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An Efficient Method for Cyclopentene Annulation onto α,*β*-Unsaturated Ketones: W(CO)$_5$(L)-Catalyzed 5-Endo-Dig Cyclization of 6-Siloxy-5-en-1-ynes

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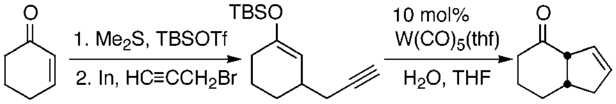
ABSTRACT



A highly efficient method for the cyclopentene annulation onto α,*β*-unsaturated ketones is described. Indium-mediated 1,4-propargylation onto α,*β*-unsaturated ketones in the presence of *tert*-butyldimethylsilyl triflate and dimethyl sulfide gives the 6-siloxy-5-en-1-yne derivatives, which undergo W(CO)$_5$(L)-catalyzed 5-endo-dig cyclization to give the corresponding cyclopentene derivatives in good yield.

Development of concise methods for the annulation of a five-membered ring onto alkenes is highly valuable in the field of synthetic organic chemistry because such methods enable a facile construction of useful carbon frameworks found in various biologically active natural products.[1,2] Although a variety of methods have been developed for this purpose, it is not necessarily easy to realize annulation of a simple three-carbon unit onto α,*β*-unsaturated ketones by a concise procedure.

For instance, Danheiser et al. have developed a highly useful method for a one-step [3 + 2] annulation of substituted trimethylsilylallenes and α,*β*-unsaturated ketones in the presence of a stoichiometric amount of $TiCl_4$ to afford substituted cyclopentene derivatives.[3] However, it is difficult to obtain the parent, nonsubstituted cyclopentene derivative because trimethylsilylpropa-1,2-diene itself failed to participate in this reaction.

We recently reported a novel, W(CO)$_5$(L)-catalyzed cyclization of *ω*-acetylenic silyl enol ethers,[4] where 5-siloxy-5-en-1-ynes undergo 6-endo cyclization,[4a] while 7-siloxy-6-en-1-ynes undergo either 5-exo or 6-endo cyclization by

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† Tokyo Institute of Technology.
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[1] For a review on the cyclopentene annulation, see: (a) Ramaiah, M. *Synthesis* **1984**, *529*. (b) Trost. B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.

[2] For recent examples of cyclopentannulation, see: (a) Crimmins, M. T.; Tabet, E. A. *J. Org. Chem.* **2001**, *66*, 4012. (b) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (c) Barluenga, J.; Martínez, S.; Suárez-Sobrino, A. L.; Tomás, M. *J. Am. Chem. Soc.* **2002**, *124*, 5948. (d) Ding, P.; Ghosez, L. *Tetrahedron* **2002**, *58*, 1565. (e) Mahuteau-Betzer, F.; Ghosez, L. *Tetrahedron* **2002**, *58*, 6991 and references therein.

[3] (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (b) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. (c) Danheiser, R. L.; Fink, D. M.; Tsai, Y.-M. *Org. Synth.* **1988**, *66*, 8. See also: Panek, S. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 596−607.

[4] (a) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928. (b) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871. (c) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518. (d) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2002**, *4*, 2569 and references for W(CO)$_5$(L)-promoted reactions cited therein. See also: (e) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *Tetrahderon Lett.* **1999**, *40*, 4081. (f) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Sudo, T.; Asao, N.; Yamamoto, Y. *Can. J. Chem.* **2001**, *79*, 1624.

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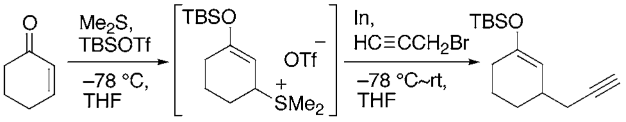
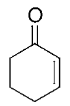
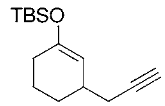
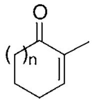
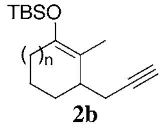
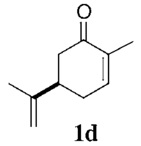
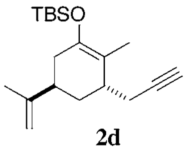
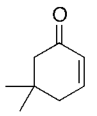
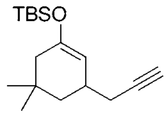
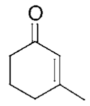
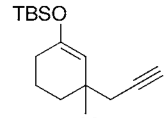
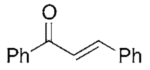
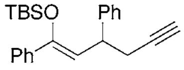
the appropriate choice of the reaction conditions.[4b] On the other hand, only one specific example was disclosed for the 5-endo cyclization of the 6-siloxy-5-en-1-yne derivative.[4a] One reason for this scarcity is the lack of a good and simple method for the preparation of the requisite substrates. Therefore development of a concise method for the direct 1,4-propargylation onto α,β-unsaturated ketones with simultaneous silylation of the produced enolates is highly desirable.[5,6] Recently, we reported that 3-*tert*-butyldimethylsilylsiloxyalk-2-enylsulfonium salts generated in situ by the reaction of α,β-unsaturated ketones with *tert*-butyldimethylsilyl triflate and dimethyl sulfide undergo 1,4-allylation with allylindium reagents to afford the corresponding 1,4-allylated silyl enol ethers (formal 1,4-addition onto α,β-unsaturated ketones) in good yields.[7] We thought of applying this protocol for the preparation of 6-siloxy-5-en-1-yne derivatives using propargyl bromide instead of allyl bromide.[8] We then decided to examine the indium-mediated 1,4-propargylation onto α,β-unsaturated ketones in the presence of *tert*-butyldimethylsilyl triflate and dimethyl sulfide.

To a THF solution of cyclohex-2-en-1-one **1a** were added *t*-butyldimethylsilyl triflate and dimethyl sulfide successively to afford in situ 3-*tert*-butyldimethylsiloxycyclohex-2-enylsulfonium salt, which was treated at −78 °C with organoindium reagent generated in situ from indium-metal and propargyl bromide in THF at room temperature.[7] Gratifyingly, usual workup of the reaction mixture gave the desired silyl enol ether **2a** in 76% yield. Trace amounts of the 1,2-adduct and allenylated products were detected by ^{1}H NMR spectra of the crude product. As summarized in Table 1, the present preparative method was found to be generally applicable to the conjugate propargylation onto cyclic alkenones. On the other hand, the reaction onto acyclic alkenones did not proceed as expected, and a rather low yield of the desired product was obtained when chalcone **2g** was employed.

Table 1. Indium-Mediated 1,4-Propargylation of α,β-Unsaturated Ketones



α,β-unsaturated ketone	product	yield/%
 **1a**	 **2a**	76
 **1b**: n = 0 **1c**: n = 1	 **2b** **2c**	66 76
 **1d**	 **2d**	72
 **1e**	 **2e**	48
 **1f**	 **2f**	34
 **1g**	 **2g**	26

Since various requisite substrates were obtained by this method, we next examined the $W(CO)_5(thf)$-catalyzed 5-endo cyclization of these substrates. When the 6-siloxy-5-en-1-yne derivative **2a** was treated with 10% molar amounts of preformed $W(CO)_5(thf)$ in the presence of 1 equiv of H_2O, it was completely consumed at room temperature within 5 days to give the endo-cyclized bicyclo[4.3.0]non-7-en-5-one **3a** in 72% yield. The reaction is thought to proceed as follows: treatment of **2a** with $W(CO)_5(thf)$ would give an alkyne−$W(CO)_5$ π-complex **A**, which is in equilibrium with the 1,2-hydrogen-migrated vinylidene complex **B**; nucleophilic attack of the silyl enol ether to the π-complex **A** and/or the vinylidene complex **B** occurs to give the vinylmetallic species **C** or **D**, which is protonated by H_2O to give **3a** (Scheme 1).[9,10]

As summarized in Table 2, the 5-endo cyclization mostly proceeded smoothly to give the corresponding cyclopentene derivatives **3** in good yields using 5−10% molar amounts of $W(CO)_5(thf)$.[11] Only in the case of the acyclic substrate **2g** was it necessary to employ 30% molar amounts of

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(5) Generally, 1,4-propargylation onto α,β-unsaturated ketones is not an easy process because 1,2-addition of propargyl (or allenyl) metallic reagents usually occurs preferentially. Some exceptions were reported using allenyltin and several other reagents; see: (a) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1389. (b) Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853. (c) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (d) Paquette, L. A.; Han. Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1831.

(6) Reaction with allyltri-*n*-butyltin with chalcone in the presence of $TaCl_5$ and TMSCl was reported to give the conjugate adduct as a silyl enol ether.[5a] When we carried out the conjugate addition of allenyltri-*n*-butyltin with chalcone in the presence of $TaCl_5$ and a silyl chloride such as TMSCl or TBSCl, only hydrolyzed conjugate adduct was obtained and none of the desired silyl enol ether was detected in the crude mixtures.

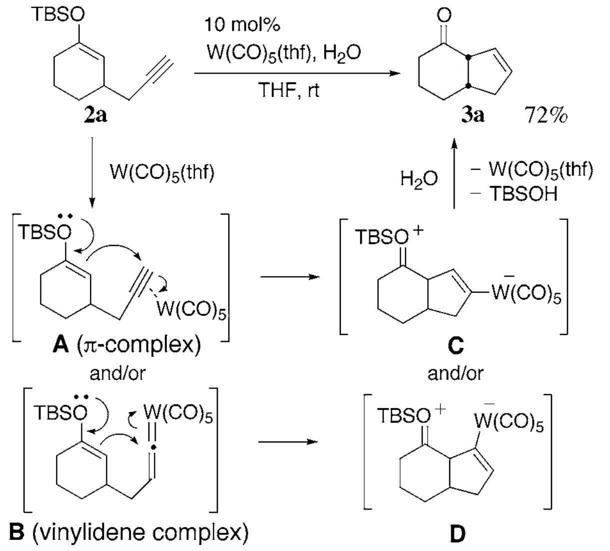
(7) Lee, P. H.; Lee, K.; Kim, S. *Org. Lett.* **2001**, *3*, 3205.

(8) For examples of In-mediated propargylation or allenylation, see: (a) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453. (b) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472. (c) Isaac, M. B.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003.

(9) To obtain information on the mechanism of this reaction, we have carried out D_2O experiments. The reaction of **2d** in the presence of 3.0 equiv of D_2O instead of H_2O revealed that both olefinic protons were partially deuterated and that the degree of deuterium incorporation at the two olefinic protons was a total of about one proton. On the basis of these results, we propose that the cyclization takes place both through the alkyne−$W(CO)_5$ π-complex and the vinylidene complex: the ratio of two reaction pathways is about 7:3 (π-complex vs vinylidene complex) for **2d**.

(10) Stereochemistry of the ring junction is assigned as cis by a NOE experiment; for details, see Supporting Information.

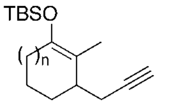
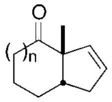
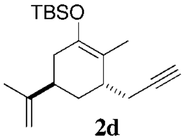
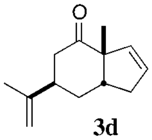
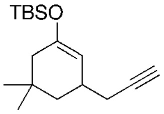
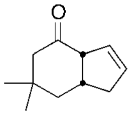
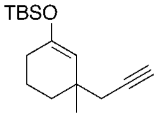
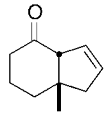
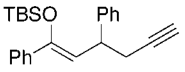
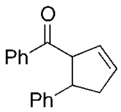
Scheme 1



$W(CO)_5(thf)$ to give the desired product **3g** in good yield. Although 5-endo-dig cyclization is a favored process according to the Baldwin's rule,[12] there are very few reports on this type of cyclization, in particular, for the nucleophilic carbocycle formations.[13]

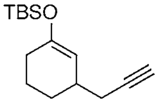
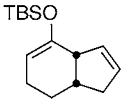
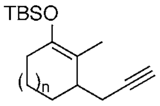
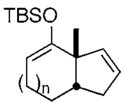
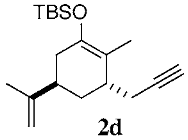
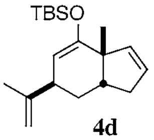
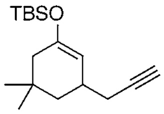
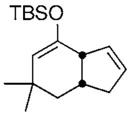
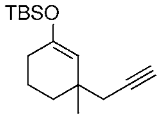
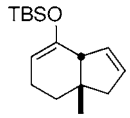
We next carried out this cyclization in the presence of DABCO instead of H_2O.[4d] When the reaction was performed with 10% molar amounts of $W(CO)_6$ in toluene under photoirradiation conditions[14] for 10 h in the presence of 2 molar amounts of DABCO, all the reactions proceeded

Table 2. 5-Endo Cyclization of *ω*-Acetylenic Silyl Enol Ethers Using a Catalytic Amount of $W(CO)_5(thf)$ in THF[a]

substrate	product	yield/%
 **2b**: n = 0 **2c**: n = 1	 **3b** **3c**	91[b] 91[c]
 **2d**	 **3d**	92[c]
 **2e**	 **3e**	77[b]
 **2f**	 **3f**	91[b]
 **2g**	 **3g**	78[d]

[a] Stereochemistry of the ring junction was assigned by a NOE experiment except for **3g**. For details, see Supporting Information. [b] Conditions: A preformed 10% molar amount of $W(CO)_5(thf)$ and 1 equiv of H_2O were added to the substrate. The mixture was stirred at room temperature for 4−5 days. [c] $W(CO)_5(thf)$ (5% molar amount) was used. [d] $W(CO)_5(thf)$ (30% molar amount) was used.

Table 3. 5-Endo Cyclization of *ω*-Acetylenic Silyl Enol Ethers Using a Catalytic Amount of $W(CO)_5(dabco)$ in Toluene[a]

substrate	product	yield/%
 **2a**	 **4a**	84
 **2b**: n = 0 **2c**: n = 1	 **4b** **4c**	84 72
 **2d**	 **4d**	83
 **2e**	 **4e**	59
 **2f**	 **4f**	81

[a] Stereochemistry of the ring junction was assigned by a NOE experiment. For details, see Supporting Information. Conditions: A toluene solution of the substrate, a 10% molar amount of $W(CO)_6$, and 2 molar amounts of DABCO was irradiated at ambient temperature for 8−10 h.

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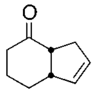
(11) Products **3a**−**f** were accompanied by a small amount (about 3% of the product) of an olefinic regioisomer such as **3a′**. The reason for the formation of this compound is not yet obvious.

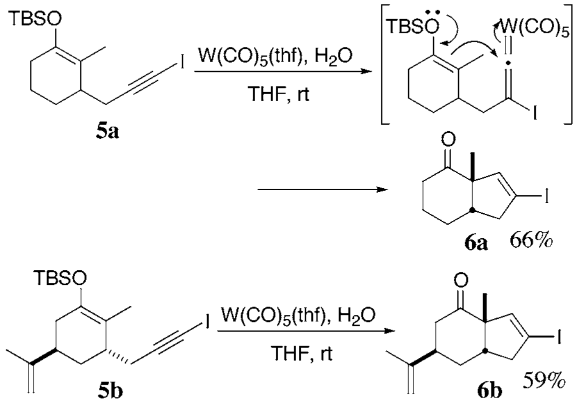

3a'

(12) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

(13) To our knowledge, only two methods have been reported for the transition metal-promoted nucleophilic 5-endo-dig carbocyclization besides our original contribution;[4a] see: (a) McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691. (b) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339. (c) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1071. See also: (d) Amrein, S.; Studer, A. *Chem. Commun.* **2002**, 1592. (e) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492.

(14) Reaction in the presence of DABCO needs photoirradiation for smooth conversion.[4d] It is known that photoirradiation enhances dissociation of an amine from the $W(CO)_5(amine)$ complex; see: Kirtley, S. W. In *Comprehensive Organometallics Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds; Pergamon Press: Oxford, UK, 1982; Vol. 3, p 1079.

Scheme 2



without any problem to afford the desired bicyclic silyl enol ethers **4** in good yields as summarized in Table 3.[15] The produced silyl enol ethers would be employable for further carbon−carbon bond-forming reaction.

Finally, this 5-endo cyclization was applied to another useful reaction, that is, the reaction of the iodinated vinylidene complexes generated from 1-iodo-1-alkynes and $W(CO)_5$(thf).[4c] Thus, when the ω-iodoacetylenic silyl enol ether **5a** was treated with an equimolar amount of $W(CO)_5$(thf) in the presence of 15 molar amounts of H_2O, the reaction proceeded smoothly at room temperature to give the iodo-substituted cyclopentene derivative **6a** in 66% yield. Although this cyclization required a stoichiometric amount of $W(CO)_5$(thf), the iodo-substituted cyclopentene derivatives were obtained in good yields without formation of the alternative iodine positional isomer.

In conclusion, we have developed an efficient method for the annulation of a simple three carbon unit onto α,β-unsaturated ketones by the indium-mediated propargylation followed by the $W(CO)_5$(thf)-catalyzed cyclization to give cyclopentene derivatives in good yield. Very rare 5-endo-dig carbocyclization was found to proceed smoothly in all cases. This reaction should be of practical use due to its simple procedure and the high utility of the products.

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Supporting Information Available: Preparative methods and spectral and analytical data of compounds **2**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Isolated products **4a**, **4e**, and **4f** were gradually isomerized to the bicyclo[4.3.0]nona-1,8-diene derivatives.