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Construction of Methylenecycloheptane Frameworks through 7-*Exo-Dig* Cyclization of Acetylenic Silyl Enol Ethers Catalyzed by Triethynylphosphine−Gold Complex

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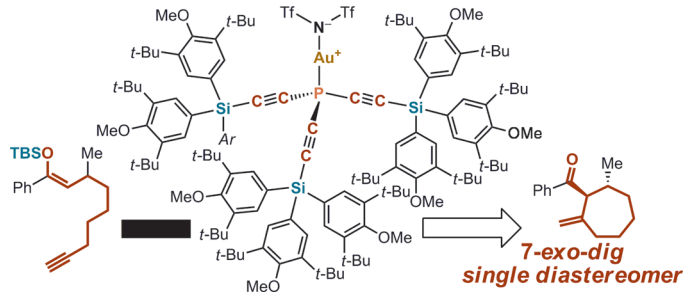
ABSTRACT



A cationic gold(I) complex bearing a semihollow-shaped triethynylphosphine ligand efficiently catalyzed the 7-*exo-dig* cyclization of silyl enol ethers with an ω-alkynic substituent. The reaction gave various methylenecycloheptane derivatives with an exo- or endocyclic carbonyl group. The protocol was applicable not only to cyclic substrates that form bicyclic frameworks but also to acyclic ones with or without substituents in a carbon chain tether.

Metal-catalyzed intramolecular reactions of silyl enol ethers with alkynes are powerful methods for the construction of carbocyclic compounds.[1,2] To date, 5-*exo*-, 5-*endo*-, 6-*exo*-, and 6-*endo-dig* cyclizations have been developed by using various metal catalysts such as mercury,[1a−d] tungsten,[1e−l] rhodium,[1m] rhenium,[1n,o] platinum,[1p] palladium,[1q] silver,[1r] and gold.[2] This method, however, has yet to be extended toward a seven-membered ring formation, which seems to be difficult because of the distal location of the nucleophilic center and the alkyne moiety.[3,4]

Previously, we reported that semihollow-shaped triethylnylphosphine **L1** (Figure 1)[5a] exerted marked acceleration effects in the gold(I)-catalyzed Conia−ene reactions of acetylenic keto esters and enyne cycloisomerizations, expanding the scope of the reactions to six- and seven-membered ring formations, which had been difficult with the conventional catalytic systems.[5b,c,6] We proposed that the cavity in the ligand forces the nucleophilic center close to gold-bound alkyne, resulting in the entropy-based rate enhancement.

Here, we report the efficient construction of seven-membered rings through a 7-*exo-dig* cyclization of acetylenic silyl enol ether catalyzed by the triethynylphosphine (**L1**)−gold(I) complex. The cyclization reactions afforded a variety of methylenecycloheptane derivatives that are difficult to prepare by other methods (Figure 1).

First, we optimized reaction conditions for the construction of a 2-methylene bicyclo[4.3.1]decane framework, which is

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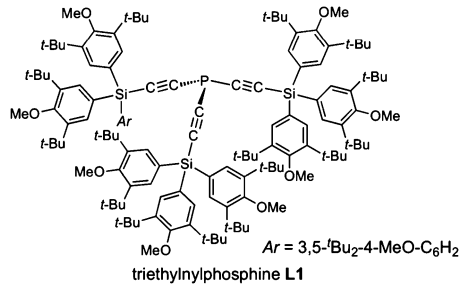


Figure 1. Semihollow-shaped triethynylphosphine (**L1**).

found in natural diterpenoid (+)-sanadaol **4** (Figure 2).[7] As a result, the reaction of a cyclic silyl enol ether **1a** (0.1 mmol) bearing an ω-alkynic substituent was efficiently catalyzed by a cationic gold−triethynylphosphine complex [Au(NTf_2)(**L1**)] (5 mol %) in the presence of ^{t}BuOH (0.10 mmol) and MS4A (100 mg) in anhydrous CH_2Cl_2 (5.0 mL) at rt; the reaction was complete within 5 min to afford 7-*exo-dig* cyclization product **2a** in 99% isolated yield (Table 1, entry 1). Notably, the reaction was not accompanied by either the direct protonation of the silyl enol ether (**1a**) or the double bond shift of the β,γ-unsaturated ketone (**2a**) to a conjugated enone, which are common side reactions of the metal-catalyzed cyclization of acetylenic silyl enol ethers.[1,2]

Observations concerning the reaction conditions are summarized in Table 1, entries 2−12. The use of MeOH instead

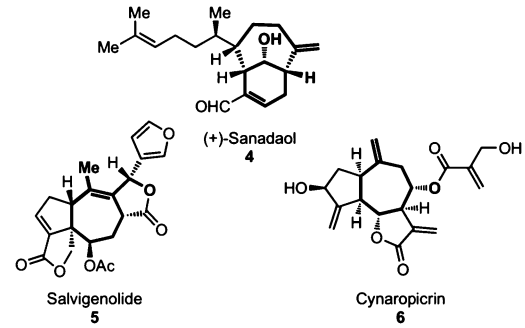


Figure 2. Natural terpenoids that involve a part structure relevant to the 7-*exo-dig* cyclization products of ω-acetylenic silyl enol ethers.

of ^{t}BuOH as a proton source did not affect the result (entry 2). The reaction without an alcohol resulted in a poor yield and afforded unidentified side products (entry 3), indicating that a proton source is indispensable for the formation of **2a**. The reaction without MS4A yielded **2a** in low yield (50%) along with direct protonation product **3a** in 34% yield (entry 4). A similar result was obtained in the absence of both ^{t}BuOH and MS4A (entry 5).

Cationic Au catalysts with counteranions other than NTf_2^- such as [Au(SbF_6)(**L1**)], [Au(OTf)(**L1**)], and [Au(BF_4)(**L1**)] were less effective (entries 6−8). The use of PPh_3 as a ligand resulted in no reaction (entry 9). A gold complex with a phosphite ligand such as $P(OPh)_3$, whose electron-donating power is as low as the triethynylphosphine **L1**,[5a] was virtually inactive, suggesting that the rate enhancement by **L1** is not due to an electronic effect (entry 10). While the ligands such as IPr and X-Phos are commonly employed for gold(I)-catalyzed reactions as sterically demanding and/or strongly electron-donating ligands,[6] gold complexes with these ligands did not reach full conversions of **1a** even after 3 h (entries 11 and 12). Further extension of the reaction time did not improve the yields.

With the optimal reaction conditions in hand, we examined various cyclic silyl enol ether substrates for the construction of bicyclo[4.*n*.1]alkane or bicyclo[*m*.4.1]alkane frameworks through 7-*exo-dig* cyclization (Table 2). Triisopropylsilyl enol ether **1b** was less reactive than the TBS ether **1a** but was rapidly ($\leq$5 min) and quantitatively converted to **2a** at 80 °C (entry 1). The reaction of the substrate bearing benzoyl group **1c** required slight heating (40 °C) and resulted in a

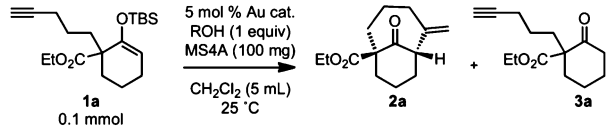
(1) For metal-mediated cyclization of acetylenic silyl enol ether, see: (a) Drouin, J.; Boaventura, M.-A.; Conia, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 1726. (b) Drouin, J.; Boaventura, M.-A. *Tetrahedron Lett.* **1987**, *28*, 3923. (c) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 2773. (d) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4081. (e) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928. (f) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871. (g) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2002**, *4*, 2569. (h) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463. (i) Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Kim, H.; Kim, S.; Lee, P. H.; Iwasawa, N. *Org. Lett.* **2003**, *5*, 1725. (j) Kusama, H.; Onizawa, Y.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 16500. (k) Grandmarre, A.; Kusama, H.; Iwasawa, N. *Chem. Lett.* **2007**, *36*, 66. (l) Onizawa, Y.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 802. (m) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809. (n) Kusawa, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468. (o) Saito, K.; Onizawa, Y.; Kusama, H.; Iwasawa, N. *Chem.—Eur. J.* **2010**, *16*, 4716. (p) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2003**, *9*, 2627. (q) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764. (r) Godet, T.; Belmont, P. *Synlett* **2008**, 2513.

(2) For gold-catalyzed cyclization of acetylenic silyl enol ether, see: (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (b) Lee, K.; Lee, P. H. *Adv. Synth. Catal.* **2007**, *349*, 2092. (c) Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287. (d) Barablé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236. (e) Kusama, H.; Karibe, Y.; Onizawa, Y.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4269.

(3) Gold-catalyzed 7-*exo*- or 7-*endo-dig* cyclization reactions have been reported. Most studies employed the substrates biased for cyclization bearing *gem*-substituents or double bonds in a linker chain. See: (a) Wilckens, K.; Uhlemann, M.; Czekelius, C. *Chem.—Eur. J.* **2009**, *15*, 13323. (b) Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379. (c) Comer, E.; Rohan, E.; Deng, L.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 2123. (d) Dai, L.-Z.; Shi, M. *Eur. J. Org. Chem.* **2009**, *3129*. (e) Odabachian, Y.; Goff, X. F. L.; Gagosz, F. *Chem.—Eur. J.* **2009**, *15*, 8966. For notable exceptions, see: (f) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (g) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358.

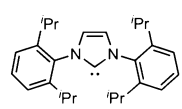
(4) For examples of the synthesis of seven- or eight-membered rings via gold catalysis, see: (a) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306. (b) Bae, H. J.; Baskar, B.; An, S. E.; Cheong, J. Y.; Thangadurai, D. T.; Hwang, I.-C.; Rhee, Y. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2263. (c) Baskar, B.; Bae, H. J.; An, S. E.; Cheong, J. Y.; Rhee, Y. H.; Duschek, A.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 2605. (d) Boyer, F.-D.; Goff, X. L.; Hanna, I. *J. Org. Chem.* **2008**, *73*, 5163. (e) Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056. (f) Benitez, D.; Tkatchouk, E.; Gonzalez, A. Z.; Goddard, W. A., III; Toste, F. D. *Org. Lett.* **2009**, *11*, 4798. (g) Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *Chem.—Eur. J.* **2009**, *15*, 3336. (h) Hashmi, A. S. K.; Haufe, P.; Schmid, C.; Nass, A. R.; Frey, W. *Chem.—Eur. J.* **2006**, *12*, 5376. (i) Hashmi, A. S. K.; Blanco, M. C.; Kurpejovic, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709.

Table 1. Optimization of Reaction Conditions[a]

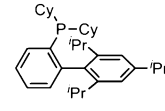


entry	Au cat.	alcohol	time (min)	convn[b] (%)	yield (%) 2a[b]	yield (%) 3a[c]
1	[Au(NTf$_2$)(**L1**)]	^{t}BuOH	5	100	99[e]	0
2	[Au(NTf$_2$)(**L1**)]	MeOH	5	100	100	0
3	[Au(NTf$_2$)(**L1**)]	none	720	45	20	0
4[d]	[Au(NTf$_2$)(**L1**)]	^{t}BuOH	5	100	50	34
5[d]	[Au(NTf$_2$)(**L1**)]	none	5	100	53	20
6	[Au(SbF$_6$)(**L1**)]	^{t}BuOH	180	33	22	3
7	[Au(OTf)(**L1**)]	^{t}BuOH	180	12	trace	0
8	[Au(BF$_4$)(**L1**)]	^{t}BuOH	180	18	trace	0
9	[Au(NTf$_2$)(PPh$_3$)]	^{t}BuOH	180	0	0	0
10	[Au(NTf$_2$){P(OPh)$_3$}]	^{t}BuOH	180	21	1	1
11	[Au(NTf$_2$)(IPr)]	^{t}BuOH	180	39	39	0
12	[Au(NTf$_2$)(X-Phos)]	^{t}BuOH	180	28	17	3

[a] Reaction conditions: Au cat., **1a** (0.10 mmol), alcohol (1.0 equiv), and MS4A (100 mg) in CH_2Cl_2 (5.0 mL) at 25 °C. [b] Determined by ^{1}H NMR. [c] Determined by GC. [d] Without MS4A. [e] Isolated yield.

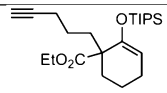
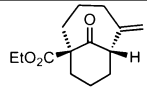
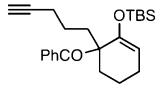
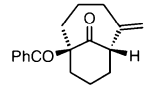
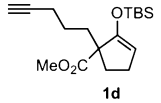
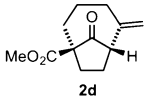
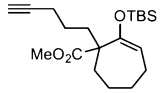
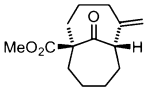
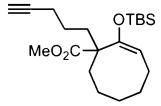
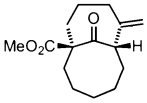


IPr



X-Phos

Table 2. Cyclization of Cyclic Alkynyl Silyl Enol Ether[a]

entry	substrate	product	temp (°C)	time	yield (%)[b]
1[c]	 1b	 2a	80	5 min	99
2	 1c	 2c	40	2 h	74
3	 1d	 2d	25	5 min	100
4	 1e	 2e	25	5 min	96
5	 1f	 2f	25	5 min	94

[a] Conditions: Au(NTf$_2$)(**L1**) (5 mol %), **1** (0.10 mmol), ^{t}BuOH (0.10 mmol), MS4A (100 mg), CH_2Cl_2 (5.0 mL). [b] Isolated yield. [c] DCE (5 mL) was used as solvent.

moderate yield (entry 2). Bicyclo[4.2.1]nonane (**2d**), bicyclo[4.4.1]undecane (**2e**), and bicyclo[5.4.1]dodecane (**2f**) frameworks were obtained from the corresponding cyclic silyl enol ethers **1d**−**f** at rt in excellent yields (entries 3−5).

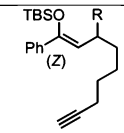
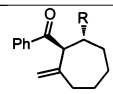
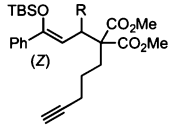
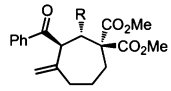
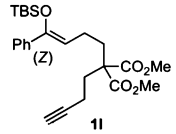
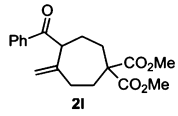
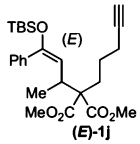
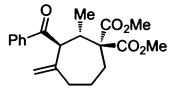
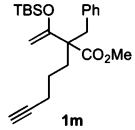
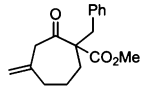
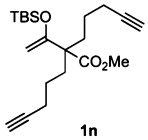
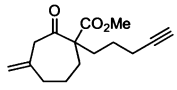
Next, we applied the gold(I)−triethynylphosphine (**L1**) complex to the synthesis of monocyclic methylenecycloheptane frameworks from acyclic silyl enol ethers, which are thought to be more challenging substrates due to their conformational flexibilities (Table 3). The acethylenic *Z*-configurated silyl enol ether (**1g**) without any substituent in the linker chain cyclized rapidly at rt to give β-methylenecycloheptane derivative (**2g**) with an exocyclic carbonyl group in 93% yield (entry 1). Notably, no double bond isomerization was observed even in this monocyclic case. While the substitution at the β-position of the acyclic substrate with a methyl group caused a slight decrease in the speed of the reaction, a *trans*-isomer of vicinally disubstituted methyl-

(5) For our previous works with triethynylphosphines, see: (a) Ochida, A.; Sawamura, M. *Chem.—Asian J.* **2007**, *2*, 609. (b) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486. (c) Ito, H.; Makida, Y.; Ochida, A.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2008**, *10*, 5051.

(6) For recent reviews on gold-catalyzed reactions, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (g) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (h) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776. (i) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675. (j) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, 692. (k) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232.

(7) (a) Ishitsuka, M.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1982**, *23*, 3179. (b) Kirkup, M. P.; Moore, R. E. *Phytochemistry* **1983**, *22*, 2527. (c) Nagaoka, H.; Kobayashi, K.; Matsui, T.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 2021. (d) Nagaoka, H.; Kobayashi, K.; Yamada, Y. *Tetrahedron Lett.* **1988**, *29*, 5945. (e) Miyaoka, H.; Yamada, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 203.

Table 3. Cyclization of Linear Alkynyl Silyl Enol Ether[a]

entry	substrate	product	temp (°C)	time	yield (%)[b]
					
1[c]	R = H (**1g**)	R = H (**2g**)	25	5 min	93
2[c]	R = Me (**1h**)	R = Me (**2h**)	25	3 h	89
					
3[c]	R = H (**1i**)	R = H (**2i**)	80	5 min	93
4	R = Me (**1j**)	R = Me (**2j**)	80	10 min	94
5[c]	R = Ph (**1k**)	R = Ph (**2k**)	80	24 h	51
6[c]	 **1l**	 **2l**	40	24 h	83
7[c]	 **(*E*)-1j**	 **2j**	80	2 h	85
8	 **1m**	 **2m**	25	5 min	90
9[d]	 **1n**	 **2n**	40	5 min	93

[a] Conditions: Au(NTf$_2$)(**L1**) (5 mol %), **1** (0.10 mmol), ^{t}BuOH (0.10 mmol), MS4A (100 mg), CH_2Cl_2 (5.0 mL) at 25 °C or CH_2Cl_2 (5.0 mL) at 40 °C or DCE (5.0 mL) at 80 °C. [b] Isolated yield. [c] An isomeric mixture was used as a substrate [**1g**, *E*/*Z* 14:86; **1h**, *E*/*Z* 13:87; **1i**, *E*/*Z* 10:90; **1k**, *E*/*Z* 4:96; **1l**, *E*/*Z* 19:81; (*E*)-**1j**, *E*/*Z* 86:14]. [d] 0.60 mmol scale in CH_2Cl_2 (30 mL).

enecycloheptane **2h** was obtained from (*Z*)-**1h** as a single diastereomer[8] in high yield at rt (entry 2).

The *Z*-silyl enol ether (**1i**) with a dimethyl malonate insert in the linker chain was less reactive than the substrate with a nonsubstituted linker (**1g**) but cyclized rapidly (≤5 min) at 80 °C, giving **2i** in 93% yield (entry 3). The reaction of (*Z*)-**1j** bearing β-methyl group in addition to the malonate insert gave *trans*-isomer **2j**[8] exclusively (entry 4). The reaction of the phenyl-substituted substrate (*Z*)-**1k** did not lead to completion even after 24 h at 80 °C and afforded diastereomerically pure **2k**[8] in a moderate yield (51%, entry 5). The diester substitution at the bishomopropargyl position as in **1l** did not significantly affect the reactivity, affording **2l** in 83% yield (entry 6). Overall, the Thorpe−Ingold effects by the malonate inserts did not operate in the gold-catalyzed 7-*exo*-*dig* cyclization (entry 1 vs entries 3 and 6).

The cyclization of the *E* isomer of **1j** gave the same stereoisomer of **2j** as that of (*Z*)-**1j** (entries 4 vs 7), while the reaction time was prolonged to 2 h at 80 °C (entry 7). The excellent *anti* diastereoselectivity observed in the reactions of (*Z*)-**1h**,**j**,**k** and (*E*)-**1j** can be explained by steric repulsions between the silyl enol ether moieties and the methyl or phenyl groups as described in the literature.[2e]

Notably, the methylenecycloheptane framework with an exocyclic carbonyl group in **2g**−**l** thus prepared (Table 2, entries 1−7) is reminiscent of a partial structure of diterpenoid salvigenolide **5** (Figure 2).[9]

The reaction of silyl enol ethers **1m** and **1n** afforded methylenecycloheptane derivatives **2m** and **2n** involving an endocyclic carbonyl group, respectively, in excellent yields (entries 8 and 9). These compounds can be structurally related to natural sesquiterpenoid cynaropicrin **6** and their derivatives (Figure 2).[10]

In summary, the 7-*exo*-*dig* cyclization of silyl enol ethers with an ω-alkynic substituent was efficiently catalyzed by a cationic gold(I) complex bearing a semihollow-shaped triethynylphosphine ligand. The reaction furnished various methylenecycloheptane derivatives with exo- or endocyclic carbonyl groups. The protocol was applicable not only to cyclic substrates that form bicyclic frameworks but also to acyclic ones with or without substituents in a carbon chain tether. Further studies to expand the applicability of the semihollow-shaped ligand are ongoing.

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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) The relative configurations of **2h**, **2j**, and **2k** were determined by X-ray crystal structure analysis and ^{1}H NMR. For details, see the Supporting Information.

(9) Esquivel, B.; Cárdenas, J.; Toscano, A.; Soriano-Garcia, M.; Rodríguez-Hahn, L. *Tetrahedron* **1985**, *41*, 3213.

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