF_6$	0.007	45	14	–

[a] Yields determined by ^1H NMR using 1,4-diacetylbenzene as an internal standard. Isolated yields in parentheses.



substrate concentration. Thus, when the reaction was performed under concentrated conditions in the presence of catalyst **A** (3 mol %) at 23 °C, the NMR yield of 13-membered ring macrocycle **9** was not higher than 23% (Table 1, entry 1). Gratifyingly, decreasing the concentration to 0.007 M led to the formation of the cyclobutene in a good yield with a 2.3:1 dr (Table 1, entry 4). Heating the

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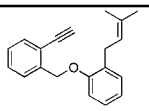
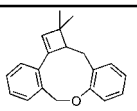
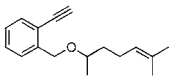
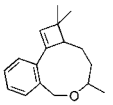
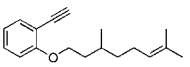
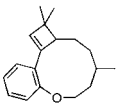
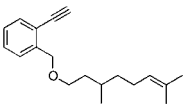
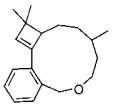
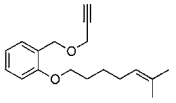
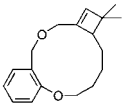
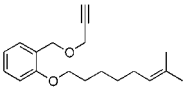
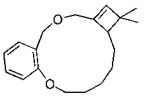
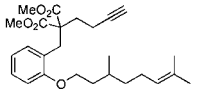
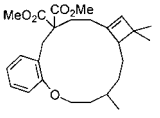
Table 2. Gold(I)-Catalyzed Macrocyclization of Various 1,10- to 1,15-Enynes[a]

entry	substrate	time (h)	product	yield (%)
1[c]	 **10**	23	 **11**	66[b]
2	 **12**	19	 **13**	51[b] (5:1)
3[d]	 **14**	2	 **15**	20[b] (4:1)
4	 **16**	24	 **17**	25[e]
5	 **18**	16	 **19**	29[b]
6	 **20**	19	 **21**	57[b]
7	 **22**	16	 **23**	70[b]

[a] Reactions carried out with **A** (3 mol %) at 23 °C. [b] Isolated yields. [c] Reaction run at 45 °C. [d] Reaction run at 70 °C. [e] Yield determined by ^{1}H NMR using 1,4-diacetylbenzene as an internal standard.

reaction allowed increasing the rate of the reaction but at the expense of the isolated yields (Table 1, entries 3 and 5). Presumably, oligomerization of the enyne or decomposition of the cyclobutene can occur more easily under these reaction conditions. Alternative gold(I) complexes were examined in the macrocyclization of substrate **8** to explore the impact of the ligand on the reactivity. Catalyst **A** was modified by adding methoxy or methyl groups onto the biphenyl moiety (**D** and **E**)[14−16] to increase the bulkiness around the metal center in an attempt to make the catalyst

Figure 1. ORTEP drawing of macrocycle **11**.

even more selective for the cycloaddition reaction. However, the new catalysts did not afford the corresponding macrocyclobutene **9** in better yields (Table 1, entries 8 and 9). A direct relationship between the bulkiness around the metal center and the reactivity can be observed. For example, in the presence of catalyst **B**, a complete conversion occurred within 1 h, but the cyclobutene was only obtained in 26% yield (Table 1, entry 6). We also found that the cationic gold(I) complexes are much more efficient than the neutral gold(I) complex combined with a silver salt to generate the active catalyst in situ (Table 1, entry 10), whereas no formation of **9** was observed using Pt(II), Pt(IV), and Ag(I) salts or complexes (Table 1, entries 11−14). Based on these different experiments, complexes **A** and **D** were found as the optimal catalysts, although the former was preferred because of its easier preparation.

To explore the scope of the reaction, macrocyclizations were performed with 1,10- to 1,15-enynes bearing different spacers (Table 2).[17] In general, reactions were carried out at 23 °C in CH_2Cl_2 in the presence of 3 mol % of complex **A** as the catalyst (Table 2, entries 2 and 4−7). In addition, the reactions do not require highly diluted conditions (0.15 or 0.3 M instead of 0.007 M).[18] Under these reaction conditions, the corresponding macrocyclic compounds were obtained in moderate to good yields (up to 70%). Some substrates reacted more slowly and required heating to furnish the macrocyclic products (Table 2, entries 1 and 3). Increasing the length of the spacer leads to better yields (Table 2, entries 4−7), probably as a consequence of the relief in transannular strain.

In the case of substrate **10**, the structure of 9-membered ring **11** was confirmed by X-ray crystallography (Figure 1).[19]

This method also provides access to *m*-cyclophanes. This class of compound exhibits interesting chemical and physical properties that result from their unusual architecture.[20,21]

(14) Barabé, F.; Levesque, P.; Korobkov, I.; Barriault, L. *Org. Lett.* **2011**, *13*, 5580–5583.

(15) X-ray crystallographic data: CCDC 912987 (**D**), CCDC 912986 (**E**).

(16) Related BrettPhosAuNTf and Me_4tBuXPhosAuNTf$_2$ had been reported by the group of Zhang: (a) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236–3239. (b) Wang, Y.; Ji, K.; Lan, S.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1915–1918.

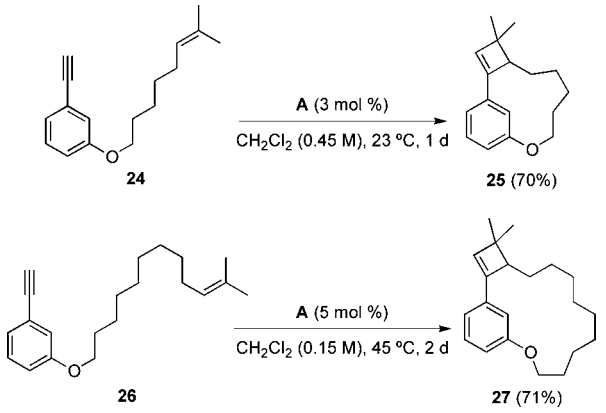
(17) No macrocyclization reaction occurred when the dimethyl group was removed or replaced by styrene-type alkenes.

(18) See Supporting Information for details.

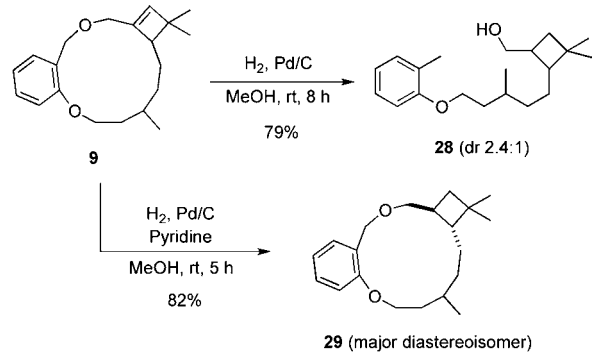
(19) X-ray crystallographic data: CCDC 912988.

(20) Gleiter, R.; Hopf, H. *Modern Cyclophane Chemistry*; Wiley VCH: Weinheim, 2004.

Scheme 4. Synthesis of *m*-Cyclophanes **25** and **27**



Scheme 5. Hydrogenation of Macrocycle **9**



In the case of substrates **24** and **26**, the corresponding macrocycles **25** and **27** were obtained in 70−71% yields (Scheme 4).[22] The reaction with the largest enyne **26** required a higher catalyst loading (5 mol %) and proceeded at 45 °C in 2 days.

The cyclobutene can be hydrogenated in the presence of Pd/C in methanol at 23 °C. However, a debenzylation of **9** was also observed (Scheme 5). This problem can be circumvented by the addition of pyridine to furnish **29** in 82% yield.[23,24]

In summary, a variety of macrocycles can be assembled in moderate to good yields from large 1,*n*-enynes ($n > 9$) via a [2 + 2]-cycloaddition catalyzed by gold(I) under mild conditions. Whereas the intermolecular gold(I)-catalyzed [2 + 2] cycloaddition was essentially limited to aryl alkynes,[10] macrocyclization takes place satisfactorily with alkyl-substituted alkynes. This study demonstrates that gold catalysis is not limited to cycloisomerizations of small 1,*n*-enynes ($n = 5-8$) but can also be a valuable tool for reactions involving larger ones.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Gulder, T.; Baran, P. *Nat. Prod. Rep.* **2012**, *29*, 899–934 and references cited therein.

(22) Macrocycles **25** and **27** were obtained as 4−5:1 mixtures of two atropoisomers.

(23) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465–3468.

(24) Compounds **28** and **29** were obtained as a mixture of diastereoisomers. See the Supporting Information for details.

The authors declare no competing financial interest.