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A Novel Reaction for Annulation onto α,β-Unsaturated Ketones: $W(CO)_5$·L Promoted *Exo*- and *Endo*-Selective Cyclizations of ω-Acetylenic Silyl Enol Ethers Prepared by 1,4-Addition of Propargyl Malonate to Enones

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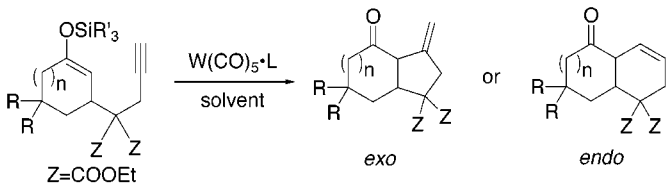
ABSTRACT



A highly useful method for five- and six-membered ring annulation onto α,β-unsaturated ketones is described. 1,4-Addition of propargylmalonate to α,β-unsaturated ketones in the presence of silyl triflate gives 7-siloxy-6-en-1-yne derivatives in good yield. $W(CO)_5$·L-catalyzed cyclization of these substrates can be induced to give preferentially either *exo*- or *endo*-cyclized products in good yield simply by changing the reaction solvent.

The development of useful methods for annulating a five- or six-membered ring onto alkenes continues to be of great importance for the preparation of cyclic carbon frameworks. Especially desirable are methods allowing selective preparation of either five- or six-membered carbocycles from the same starting materials by slight adjustment of the reaction conditions.[1] We have recently reported a novel method for the *endo*-selective cyclization of ω-acetylenic silyl enol ethers using a catalytic amount of $W(CO)_5$·THF, and when a 7-siloxy-6-en-1-yne derivative was employed as substrate under these conditions, either the *exo*- or *endo*-cyclized product could be obtained via the alkyne−$W(CO)_5$ π-complex and/or the corresponding vinylidene complex by changing the reaction solvent.[2,3] In this Letter is described a highly useful method for five- and six-membered ring annulation

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(1) Only a few papers on such reactions have been reported. See for examples: (a) Negishi, E.; Tour, J. M. *Tetrahedron Lett.* **1986**, *27*, 4869. (b) Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544. (c) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Tetrahedron Lett.* **1996**, *37*, 2003. (d) Kim, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 67.

(2) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928. See also: (a) Maeyama, K.; Iwasawa, N. *J. Org. Chem.* **1999**, *64*, 1344. (b) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226. (c) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814.

(3) There are only a few methods for the *endo*-selective intramolecular nucleophilic addition of carbon nucleophiles to alkynes. For examples, 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) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4081. See also: McDonald, F. E. *Chem. Eur. J.* **1999**, *5*, 3103.

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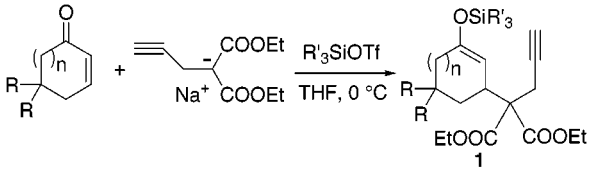
onto α,β-unsaturated ketones based on the following strategy: 1,4-addition of propargylmalonate to α,β-unsaturated ketones in the presence of silyl triflate, followed by either an *exo*- or an *endo*-selective cyclization, both catalyzed by $W(CO)_5$·L.

In the first place, the 1,4-addition of propargylmalonate to cyclohexenone followed by in situ trapping of the intermediate enolate as a silyl enol ether was examined. Although no reaction occurred when the Na salt of propargylmalonate was treated with cyclohexenone in THF at 0 °C, addition of TBSOTf to the reaction mixture induced instantaneous formation of the desired substrate **1a**, a 7-siloxy-6-en-1-yne, in good yield.[4] Several cycloalkenones were converted to the corresponding products according to this procedure in moderate to good yields as shown in Scheme 1.

Scheme 1



n=1, R=H, R'$_3$Si=*t*-BuMe$_2$Si (**1a**): 80% n=1, R=Me, R'$_3$Si=*i*-Pr$_3$Si (**1d**): 79%
n=1, R=H, R'$_3$Si=*i*-Pr$_3$Si (**1b**): 81% n=2, R=H, R'$_3$Si=*i*-Pr$_3$Si (**1e**): 59%
n=0, R=H, R'$_3$Si=*i*-Pr$_3$Si (**1c**): 85% n=3, R=H, R'$_3$Si=*i*-Pr$_3$Si (**1f**): 49%

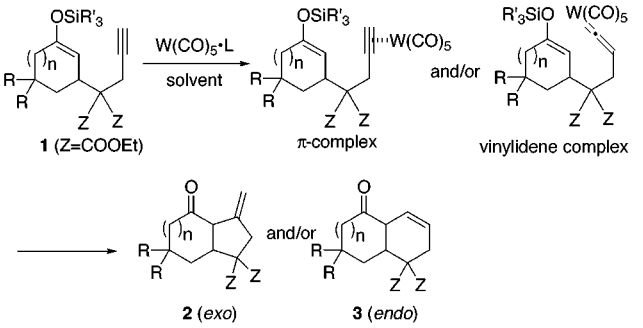
Since an efficient method for preparation of the requisite substrates had been established, the reaction conditions for the $W(CO)_5$·L catalyzed cyclization were next examined employing **1a** (n = 1, R = H, R′$_3$Si = *t*-BuMe$_2$Si) as a substrate. For *exo*-cyclization, the reaction proceeded cleanly through an alkyne−$W(CO)_5$ π-complex on carrying out the reaction at room temperature in THF with a 10 mol % amount of preformed $W(CO)_5$·THF in the presence of H_2O (conditions A), to give bicyclo[4.3.0]nonanone **2a** (n = 1, R = H) in high yield[5] (Table 1, entry 1). On the other hand, the most favorable conditions for the *endo*-cyclization reported earlier ($W(CO)_6$, H_2O, CH_2Cl_2, direct irradiation)[2] gave only about a 1:1 mixture of *endo*- and *exo*-cyclized products (Table 1, entry 2). We went on to examine how to improve this selectivity, the results being summarized in Table 1. As is clear from this table, the bulkiness of the silyl group has a significant influence on the *endo* vs *exo* selectivity, with a bulky silyl group[6] favoring formation of the *endo*-cyclized product. Of the several solvents examined, toluene gave the best result. Thus, by directly irradiating a mixture of $W(CO)_6$ and a substrate containing the TIPS group **1b** (n = 1, R = H, R′$_3$Si = *i*-Pr$_3$Si) in toluene in the presence of H_2O (conditions B), the cyclized product was obtained in 81% yield with high *endo* vs *exo* selectivity (*endo* **3a**:*exo* **2a** = 97:3).[5,7,8] In this reaction, both *exo*- and *endo*-cyclized products were obtained as single diastereomers, whose stereochemistries were assigned as *cis* in both cases using NOE experiments.

(4) It should be noted that TBSOTf does not silylate Na propargylmalonate but works as an effective activator of cyclohexenone.

(5) It is necessary to carry out column chromatography using silica gel deactivated with 10% H_2O, as otherwise, partial isomerization of the double bond occurs to give α,β-unsaturated ketones.

(6) Rücker, C. *Chem. Rev.* **1995**, *95*, 1009.

Table 1. Influenece of the Reaction Solvent and the Silyl Group on the *Exo* vs *Endo* Selectivity Using **1a** and **1b** (n = 1, R = H) as Substrate



entry	SiR′$_3$	solvent	yield/%	*exo*:*endo*
1	SiMe$_2$*t*-Bu (**1a**)	THF[a]	97	>95:5
2	SiMe$_2$*t*-Bu	CH_2Cl_2[b]	62	42:58
3	SiMe$_2$*t*-Bu	benzene[b]	89	17:83
4	SiMe$_2$*t*-Bu	toluene[b]	73	15:85
5	Si*i*-Pr$_3$ (**1b**)	CH_2Cl_2[b]	79	9:91
6	Si*i*-Pr$_3$	toluene[b]	81	3:97

[a] Conditions A: 10 mol % of $W(CO)_5$·THF, ~3 molar amounts of H_2O, rt. [b] Conditions B: 110−150 mol % of $W(CO)_6$, ~3 molar amounts of H_2O, *hν*.

Since the optimal conditions for the selective preparation of both *exo*- and *endo*-cyclized products have been established, reactions of several other cyclic substrates **1c** to **1f** were examined under these conditions. As summarized in Table 2, all the *exo*-cyclizations proceeded smoothly to give the corresponding bicyclic methylenecyclopentane derivatives **2**[5,9] in high yields by the use of a 10 mol % amount of $W(CO)_5$·THF (conditions A). For the *endo*-selective cyclization, a modest to good level of selectivity for formation of cyclohexene derivatives **3** was realized in most cases by directly irradiating a mixture of $W(CO)_6$ and substrate in

Table 2. Construction of Bicyclo[*m*.3.0] and Bicyclo[*m*.4.0] Systems Using $W(CO)_5$·L Catalyzed Cyclization ($m = n + 3$)

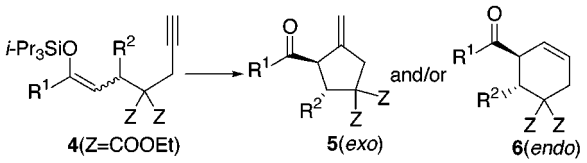
		conditions A[a]		conditions B[b]	
n	R	yield/%	*exo*:*endo*	yield/%	*exo*:*endo*
0	H (**1c**)	quant.	>95:5	86	13:87
1	H (**1b**)	quant.	>95:5	81	3:97
1	Me (**1d**)	quant.	>95:5	80	30:70
2	H (**1e**)	quant.	>95:5	44	25:75
3	H (**1f**)	95	91:9	77[c]	17:83

[a] Conditions A: 10 mol % of $W(CO)_5$·THF in THF, ~3 molar amounts of H_2O, rt. [b] Conditions B: 110−150 mol % of $W(CO)_6$ in toluene, ~3 molar amounts of H_2O, *hν*. [c] MeOH was used as a proton source.

toluene in the presence of H_2O (conditions B).[5,7,10] Thus, we can prepare synthetically useful bicyclo[*m*.3.0] and bicyclo-[*m*.4.0] systems from the same starting materials via the same intermediates simply by changing the reaction conditions in the final step.

We next applied this annulation reaction to acyclic systems.[11] On carrying out the reaction in THF with a 10 mol % amount of $W(CO)_5$·THF, *exo*-selective cyclization proceeded again without any problem and the corresponding methylenecyclopentanes **5** were obtained in high yields (Table 3). In every case examined only one diastereomer

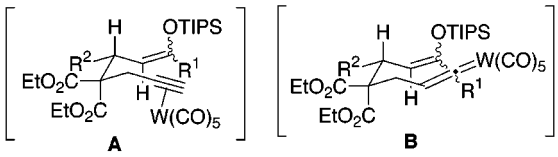
Table 3. *Exo*- and *Endo*-Selective Cyclization of Acyclic Systems



		conditions A[a]		conditions C[b]	
R^1	R^2	yield/%	*exo*:*endo*	yield/%	*exo*:*endo*
Ph	Ph(major)	99	>95:5	71	23:77
Ph	Ph(minor)	88	>95:5	70	23:77
Ph	Me	quant.	>95:5	70	16:84
Et	Me	96	>95:5	68	30:70

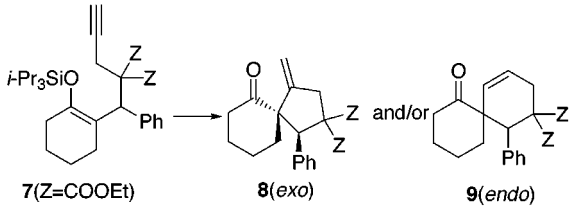
[a] Conditions A: 10 mol % of $W(CO)_5$·THF in THF, ~3 molar amounts of H_2O, rt. [b] Conditions C: 100−130 mol % of $W(CO)_5$·MeOH in toluene, ~4 molar amounts of MeOH, rt.

was obtained, whose relative stereochemistry was confirmed by NMR analysis to be *trans* regardless of the geometry of the starting material double bond.[12] The corresponding *endo*-cyclized products **6** were obtained in moderate to good selectivity on carrying out the reaction in toluene, employing the complex prepared by irradiating $W(CO)_6$ in toluene in the presence of MeOH (conditions C).[13] Again, only one diastereomer (*trans*) was obtained.[11] These diastereoselectivities are readily understood by considering the conformation of the molecules when the silyl enol ether attacks the π-complex or the vinylidene complex as depicted in **A** and **B**.



Finally, this reaction was applied to the formation of a spirocyclic skeleton. Although the selectivity for formation of the *endo*-cyclized product **9** was not necessarily high, both *exo*- and *endo*-cyclized spirocyclic compounds could be obtained as a single diastereomer by changing the reaction solvent. The stereochemistry of the *exo*-cyclized product **8** was determined to be as shown in Scheme 2 by X-ray analysis.

Scheme 2



conditions A: 94% yield, *exo* only
conditions C: 71% yield, *exo* : *endo* = 40 : 60.

In conclusion, we have developed a useful method for five- and six-membered ring annulation onto α,β-unsaturated ketones. By this novel protocol, we can prepare two types of synthetically useful compounds from the same starting materials via the same intermediates simply by changing the reaction conditions. Due to its simple reaction procedure and wide generality, this reaction should find wide use in the synthesis of such cyclic molecules.

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Supporting Information Available: Preparative methods and spectral and analytical data of compounds **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) It is necessary to control the irradiation time when the reaction is run under conditions B. Longer irradiation results in a decrease in yield of the *endo*-cyclized product.

(8) Use of a catalytic amount of $W(CO)_6$ in toluene slightly lowered the *endo* selectivity, while the reaction with a stoichiometric amount of $W(CO)_5$·THF in THF gave the *exo*-cyclized product selectively. Thus, the amount of $W(CO)_6$ employed is not the cause for this difference of the *exo* vs *endo* selectivity.

(9) Under conditions A, *exo*-cyclized products **2a**−**2e** were obtained as a single isomer, whose stereochemistry (ring junction) was confirmed to be *cis* by NOE experiments. **2f** was obtained as a 10:1 isomeric mixture of two *exo*-cyclized products, accompanied by a small amount of *endo*-cyclized product **3f**.

(10) Under conditions B, all *endo*-cyclized products **3a**−**3f** were obtained as a single isomer. The stereochemistry (ring junction) of **3a**−**3d** was confirmed to be *cis* by NOE experiments. That of **3e** and **3f** was tentatively assigned as *trans*, because we could not observe NOE between protons on the ring junction. We are currently trying to confirm the stereochemistry of these two products.

(11) When acyclic α,β-unsaturated ketones were employed as Michael acceptors, in some cases 1,4-addition of propargylmalonate did not proceed smoothly in THF. In such cases, the Na propargylmalonate was prepared in Et_2O, the solvent was removed in vacuo, and then the 1,4-addition reaction was carried out in the presence of TIPS triflate in CH_2Cl_2. By this modified procedure, the desired substrates **4** were obtained in good yields.

(12) See the Supporting Information for the details of the method for the determination of the stereochemistry of the starting materials and the products.

(13) Use of $W(CO)_5$·MeOH complex prepared by irradiation of $W(CO)_6$ in toluene in the presence of MeOH (conditions C) gave slightly better results than the direct irradiation method (conditions B).