Cyclization

Construction of Eight-Membered Carbocycles through Gold Catalysis with Acetylene-Tethered Silyl Enol Ethers**

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The development of efficient methods for the construction of medium-sized (eight- to eleven-membered) carbocycles remains an important challenge in organic synthesis.[1] Despite their ubiquitous existence within various biologically active natural products and pharmaceuticals (Figure 1),[2] the formation of medium-sized rings is generally difficult because of entropic effects and transannular interactions.[3]
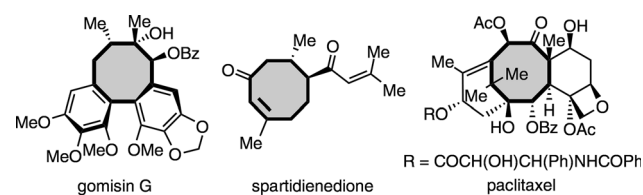
Figure 1. Natural products that possess an eight-membered carbocycle. Bz = benzoyl.

Figure 2. Semihollow triethynylphosphanes.

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Although various metal-catalyzed or metal-mediated methods have been developed, the direct formation of medium-sized carbocycles through the cyclization of acyclic precursors has remained relatively unexplored.[4–6] Studies involving homogeneous gold catalysis have shown that the ionization of nonpolar unsaturated carbon–carbon bonds through gold π-coordination can initiate a variety of cyclization reactions with remarkably high efficiencies, thus providing powerful strategies for the construction of cyclic structures.[7] Such strategies, however, have not yet been successfully employed in the direct ring closure of medium-sized rings.[8] To date, the construction of benzannulated structures mostly involves highly constrained aromatic molecules, with the single exception featuring the formation of a nine- or ten-membered ring using 1,9- or 1,10-diynes with one or more unsaturated moieties in the linker.[8c] Herein, we report the use of novel semihollow triethynylphosphane ligands (abbreviated hereafter as C-dtbm and C-btms, Figure 2)[9] in the gold-catalyzed 8-*exo-dig* cyclization of acetylene-tethered
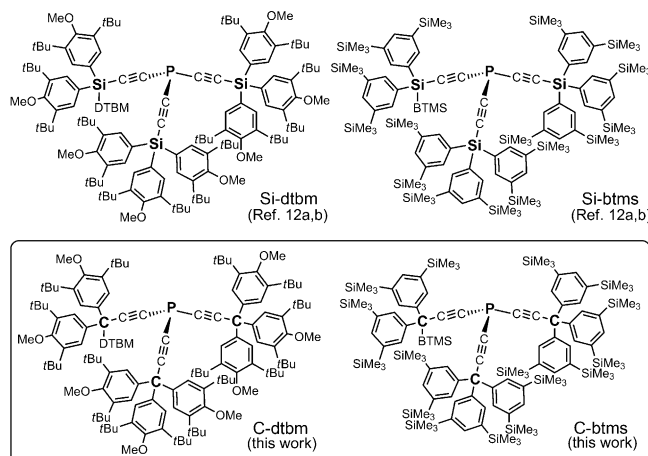
silyl enol ethers toward the formation of eight-membered-ring carbocyclic compounds. Our methodology is applicable not only to annulations leading to bicyclic structures, but also to the cyclization of acyclic molecules in the formation of nonfused carbocycles.
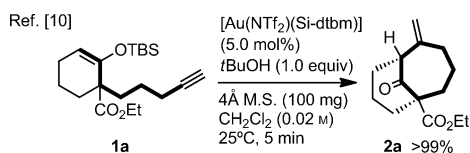
We previously demonstrated the utility of a semihollow triethynylphosphane ligand that possesses bulky triarylsilyl groups at the alkyne termini (Si-dtbm, Figure 2) in the formation of seven-membered carbocyclic compounds through gold-catalyzed 7-*exo-dig* cyclizations of acetylene-tethered silyl enol ethers.[10,11] For these reactions, we proposed that the gold-bound substrates adopt a bent conformation to fit into the cavity of the semihollow ligand, resulting in an entropy-based rate enhancement of the nucleophilic attack of the silyl enol ether on the ionized alkyne moiety as a result of the proximity between the two reaction sites.[12,13] Specifically, the cationic gold(I)/Si-dtbm complex catalyzed the cyclization of **1a** to afford the seven-membered-ring compound **2a** quantitatively. In contrast, such cyclizations were not observed using conventional ligands, such as Ph$_3$P (Scheme 1).[10,14] Unfortunately, attempts to expand our methodology to the formation of more challenging eight-membered or larger rings have been less successful; for instance, the reaction of **3a** at 85°C for one hour afforded methylene cyclooctane derivative **4a** in merely 12% yield with 14% substrate conversion (Table 2, entry 1). The triethynylphosphane ligand (Si-btms, Figure 2) with trimethylsilyl (TMS) groups on the aromatic rings did not induce any cyclization (Table 2, entry 2).

In an attempt to overcome this problem, we synthesized various novel triethynylphosphanes (C-type triethynylphos-

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Scheme 1. Gold(I)-catalyzed 7-*exo-dig* cyclization of acetylene-tethered silyl enol ether **1a**.

phanes C-dtbm and C-btms, Figure 2) featuring trityl-based end caps at the acetylenyl terminus of the triethynylphosphane instead of the triarylsilyl end caps (as in Si-type triethynylphosphanes Si-dtbm and Si-btms). The synthesis of these phosphanes was straightforward and efficient (Scheme 2). According to molecular modeling (Spartan/
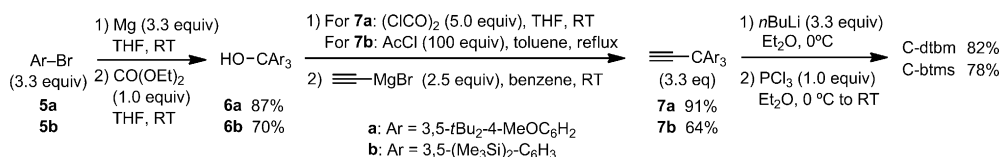
Scheme 2. Synthesis of the C-type semihollow triethynylphosphanes (**C-dtbm** and **C-btms**).

MMFF), the new phosphane ligands possess a deeper cavity with a narrower opening than Si-dtbm; the estimated depths (d) and opening diameters (l) of the cavities are listed in Table 1. Furthermore, according to the ^{31}P NMR spectra of the free ligands and their [AuCl(phosphane)]-type gold(I) complexes (Table 1), substitution of the Si with the C atom caused only marginal differences in the electronic properties (electron density and hybridization) of the central P atom. As a note, the air and moisture stability behavior was similar among the triethynylphosphane ligands.

Interestingly, the cationic gold complex that was coordinated with C-type triethynylphosphane C-dtbm, [Au(NTf$_2$)-(C-dtbm)] (5 mol%), was significantly more effective than those with Si-type ligands, promoting the 8-*exo-dig* cyclization of **3a** to afford **4a** in 70% yield with 91% conversion (Table 2, entry 3). The reaction was carried out in the presence of *t*BuOH (1 equiv) and activated 4 Å molecular sieves[15]

Table 1: Estimated structural parameters: depth (d), opening diameter (l), and ^{31}P NMR chemical shifts of the semihollow triethynylphosphane ligands (L) and the gold(I) complexes (Spartan/MMFF).

Entry	Phosphane	Depth (d) [Å]	Opening diameter (l) [Å]	δ [ppm] of L	δ [ppm] of [AuCl(L)]
1	Si-dtbm	4.1	17	−85.2[a]	−62.5[a]
2	Si-btms	4.1	18	−83.0[a]	−61.8[a]
3	C-dtbm	4.3	13	−81.5	−63.9
4	C-btms	4.5	14	−81.8	−60.4

[a] The ^{31}P NMR chemical shifts (in CDCl$_3$) were taken from Ref. [12b].

(100 mg) in anhydrous 1,2-dichloroethane (0.01 M) at 85°C for one hour; it is important to note that the concentration of the reaction mixture is moderately low. On the other hand, under similar reaction conditions, the gold complex involving the other C-type ligand (C-btms) with Me$_3$Si substituents at the aromatic rings was also effective and afforded **4a**, albeit with a lower yield (37%; Table 2, entry 4). In contrast, conventional monodentate ligands, such as Ph$_3$P, (PhO)$_3$P, XPhos, and IPr, were not effective in promoting this cyclization reaction.[16]

Interestingly, the reaction was affected by the nature of the counteranion in the complex; the use of NTf$_2^-$ was essential for the activity of the [Au(C-dtbm)]$^+$ catalyst, whereas anions such as SbF$_6^-$, OTf$^-$, and BARF$^-$ decreased the yields to 7%, 0%, and 6%, respectively (Table 2, entries 5–7). With regard to the proton source, switching from *t*BuOH to MeOH significantly improved the catalytic activity of [Au(NTf$_2$)-(C-dtbm)], thus increasing the yield of **4a** to 83% with 99% conversion of **3a** (69% yield of analytically pure product;[17] Table 2, entry 3 versus entry 8). Substitution of the *tert*-butyldimethylsilyl (TBS) group in the siloxyalkene moiety with either triethylsily or triisopropylsilyl groups resulted in lower yields.[16]

Gold catalysts with C-type triethynylphosphane ligands were also effective in the 8-*exo-dig* annulation of monocyclic silyl enol ethers with different ring sizes in the construction of various bicyclo[5.n.1]alkane frameworks (Table 3). In the case of cyclopentanone-based silyl enol ether **3b**, the use of C-btms, which possesses 3,5-bis(trimethylsilyl)phenyl substitu-

Table 2: Gold(I)-catalyzed 8-*exo-dig* annulation of **3a** under various conditions.[a]

Entry	Au cat.	ROH	Conv. of **3a** [%][b]	Yield of **4a** [%][b]
1	[Au(NTf$_2$)(Si-dtbm)]	*t*BuOH	14	12
2	[Au(NTf$_2$)(Si-btms)]	*t*BuOH	10	0
3	[Au(NTf$_2$)(C-dtbm)]	*t*BuOH	91	70
4	[Au(NTf$_2$)(C-btms)]	*t*BuOH	66	37
5	[Au(SbF$_6$)(C-dtbm)]	*t*BuOH	14	7
6	[Au(OTf)(C-dtbm)]	*t*BuOH	11	0
7	[Au(BARF)(C-dtbm)]	*t*BuOH	47	6
8	[Au(NTf$_2$)(C-dtbm)]	MeOH	99	83 (69)[c]

[a] Reaction conditions: Au catalyst (5.0 μmol, 5.0 mol%), **3a** (0.10 mmol), alcohol (0.10 mmol), 4 Å molecular sieves (100 mg), 1,2-dichloroethane (10 mL), 85°C, 1 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield after purification by column chromatography on silica gel followed by gel-permeation chromatography (GPC).
BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate; Tf = trifluoromethanesulfonyl.

Table 3: Gold-catalyzed 8-*exo-dig* cyclization of monocyclic siloxyalkenes with ω-acetylenic alkyl pendants in the construction of bicyclo-[5.*n*.1]alkane frameworks.[a]

Entry	Substrate 3	Ligand	Product 4	Yield [%][b]
1	3b	C-dtbm	4b	28
2		C-btms		52 (30)[c]
3	3c	C-dtbm	4c	73 (62)[c]
4		C-btms		69
5	3d	C-dtbm	4d	60 (48)[c]
6		C-btms		38

[a] Reaction conditions: [Au(NTf₂)(ligand)] (5.0 μmol, 5.0 mol%), 3 (0.10 mmol), *t*BuOH (0.10 mmol), 4Å molecular sieves (100 mg), 1,2-dichloroethane (10 mL), 85 °C, 1 h. [b] Determined by ¹H NMR spectroscopy. [c] Yield after purification by column chromatography on silica gel followed by GPC.

Table 4: Synthesis of dibenzocyclooctane 4e.[a]

Entry	Ligand	Catalyst loading [mol%]	Yield of 4e [%][b]
1	C-dtbm	5	92 (85)[c]
2	C-dtbm	1	82
3	C-btms	5	80
4	PPh₃	5	9

[a] Reaction conditions: [Au(NTf₂)(ligand)] (5.0 μmol, 5.0 mol% or 1.0 μmol, 1.0 mol%), 3e (0.10 mmol), *t*BuOH (0.10 mmol), 4Å molecular sieves (100 mg), 1,2-dichloroethane (10 mL), 85 °C, 1 h. [b] Determined by ¹H NMR spectroscopy. [c] Yield after purification by column chromatography on silica gel followed by GPC.

ents, resulted in a high yield of bicyclo[5.2.1]decane derivative **4b** (52%; Table 3, entry 2). The use of C-dtbm was however not very effective, resulting in a relatively low yield (28%; Table 3, entry 1), which may be attributable to the ring strain of the bicyclo[5.2.1]decane framework, or to the unfavorable directionality of the ω-acetylenic alkyl pendant relative to the π-face of the siloxyalkene. In contrast, C-dtbm was more effective than C-btms in the formation of bicyclo-[5.5.1]tridecane **4d** from cyclic silyl enol ether **3d** (Table 3, entries 5 and 6). Both C-dtbm and C-btms were effective in enhancing the reaction of cycloheptenone-derived siloxyalkene **3c** to afford bicyclo[5.4.1]dodecane derivative **4c** in useful yields (Table 3, entries 3 and 4). Unfortunately, neither C-dtbm nor C-btms were effective in the cyclization of nonterminal acetylene-tethered silyl enol ethers or the formation of nine-membered rings.

With both C-dtbm and C-btms as ligands, the cyclization of acetylenic silyl enol ether **3e**, which features a biphenyl-based rigid linker, occurred more readily than that of the aliphatic monocyclic substrates **3a–d**, affording dibenzocyclooctane derivative **4e** in 92% and 80% yield, respectively (Table 4, entries 1 and 3). Furthermore, the catalyst loading of [Au(NTf₂)(C-dtbm)] can be reduced to 1 mol% without significant reduction of the yield (82%; Table 4, entry 2). The cyclization proceeded even when a PPh₃-based catalyst (5 mol%) was used, albeit with much lower efficacy (9% yield; Table 4, entry 4).[5] It is important to note that cyclization product **4e** contains the dibenzocyclooctane core structure of the lignan family of natural products, some of which possess important biological properties;[3a,b] in particular, gomisin G has exhibited potent anti-HIV activity (Figure 1).[2a]

Moreover, the gold catalysts were also effective in the 8-*exo-dig* cyclization of acyclic substrates to afford nonfused methylenecyclooctane derivatives (Table 5). The reaction of substrate **3f**, which possesses an unbranched linker between the siloxyalkene and acetylene moieties, in the presence of

Table 5: Construction of nonfused eight-membered carbocycles through a gold(I)-catalyzed 8-*exo-dig* cyclization of acyclic acetylene-tethered siloxyalkenes.[a]

Entry	Substrate 3	Ligand	Product 4	Yield [%][b]
1	3f (Z/E 80:20)	C-dtbm	4f	9
2		C-btms		22 (23)[c]
3	3g (Z/E 77:23)	C-dtbm	4g	18
4		C-btms		69 (59)[c]
5	3h	C-dtbm	4h	66
6		C-btms		60 (50)[c]
7	3i	C-dtbm	4i	51
8		C-btms		54 (47)[c]
9	3j	C-dtbm	4j	42
10		C-btms		57 (48)[c]
11	3k	C-dtbm	4k	37
12		C-btms		58 (42)[c]
13	3l	C-dtbm	4l	37
14		C-btms		54 (43)[c]
15	3m	C-dtbm	4m	32
16		C-btms		72 (66)[c]

[a] Reaction conditions: [Au(NTf₂)(ligand)] (5.0 μmol, 5.0 mol%), 3 (0.10 mmol), *t*BuOH (0.10 mmol), 4Å molecular sieves (100 mg), 1,2-dichloroethane (10 mL), 85 °C, 1 h. [b] Determined by ¹H NMR spectroscopy. [c] Yield after purification by column chromatography on silica gel followed by GPC or preparative thin-layer chromatography (PTLC).

gold complexes with either the C-dtbm or the C-btms ligand (85 °C, 1 h) afforded 2-acylmethylenecyclooctane **4f**, albeit in yields of merely 9 % and 22 %, respectively (Table 5, entries 1 and 2). In both cases, starting material **3f** was almost completely consumed, unfortunately resulting in the formation of a ketone by-product as a result of the protonation at the siloxyalkene moiety, along with other unidentified compounds. The low cyclization efficacy can be attributed to the flexibility of the unbranched substrate.

Although the reaction of the siloxyalkene **3g**, which features a dimethyl malonate moiety at the homoallylic position, with C-dtbm produced **4g** in an unsatisfactory yield as low as 18 %, more efficient cyclization occurred with C-btms, improving the yield to 69 % (Table 5, entries 3 and 4). The higher cyclization efficacy of the formation of **4g** compared to that of **4f** can be attributed to the Thorpe–Ingold effect.

In the case of benzyl-substituted terminal siloxyalkene **3h**, the reactions involving both C-dtbm and C-btms proceeded smoothly to form methylenecyclooctane derivative **4h** (Table 5, entries 5 and 6; 66 and 60 % yield, respectively), which possesses an endocyclic carbonyl group and is structurally related to spartidienedione (Figure 1).[2b] Substituents such as methoxy (**3i**), bromo (**3j** and **3k**), or iodo groups (**3l**) at the *ortho* or *para* position of the aromatic ring of **3h** did not significantly affect the cyclization efficiencies, with either C-dtbm or C-btms ligands; in all cases, the corresponding carbocycles **4i**–**4l** were obtained in useful yields (Table 5, entries 7–14). Silyl enol ether **3m**, which possesses two terminal alkyne moieties, was also converted to the monocyclic compound **4m** (Table 5, entries 15 and 16); in the case of C-btms, the product was obtained with a yield of 72 %.

In summary, the use of two triethynylphosphane ligands (C-dtbm and C-btms) enabled the gold(I)-catalyzed 8-*exo-dig* cyclization of acetylene-tethered silyl enol ethers to eight-membered carbocycles. These novel semihollow triethynylphosphanes possess a cavity that is smaller than that of the corresponding silicon-type ligands, and were synthesized in a straightforward manner. Further studies to expand the applicability of the semihollow triethynylphosphanes are ongoing.

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[14] The C-dtbm ligand was also effective in the gold-catalyzed 7-*exo-dig* cyclization of acetylene-tethered silyl enol ethers; **2a** was obtained in 95 % yield under conditions that were otherwise the same. C-dtbm and Si-dtbm showed comparable ligand performances in other gold-catalyzed alkyne cyclizations toward five- to seven-membered rings that we reported previously (Refs. [12a,c,d]).

[15] For effects of 4 Å molecular sieves, see Ref. [10].

[16] See the Supporting Information for details.

[17] On a few occasions, traces of impurities derived from the triethynylphosphanes or silyl enol ethers were detected in the products following column chromatography on silica gel. In these cases, the products were further purified using GPC or PTLC to obtain analytically pure products.