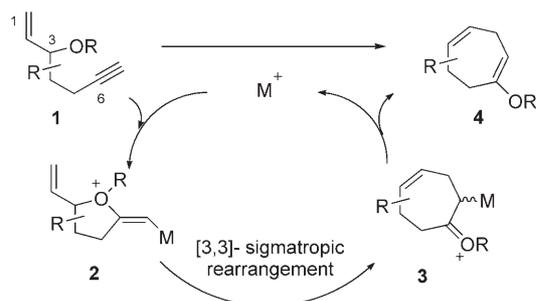


Gold(I)-Catalyzed Cycloisomerization of 3-Methoxy-1,6-enynes Featuring Tandem Cyclization and [3,3]-Sigmatropic Rearrangement**

Hyo J. Bae, Baburaj Baskar, Sang E. An, Jae Y. Cheong, Daniel T. Thangadurai, In-Chul Hwang, and Young H. Rhee*

The transition-metal-catalyzed cycloisomerization of 1,6-enynes is one of the most powerful strategies for the synthesis of highly functionalized carbocyclic compounds.^[1] Recent studies on the gold- and platinum-catalyzed cycloisomerizations are particularly noteworthy because of the structural diversity of the products provided by these reactions.^[2] Numerous carbocyclic frameworks have been assembled by using structurally simple 1,6-enyne precursors. In many reactions, addition of internal olefins to the metal-activated alkynes has been proposed as the key event.^[3]

Unlike the structurally simple 1,6-enynes mentioned above, 3-alkoxy-1,6-enynes **1** offer an alternative mode of reaction as depicted in Scheme 1. In this case, the oxygen atom can participate as a competing nucleophile in the addition to the metal-activated alkynes. The resulting cyclic

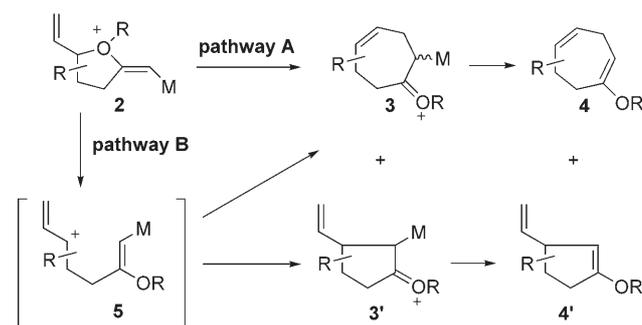


Scheme 1. Proposed mechanism for the gold(I)-catalyzed cycloisomerization of 3-alkoxy-1,6-enynes.

oxonium ion **2** has a structural platform for a [3,3]-sigmatropic rearrangement, which generates cycloheptenyl cation **3**.^[4] Elimination of the cationic metal species produces 1-alkoxy-1,4-cycloheptadiene **4** in a catalytic manner.

On the basis of the recent reports on Lewis acid promoted (or catalyzed) Claisen rearrangement of cyclic enol ethers,^[5] we envisioned that the involvement of the oxonium ion intermediate **2** could facilitate the key [3,3]-sigmatropic process. Moreover, the enol ether moiety in **4** can be chemoselectively transformed into a variety of other functional groups. Thus, we envisaged that the proposed reaction would provide highly efficient access to cycloheptene frameworks having diverse functional groups, which are important building blocks in a variety of bioactive natural products.^[6]

In light of the proposed catalytic cycle, a potentially competing pathway is the metal-catalyzed carboalkoxylation (Scheme 2; pathway B).^[7] This alternative pathway would



Scheme 2. Sigmatropic rearrangement (pathway A) versus carboalkoxylation (pathway B).

result in a mixture of cycloheptadiene **4** and cyclopentene **4'** formed from allylic cation **5**, whereas the concerted nature of the proposed sigmatropic pathway leads to the selective formation of **4** (Scheme 2; pathway A).^[8]

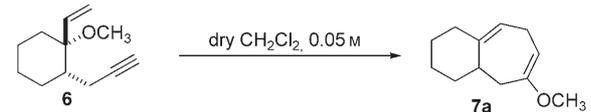
To investigate this mechanistic proposal, we initially examined various platinum and gold complexes by using **6** as the substrate (Table 1). Preliminary investigations using a platinum catalyst (Table 1, entry 1)^[7c,d] or neutral [Au{P-(C₆H₅)₃}Cl] (Table 1, entry 2) failed to give the desired bicyclic heptadiene **7a**. To our delight, switching to pregenerated cationic gold complex **8a** (5 mol%) in CH₂Cl₂ produced the cycloisomerized product **7a** in 55% yield within 10 minutes at room temperature, and there was no evidence of the formation of carbocyclic five-membered rings (Table 1, entry 3).^[9] Notably, employing a more electrophilic catalyst (**8b**)^[10] gave **7a** almost instantaneously in 92% yield

[*] H. J. Bae, B. Baskar, S. E. An, J. Y. Cheong, D. T. Thangadurai, Prof. Dr. Y. H. Rhee
Department of Chemistry
POSTECH (Pohang University of Science and Technology)
Pohang, 790-784 (Korea)
Fax: (+82) 54-279-3399
E-mail: yhrhee@postech.ac.kr
Dr. I.-C. Hwang
Department of Chemistry
Center for Superfunctional Molecules
Center for Basic Sciences
POSTECH (Pohang University of Science and Technology) (Korea)

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Table 1: Optimization of the reaction conditions.

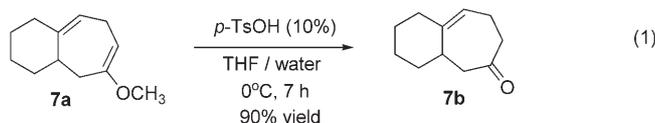


Entry	[Au{P(C ₆ H ₅) ₃ }Cl] / AgSbF ₆ (8a)		[Au{P(C ₆ F ₅) ₃ }Cl] / AgSbF ₆ (8b)		Yield [%] ^[a]
	Catalyst [mol %]	Solvent	T	t	
1	PtCl ₂ /CO (5 %)	toluene	80 °C	6 h	— ^[b]
2	[Au{P(C ₆ H ₅) ₃ }Cl]	CH ₂ Cl ₂	RT	1 h	n.r.
3	8a (5 %)	CH ₂ Cl ₂	RT	10 min	55
4	8b (5 %)	CH ₂ Cl ₂	RT	2 min	92
5	8b (5 %)	CH ₂ Cl ₂	−15 °C	2 min	95
6	8b (1 %)	CH ₂ Cl ₂	−15 °C	2 min	> 99 (97 ^[c])
7	8b (0.3 %)	CH ₂ Cl ₂	−15 °C	10 min	95 (91 ^[c])
8	8b (1 %)	CH ₃ CN	RT	6 h	25 ^[d]

[a] Yield determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. RT = room temperature, n.r. = no reaction. [b] A mixture of unidentified compounds was obtained. [c] Yield of isolated product. [d] A significant amount of **6** was recovered (ca. 60%).

(Table 1, entry 4). Lowering the temperature to −15 °C increased the yield with little effect on the rate of the reaction (Table 1, entry 5). Interestingly, reducing the catalyst loading to 1 mol % produced **7a** in almost quantitative yield (Table 1, entry 6). Moreover, purification of this acid-labile compound by silica gel chromatography (deactivated with triethylamine) gave an analytically pure isolated sample of **7a** in 97 % yield. Reduction of the catalyst loading to 0.3 mol % resulted in a completed reaction within 10 minutes, albeit with a small decrease in the yield (Table 1, entry 7).^[11] Changing the solvent to CH₃CN significantly slowed the formation of **7a** (Table 1, entry 8).

Conversion of **7a** into bicyclic cyclohept-4-en-1-one **7b** was investigated to demonstrate the synthetic utility of the cycloisomerization process. After extensive optimization, we found that using catalytic *p*-TsOH (10 mol %) in aqueous THF furnished **7b** in 90 % yield [Eq. (1)].^[12]

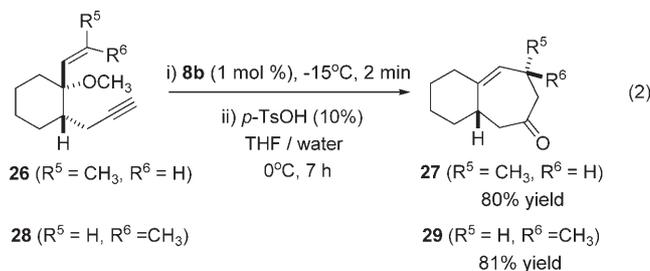


By using 1–5 mol % of the optimized catalyst shown in Table 1, various 3-methoxy-1,6-enynes were converted into 1-methoxy-1,4-cycloheptadienes in high yields (Table 2). Furthermore, all of the cycloisomerized products obtained were transformed into the corresponding cyclohept-4-en-1-ones by using the optimized conditions [Eq. (1)].^[13a] As shown in Table 2, substrates with a cyclopentane framework (**9** and **11**) reacted with comparable efficiency to give cycloheptadienes (**10a** and **12a**) in nearly quantitative yields (Table 2, entries 1 and 2). Gratifyingly, acyclic substrate **13** also furnished the monocyclic product **14a** in high yield (Table 2, entry 3). The cycloisomerization was tolerant of the methyl substitution on

the internal position (Table 2, entry 4), as well as on the terminal positions of the vinyl group (Table 2, entries 5 and 6). Interestingly, no significant difference in the yield was observed between the two latter examples.

Remarkably, even substrate **20**, which possesses dimethyl substituents at the terminal vinylic positions, produced ketone **21b** with a quaternary carbon center in good yield after hydration (Table 2, entry 7).^[13b,14] Introducing an alkyl substituent on the homopropargylic position had little effect on the yield of the cycloisomerization reaction (Table 2, entry 8). Notably, substrate **24**, bearing a phenyl substituent at the allylic position, also produced cycloheptadiene **25a** in near-quantitative yield (Table 2, entry 9).

The data compiled in Table 2 are consistent with the working hypothesis involving the concerted sigmatropic pathway (Scheme 2, pathway A) because the exclusive formation of cycloheptadienes was observed in all cases, even when the substrate containing a carbocation stabilizing phenyl group (**24**) was employed.^[15] To investigate the nature of the rearrangement of the oxonium-ion intermediate **2**, two olefin isomers (**26** and **28**) were tested. The *E* olefin substrate **26** was converted into ketone **27** in 80 % yield as a single diastereomer [Eq. (2)],^[16] and the structure was unambiguously



biguously determined by the X-ray crystallographic analysis (Figure 1).^[17] Under identical conditions, *Z* olefin substrate **28** produced the diastereomeric ketone **29** in a comparable yield (81 %) without evidence of the formation of **27**.^[16] The complete transfer of stereochemical information observed in these experiments confirms the concerted nature of the rearrangement of the oxonium ion intermediate **2** (Scheme 2).

In summary, we discovered a highly efficient gold(I)-catalyzed cycloisomerization of 3-methoxy-1,6-enynes that features a tandem cyclization and an unprecedented [3,3]-sigmatropic rearrangement as the key event. Notably, the reaction can be performed under very mild conditions by using a low catalyst loading (maximum turnover number ca. 300). The synthetic potential of the reaction was demonstrated by the facile conversion into the various cyclohept-4-en-1-ones. Extrapolation of this method to the formation of other carbocyclic rings and the application to the total synthesis of bioactive natural products are currently under investigation.

Experimental Section

Cycloisomerization of 6 to 7a: Methylene chloride (10 mL) was added to a mixture of gold complex [Au{P(C₆F₅)₃}Cl] (5.1 mg,

Table 2: Scope of the gold(I)-catalyzed cycloisomerization of 3-methoxy-1,6-enynes.^[a]

Entry	Substrate	Catalyst [mol%]	Product	Yield [%] ^[b]	Ketone	Yield [%] ^[b]
1		1		96	10b	90
2	11 R ¹ = CH ₃	5	12a	95	12b	88
3		1		90	14b	84
4	15 R ² = CH ₃	1	16a	85	16b	85
5		1		89	18b	80
6	19 R ³ = H, R ⁴ = CH ₃	1	18a	95	18b	—
7 ^[e]	20 R ³ = CH ₃ , R ⁴ = CH ₃	2	21a	74 ^[c]	21b	60 ^[d]
8		5		94	23b	90
9	24	2	25a	97	25b	74

[a] Conditions: Substrate (0.05 M), catalyst **8b**, −15°C, dry CH₂Cl₂. [b] Yield of isolated product for each step. [c] Yield determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [d] Yield of isolated product for the two-step conversion. [e] The reaction was performed at room temperature.

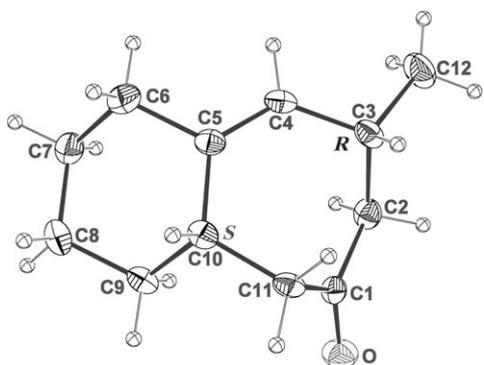


Figure 1. View of the molecular structure of compound **27** with displacement ellipsoids at 30% probability. Selected bond lengths [Å] and angles [°]: O–C1 1.212(3), C4–C5 1.329(4); O–C1–C2 120.0(2), C4–C5–C10 127.0(2).

0.0067 mmol) and AgSbF₆ (2.3 mg, 0.0067 mmol), and the reaction mixture was stirred for 10 min. The resulting solution was filtered through a pad of celite and concentrated. The residue was dried under high vacuum for 2 h and then cooled to −15°C. A solution of **6** (120 mg, 0.67 mmol) in CH₂Cl₂ (13.4 mL, 0.05 M, precooled to −15°C) was added to this residue to give a colorless solution, which was stirred for 2 min. Triethylamine (1 mL) was added to the solution and

it was stirred for 5 min. The resulting reaction mixture was passed through a pad of celite and concentrated. The residual oil was purified by flash chromatography on silica gel (deactivated by triethylamine before use, eluted with pentane/ether = 95:5) to give compound **7a** as a colorless oil (117 mg, 0.65 mmol, 97% yield). *R*_f = 0.45 (pentane/ether = 95:5); ¹H NMR (300 MHz, CDCl₃): δ = 1.14–1.47 (m, 3H), 1.66–1.77 (m, 3H), 1.87–1.95 (m, 1H), 2.04–2.14 (m, 2H), 2.38–2.40 (m, 2H), 2.45–2.57 (m, 2H), 2.64–2.74 (m, 1H), 3.47 (s, 3H), 4.79 (app t, *J* = 6.4 Hz, 1H), 5.45 ppm (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 23.6, 27.0, 28.9, 35.7, 37.5, 38.8, 39.2, 54.6, 95.7, 120.3, 143.8, 159.4 ppm; IR: $\tilde{\nu}$ = 2925, 2852, 1666, 1155 cm^{−1}; HRMS calcd for C₁₂H₁₈O: 178.1358. found: 178.1358.

Conversion of **7a** into **7b**: Water (0.1 mL) and *p*-toluenesulfonic acid (2.3 mg, 0.012 mmol) was added to a solution of **7a** (22 mg, 0.12 mmol) in THF (1 mL) at 0°C. The reaction mixture was stirred for 7 h at 0°C and then diluted with ether (20 mL). This solution was washed with a saturated aq NaHCO₃ solution (2 × 10 mL), water (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residual oil was purified by flash chromatography on silica gel (eluted with pentane/ether = 85:15) to give the compound **7b** as a colorless oil (18 mg, 0.11 mmol, 90% yield). The spectral data are in complete agreement with those in the literature.^[13a]

Crystal structure analysis: a suitable crystal was mounted onto a specially constructed apparatus^[18] with cooling in an inert atmosphere on a Bruker SMART CCD1000 APEX diffractometer and analyzed.^[17] After semi-empirical absorption correction by equalization

of like-symmetry reflections (SADABS), structure solution and refinement was carried out with the SHELX programs.^[19,20]

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