ORGANIC LETTERS

2002
Vol. 4, No. 13
2217−2219

# Stereoselective Synthesis of Cycloheptanone Derivatives via an Intermolecular [5 + 2] Cycloaddition Reaction

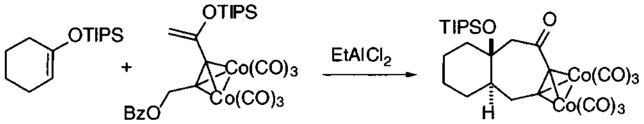
**Keiji Tanino,* Fumikatsu Kondo, Tadashi Shimizu, and Masaaki Miyashita***

*Division of Chemistry, Graduate School of Science, Hokkaido University,*
*Sapporo 060-0810, Japan*

*ktanino@sci.hokudai.ac.jp*

Received April 22, 2002

## ABSTRACT



**A [5 + 2] cycloaddition reaction of a new five-carbon unit was developed on the basis of a dicobalt hexacarbonyl propargyl cation species. Under the influence of $EtAlCl_2$, [5-benzoyloxy-2-(triisopropylsiloxy)-1-penten-3-yne)]dicobalt hexacarbonyl reacted with enol triisopropylsilyl ethers to yield seven-membered dicobalt acetylene complexes in good yield. The reactions with cyclic enol silyl ethers as well as acyclic enol silyl ethers exhibited remarkably high diastereoselectivity. The cycloadducts can be easily converted into various kinds of cycloheptanone derivatives.**

The development of an efficient method for constructing highly substituted carbocycles continues to be a significant subject in modern organic synthesis. Although a cycloaddition approach that produces two C−C bonds in one stage is advantageous from the viewpoint of efficiency, the utility of this type of reaction is critically dependent on regioselectivity as well as diastereoselectivity. In this regard, much less attention has been given to the cycloaddition approach in cycloheptane synthesis,[1] whereas the Diels−Alder reaction is recognized as a powerful method for the regio- and stereoselective construction of six-membered rings.

There are two approaches giving rise to cycloheptane derivatives, namely, a [4 + 3] and a [5 + 2] cycloaddition reaction. Although [4 + 3]-type reactions have actually found widespread use in organic synthesis,[2] a relatively small number of examples has been reported on [5 + 2]-type reactions. Thus, although intramolecular [5 + 2] cycloaddition reactions have been employed for constructing polycyclic carbon frameworks,[3,4] there has been limited work concerning intermolecular versions.[5]

Recently, we have reported an efficient method for methylenecycloheptane synthesis via an intermolecular [5 + 2] cycloaddition reaction using a hexacarbonyldicobalt acetylene complex.[6] In this transformation, the large bond angles and the rigid conformation of the dicobalt acetylene complex[7] were quite effective for stereoselective cyclization

---

[1] For a review of cycloheptane synthesis, see: (a) Ho, T. L. *Carbocycle Construction in Terpene Synthesis*; VCH Publishers: New York, 1988. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007.

[2] For reviews of [4 + 3] cycloaddition reactions, see: (a) Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 5.1, pp 593−615. (b) Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1−19. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611−4659. (d) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163−344. (e) Harmata, M. *Tetrahedron* **1997**, *53*, 6235−6280.

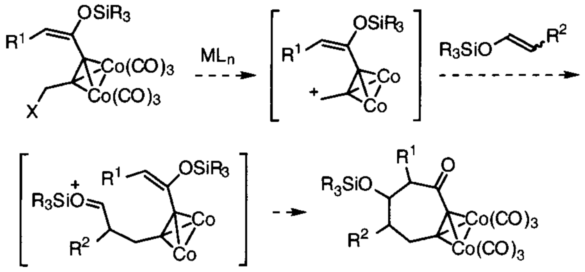
[3] For metal-catalyzed intramolecular [5 + 2] cycloaddition reactions, see: (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. (b) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203−7220. (c) Trost, B. M.; Shen, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313−2316. (d) Wender, P. A.; Bi, C. L.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105−2108 and references therein.

[4] For intramolecular [5 + 2] cycloaddition reactions using oxidopyrylium, see: (a) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954−8957. (b) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D., Jr.; Wilhelm, R. S.; Williams, P. D. *J. Am.*

10.1021/ol020086w CCC: $22.00

to a seven-membered ring.[8] The novel stereochemical outcome of the [5 + 2] cycloaddition reaction, including selective formation of a *trans*-fused bicyclic compound, led us to develop a new method for highly regio- and stereoselective synthesis of cycloheptanone derivatives (Scheme 1).

**Scheme 1**



**Scheme 2.** Preparation of the Five-Carbon Units

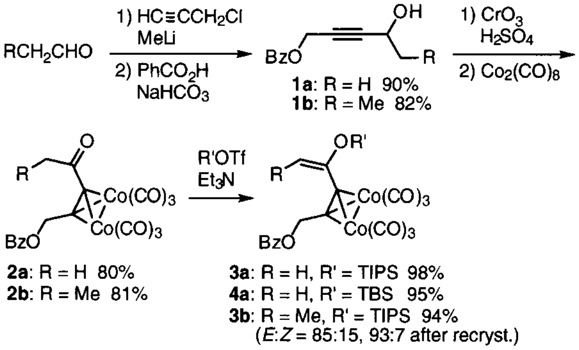
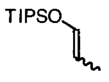
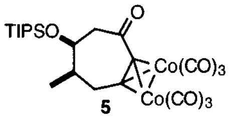
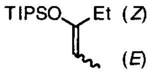
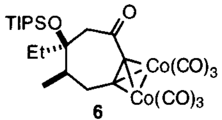
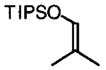
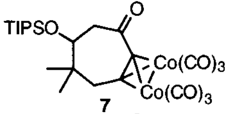
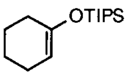
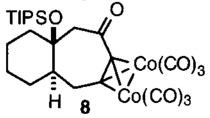
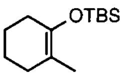
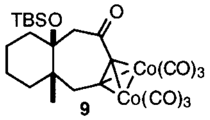
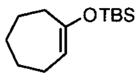
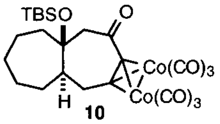


**Table 1.** [5 + 2] Cycloaddition Reactions with Enol Silyl Ethers[a]

| entry | enol silyl ether | cobalt complex | product[2] | %yield (ratio)[3] |
|---|---|---|---|---|
| 1 |  (*Z*) | **3a** |  **5** | 84<br>(93:7) |
| 2 | (*E*) | **3a** | | 82<br>(92:8) |
| 3 |  (*Z*) | **3a** |  **6** | 57<br>(single[4]) |
| 4 | (*E*) | **3a** | | 62<br>(single[4]) |
| 5 |  | **3a** |  **7** | 90<br>( - ) |
| 6 |  | **3a** |  **8** | 98<br>(single[4]) |
| 7 |  | **4a** |  **9** | 73<br>(single[4]) |
| 8 |  | **4a** |  **10** | 84<br>(single[4]) |

[a] A mixture of an enol silyl ether and 1.1 equiv of the cobalt complex in $CH_2Cl_2$ was treated with 2.2 equiv of $EtAlCl_2$ at 0 °C. [2] Structures of major diastereomers are depicted. [3] Diastereomeric ratio determined by proton NMR spectra. [4] Minor diastereomers were not detected by proton NMR spectra.

Five-carbon units **3a**, **3b**, and **4a** were easily prepared as shown in Scheme 2. The [5 + 2] cycloaddition reactions of **3a** and **4a** with several enol silyl ethers were examined under the influence of $EtAlCl_2$, and the desired cycloadducts were obtained in good to high yields (Table 1). It should be noted that only a slight amount of byproducts arising from homocoupling of **3a** or **4a** was detected, which allowed us to perform the reaction with 1.1 equiv of the five-carbon unit.

Several stereochemical features of the present cycloaddition reaction are noted:[9] (1) In the reactions of acyclic enol silyl ethers, both of the geometrical isomers afforded the same diastereomer as a major product (entries 1−4). (2) A *trans*-fused bicyclic compound was obtained from the corresponding cyclic enol silyl ether (entries 6 and 8), except that the enol silyl ether of 2-methylcyclohexanone yielded *cis*-fused cycloadduct **9** (entry 7).

These results can be rationalized by the transition state modes that correspond to the intramolecular cyclization step of a silyloxonium ion intermediate (Figure 1).[7]

In these models, the antiperiplanar transition state (**TS-1**) may be favored over the synclinal transition state (**TS-2**)

---

*Chem. Soc.* **1989**, *111*, 8957−8958. (c) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897−7898. (d) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976−12977.

(5) For intermolecular [5 + 2] cycloaddition reactions, see: (a) Wender, P. A.; Mascareñas, J. L. *Tetrahedron Lett.* **1997**, *33*, 2115−2118. (b) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−110977. (c) Wender, P. A.; Gamber, G. G.; Scanio, M. J. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3895−3897 and references therein.

(6) Tanino, K.; Shimizu, T.; Miyama, M.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 6116−6117.

(7) For reviews of synthetic utility of cobalt-complexed propargyl cations, see: (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214. (b) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 685−702.

(8) For selected examples of seven-membered dicobalt acetylene complexes, see: (a) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128−3130. (b) Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509−2520. (c) Brook, M. A.; Urschey, J.; Stradiotto, M. *Organometallics* **1998**, *17*, 5342−5346. (d) Patel, M. M.; Green, J. R. *Chem. Commun.* **1999**, 509−510. (e) Iwasawa, N.; Satoh, H. *J. Am. Chem. Soc.* **1999**, *121*, 7951−7952. (f) Iwasawa, N.; Sakurada, F.; Iwamoto, M. *Org. Lett.* **2000**, *2*, 871−873. (g) Lu, Y.; Green, J. R. *Synlett* **2001**, 243−247. (h) Green, J. R. *Synlett* **2001**, 353−356. (i) Burlison, J. A.; Gray, J. M.; Young, D. G. *Tetrahedon Lett.* **2001**, *42*, 5363−5365.

(9) The configuration of **3b**, **9**, and **11** was directly established by X-ray crystallographic structure determination. The stereochemistry of **5** and **8** was determined by X-ray crystallographic analysis of the corresponding derivatives (Supporting Information). The stereochemistry of **6** and **10** was suggested from the analogy to the corresponding analogue reported in ref 7.

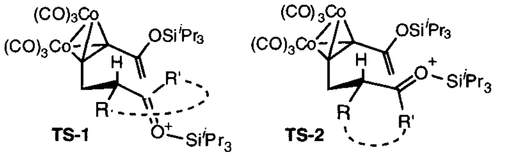
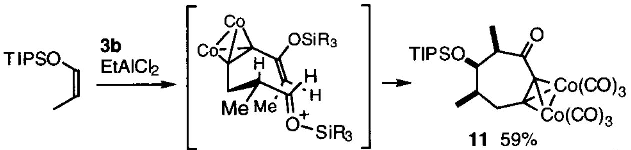


**Figure 1.** Transition-state models of the cyclization reactions.

because of the greater orbital overlap between the oxonium ion and the enol silyl ether moiety. It is noteworthy that the conformations of both **TS-1** and **TS-2** are controlled by the sole stereogenic center having an equatorial R group and an axial hydrogen. Consequently, the absence of a hydrogen at the stereogenic center may lead to different stereoselection in the cycloaddition reaction, which is consistent with the exceptional result in entry 7. The validity of the transition state models was further demonstrated by using **3b**, which afforded cycloadduct **11** in high stereoselectivity (Scheme 3).

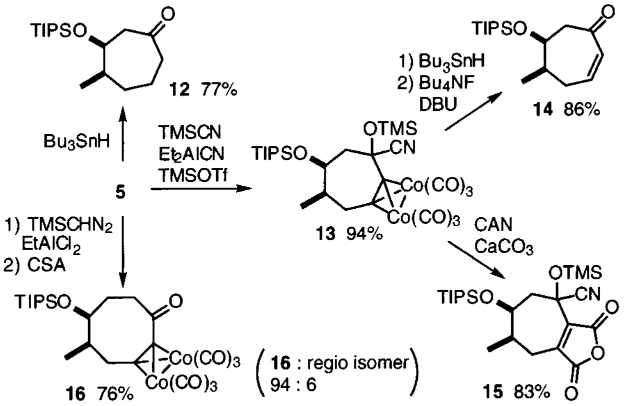
**Scheme 3**



(**11**: diastereomers = 97 : 3)

The seven-membered products having a carbonyl group as well as a dicobalt acetylene complex moiety show promise for useful transformations (Scheme 4). Under the influence of tributyltin hydride,[10] cycloadduct **5** underwent hydrogenolysis of the dicobalt acetylene complex moiety to give cycloheptanone **12**, and the corresponding cyanohydrin derivative **13** afforded an olefin that was converted to cycloheptenone **14** in high overall yield. On the other hand, treatment of **13** with ceric ammonium nitrate effected clean transformation into maleic anhydride derivative **15**.[7,11] A one-carbon ring expansion reaction mediated by (trimethylsilyl)diazomethane was also examined,[12] and cyclooctanone derivative **16** was obtained in good yield. The incorporation of a methylene group predominantly occurred at the opposite side of the bulky dicobalt acetylene complex moiety, which contrasts with the observation that a Co-complexed alkynyl group acts as an efficient migrating group in a 1,2-rearrangement reaction.[13]

**Scheme 4**



In conclusion, a new synthetic method for cycloheptanone derivatives was developed on the basis of a [5 + 2] cycloaddition reaction using a dicobalt hexacarbonyl propargyl cation species. It should be noted that there have been few examples of an intermolecular cycloaddition reaction that provides cycloheptane derivatives in high regio- and stereoselectivity. The complete regioselection and high diastereoselectivity of the present method coupled with the novel transformation of the cyclization product show promise for natural product synthesis.[14]

**Acknowledgment.** We thank Professor T. Inabe, Dr. M. Matsuda, and Mr. N. Kobayashi (Hokkaido University) for the X-ray diffraction measurements. This work was partially supported by grants from the Ministry of Education, Culture, Sports, Science and Technology, Japan (a Grant-in-Aid for Scientific Research on Priority Areas (09238104)). T.S. thanks JSPS for a predoctoral fellowship.

**Supporting Information Available:** Experimental procedures and characterization data for **1**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020086W

---

[10] Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609−2612.

[11] Schottelius, M. J.; Chen, P. *Helv. Chim. Acta* **1998**, *81*, 2341−2347.

[12] Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619−4622.

[13] Nagasawa, N.; Taya, K.; Kitamura M.; Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949−8950.

[14] (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Pavoac, F.; White, C. T. In *Total Synthesis of Natural Products*; Apsimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5, pp 333−393. (b) Fraga, B. M. *Nat. Prod. Rep.* **1996**, *13*, 307−326.