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Cyclization of Nonterminal Alkynic β-Keto Esters Catalyzed by Gold(I) Complex with a Semihollow, End-Capped Triethynylphosphine Ligand

Hideto Ito, Yusuke Makida, Atsuko Ochida, Hirohisa Ohmiya, and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

sawamura@sci.hokudai.ac.jp

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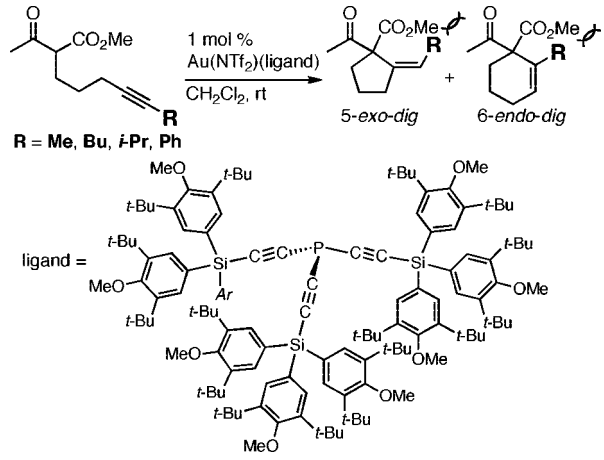
ABSTRACT



A cationic gold(I) complex with a semihollow-shaped trialkynylphosphine catalyzed 5-*exo-dig* and 6-*endo-dig* cyclizations of various internal alkynic β-keto esters, showing a marked advantage over a gold(I)−PPh_3 complex with respect to the rates of the reactions and the product yields. It is proposed that the gold-bound alkynic substrate in a catalytic pocket must be somewhat folded and that such a steric effect makes the carbon−carbon bond formation entropically more favorable.

Electrophilic activation of an alkyne by the coordination of a π−Lewis acidic metal cation induces the attack of a nucleophile that occurs at an appropriate position within the molecule. For such alkyne cyclizations, gold is the most active catalyst among various metal ions, and gold−phosphine complexes have been applied to various types of alkyne cyclizations.[1,2] The ring-forming gold catalysts, however, suffer from at least two serious problems. First, they are limited to the cases where cyclization is entropically quite favorable such as five-membered ring formations.[2a] Second, the cyclization of internal alkynes is often hampered by steric repulsion between the terminal substituent and a nucleophile at the C−C bond-forming step.[2b] We previously reported on the design and synthesis of semihollow-shaped trialkynylphosphine **1a**, which consists of a triethynylphosphine

(1) For reviews on gold catalysis, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.

(2) For gold(I)-catalyzed cyclizations of acetylenic keto esters, see: (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350–5352. (c) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

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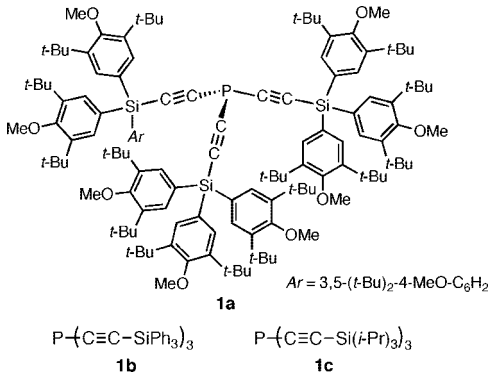


Figure 1. Semihollow, end-capped triethynylphosphine **1a** and triethynylphosphines (**1b**,**c**) with smaller silicon end caps.

core and bulky end caps (Figure 1).[3,4] This ligand (**1a**) markedly accelerated ring-forming gold(I) catalysts with various terminal alkynes, allowing for six- and seven-membered ring formations that are difficult to achieve with conventional ligands because of the flexibility of the substrates.[5] These results represented our approach to the first issue. Here we report on our challenge toward the second issue: The gold(I) complex with **1a** catalyzed the cyclizations of nonterminal alkynic β-keto esters that afford the sterically congested five- and six-membered ring compounds.

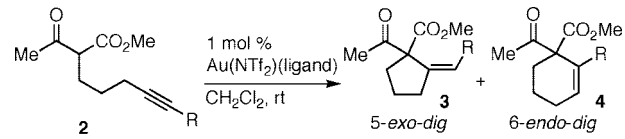
The semihollow triethynylphosphine (**1a**) showed a marked advantage over conventional phosphine ligands such as PPh_3 and $P(OPh)_3$ when applied to the gold-catalyzed cyclization of internal alkyne **2a** with a keto ester functionality (Table 1, entry 1 vs entries 4−7).[6] Thus, treatment of **2a** with a CH_2Cl_2 solution of cationic gold(I) complex [Au(NTf_2)(**1a**)] (1 mol %) resulted in smooth conversion at rt; the reaction completed within 3 h to afford 5-*exo-dig* and 6-*endo-dig* cyclization products **3a** and **4a** in a good combined yield, with preference to the former (80:20), which seems to be sterically more congested and hence energetically less favorable but entropically more favorable than the latter (entry 1). No *E*-isomer of *exo*-alkene **3a** was formed, suggesting *anti*-stereochemistry of a nucleophilic attack to a gold−alkyne π complex (Scheme 1).[2] To the best of our knowledge, the gold-catalyzed 5-*exo-dig*/6-*endo-dig* cyclization of a nonterminal alkynic keto ester has not been described in the literature.[2b]

In contrast, there was almost no reaction with the corresponding PPh_3 complex with the same reaction time (3 h, 4% conversion, entry 4). Prolonging the time to 24 h caused only a slight conversion (12% conversion, 24 h, entry 5). The complex formed with the $P(OPh)_3$ ligand, whose donor power is comparable with **1**,[3] was only as efficient as the PPh_3 complex (3 h, 6% conversion, entry 6; 24 h, 13% conversion, entry 7). Furthermore, triethynylphosphines (**1b**,**c**) bearing smaller silicon end caps such as Ph_3Si and $(i\text{-Pr})_3Si$ groups were not effective (entries 2 and 3).

Even with the internal alkynes (**2b**−**d**) bearing bulkier terminal substituents such as Bu, *i*-Pr, and Ph groups, the reaction with the Au−**1a** catalyst proceeded smoothly and afforded the corresponding five- and six-membered ring compounds (**3b**−**d**/**4b**−**d**) in high yields (Table 1, entries 8, 10, and 12). With the Au−PPh_3 catalyst, the reaction was again much slower and gave the cyclization products in only very low yields (entries 9, 11, and 13).

The effect of the terminal substituent (R) of **2** on the 5-*exo*/6-*endo* selectivity may give an insight into the mechanism of the gold-catalyzed Conia−ene reaction. As the terminal alkyl substituents became bulkier (Me < Bu < *i*-Pr), the

Table 1. Gold-Catalyzed Conia−Ene Reaction of **2a**−**d**[a]

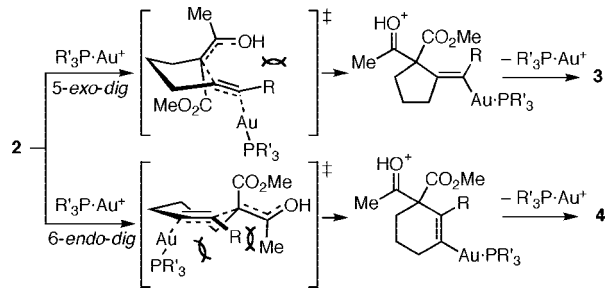


a: R = Me, **b**: R = Bu, **c**: R = *i*-Pr, **d**: R = Ph

entry	**2**	ligand	time (h)	convn of **2**[b] (%)	**3** + **4**, yield (%)	**3**/**4** ratio[b]
1	**2a**	**1a**	3	100	80[c]	80:20
2	**2a**	**1b**	24	0	0[b]	N.A.[d]
3	**2a**	**1c**	24	12	12[b]	85:15
4	**2a**	PPh_3	3	4	4[b]	N.D.[e]
5	**2a**	PPh_3	24	12	11[b]	89:11
6	**2a**	$P(OPh)_3$	3	6	6[b]	N.D.[e]
7	**2a**	$P(OPh)_3$	24	13	13[b]	85:15
8	**2b**	**1a**	12	100	97[c]	91:9
9	**2b**	PPh_3	24	21	12	95:5
10	**2c**	**1a**	20	100	94	92:8
11	**2c**	PPh_3	24	12	12[b]	100:0
12	**2d**	**1a**	24	100	86[c]	45:55
13	**2d**	PPh_3	24	23	13	54:46

[a] Conditions: **2**, 0.40 mmol; CH_2Cl_2, 1 mL. [b] Determined by NMR. [c] Isolated yield. [d] Not applicable. [e] Not determined.

Scheme 1. Proposed Mechanism for the Reaction of **2a**−**d**



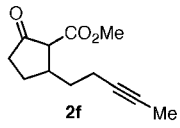
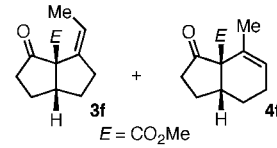
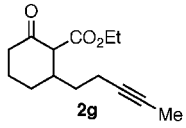
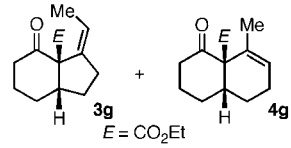
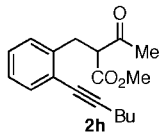
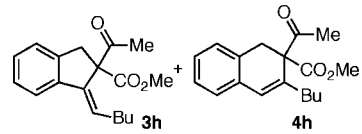
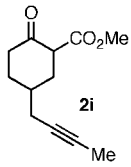
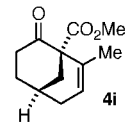
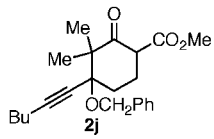
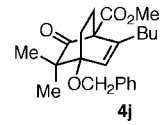
(3) Ochida, A.; Sawamura, M. *Chem.*−*Asian J.* **2007**, *2*, 609–618.

(4) For a review concerning the synthesis and applications of bowl-shaped phosphine ligands, whose steric feature is related to our triethynylphosphine ligands, see: Tsuji, Y.; Fujiwara, T. *Chem. Lett.* **2007**, *36*, 1296–1301.

(5) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486–16487.

(6) The cyclization products did not form in the presence of AuCl(**1a**), Ag(NTf_2), and $HNTf_2$ (1 mol %) under othewise identical conditions (24 h). Slight decomposition of **2a** (7%, 24 h) occurred with $HNTf_2$.

Table 2. Gold-Catalyzed Conia−Ene Reaction of Nonterminal Alkynic, Cyclic Keto Esters **2f**−**j**[a]

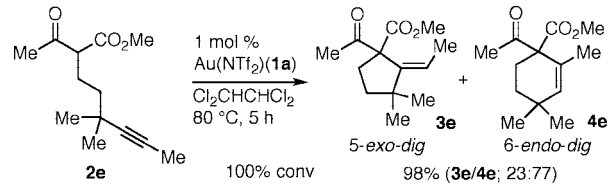
entry	alkyne	ligand	time	convn of **2**[b] (%)	product: **3** (5-*exo-dig*) + **4** (6-*endo-dig*)	**3** + **4** yield (%)	**3**/**4** ratio[b]
1	 **2f**	**1a**	24	100	 **3f** + **4f**, $E = CO_2Me$	96[c]	49:51
2		PPh_3	24	82		77[b]	43:57
3		PPh_3	48	99		66[b]	43:57
4	 **2g**	**1a**	24	100	 **3g** + **4g**, $E = CO_2Et$	87[c]	67:33
5		PPh_3	24	55		43[b]	62:38
6		PPh_3	48	87		76[b]	68:32
7	 **2h**	**1a**	24	100	 **3h** + **4h**	99[c]	63:37
8		PPh_3	24	21		21[b]	44:56
9		PPh_3	48	24		22[b]	48:52
10	 **2i**	**1a**	1	100	 **4i**	70[c]	0:100
11		PPh_3	1	22		10[b]	0:100
12		PPh	48	77		42[b]	0:100
13	 **2j**	**1a**	0.5	100	 **4j**	89[c]	0:100
14		PPh_3	0.5	42		39[b]	0:100
15		PPh_3	10	100		82[c]	0:100

[a] Conditions: **2**, 0.40 mmol; $Au(NTf_2)$ (ligand), 0.004 mmol (1 mol %); CH_2Cl_2, 1 mL; 25 °C unless otherwise noted. [b] Determined by NMR. [c] Isolated yield.

selectivity for 5-*exo* product **3** increased: 80%, 91%, and 92% with **1a** (Table 1, entries 1, 8 and 10); 89%, 95%, and 100% with PPh_3 (entries 5, 9 and 11). In the proposed C−C bond-forming transition states (Scheme 1), the terminal substituent should encounter steric repulsions not only with the incoming nucleophile but also with the Au–PR'_3 moiety. The former should be larger in the 5-*exo*-transition state (geminal), while the latter in the 6-*endo*-transition state (*cis*-vicinal). Accordingly, the increase of the *exo* selectivity upon the increase of the size of the terminal substituent R is likely due to the steric repulsion between R and the Au−PR'_3 moiety.

The catalysis of gold−**1a** appeared to be effective even when the acyclic alkyne (**2e**) has a quaternary carbon center at the internal α-position (Scheme 2). While no reaction occurred at rt, the reaction at 80 °C in DCE converted the hindered alkyne (**2e**) cleanly into a mixture of 5-*exo-dig* (**3e**) and 6-*endo-dig* (**4e**) cyclization products with a preference to the 6-*endo* isomer.[7] The observed regioselectivity is consistent with our rationale for the 5-*exo* selectivity in the reaction of **2a**−**d**: In the reaction of **2e**, the Au−PR'_3 fragment encounters more steric repulsion with the geminally substituted inner substituent than with the terminal Me substituent.

Scheme 2. Gold-Catalyzed Conia−Ene Reaction of **2e**



Albeit to a reduced extent, the advantage of **1a** over PPh_3 appeared to be significant in the synthesis of sterically congested bicyclic compounds by the annulation of cyclic compounds (Table 2). When [$Au(NTf_2)$(**1a**)] (1 mol %) was employed, the 5-*exo*/6-*endo* annulation of an alkyne pendant onto a cyclopentanone (Table 2, entry 1) and a cyclohexanone (entry 4) completed within 24 h to afford **3f**/**4f** (49:51) and **3g**/**4g** (67:33), respectively, in high yields and in complete diastereoselectivity. The same reactions also proceeded with [$Au(NTf_2)(PPh_3)$], but they were slower and formed unidentified side products, resulting in lower yields

(7) The reaction of **2e** with the Au−PPh_3 catalyst: 24 h; 41% conversion; 35% yield; **3e**/**4e**, 12:88. 48 h; 44% conversion; 44% yield; **3e**/**4e**, 12:88.

of the desired products even after complete comsumption of the alkynes (entries 2, 3, 5, and 6). Although the insertion of an aromatic ring between an alkyne and a nucleophile tends to make the cyclization easier, the reaction of **2h**, having a keto ester attached to the terminal of a side chain, appeared to be less feasible under the conventional conditions with the PPh_3 ligand (entry 8 and 9). On the contrary, the gold−**1a** catalyst achieved quatitative conversion for this transformation (entry 7).

Notably, the reaction of **2i** proceeded with complete regioselectivity to afford bicyclo[3.3.1]nonenone **4i** irrespective of the ligand used; however, **1a** showed much higher efficiency in terms of both the rate of the reaction and the yield of **4i** (Table 2, entries 10−12). Additionally, similar results were obtained in the reaction of **2j**, which provided highly substituted bicyclo[2.2.2]octenone derivative **4j** (entries 13−15).

Our molecular modeling simulations indicated that the gold-bound alkynic substrate[8] in a catalytic pocket created by the semihollow ligand must be somewhat folded. Accordingly, we assume that such a steric effect makes the carbon−carbon bond formation entropically more favorable so that the gold-catalyzed cyclization of internal alkynes becomes feasible against steric repulsions (see Scheme 1) at the transition state.

In summary, the scope of the gold-catalyzed Conia−ene reaction has substantially been expanded so as to involve 5-*exo-dig* and 6-*endo-dig* cyclizations of internal alkynic β-keto esters by employing the semihollow-shaped end-capped triethynylphosphine as a ligand of a cationic gold(I) catalyst. Studies to explore the applicability of the semihollow-shaped ligand toward various transition-metal catalysts is underway.

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

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(8) For the structure of an isolated gold(I)-alkyne complex, see: Shapiro, N. D.; Toste, F. D. *Proc. Nat. Acad. Sci. U.S.A.* **2008**, *105*, 2779–2782.