



Cyclooctanone synthesis via a formal [6+2] cycloaddition reaction of a dicobalt acetylene complex

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ABSTRACT

An efficient formal [6+2] cycloaddition reaction of a new six-carbon unit with enol silyl ether was developed on the basis of a dicobalt hexacarbonyl propargyl cation species. Under the influence of EtAlCl₂, 6-benzoyloxy-2-(triisopropylsilyloxy)-1-hexen-4-yne-dicobalthexacarbonyl reacted with enol triisopropylsilyl ethers to yield 7-(triisopropylsilyloxy)-3-cyclooctyn-1-one-dicobalthexacarbonyl derivatives in good yield. The reactions with cyclic enol silyl ethers as well as acyclic enol silyl ethers exhibited remarkably high diastereoselectivity.

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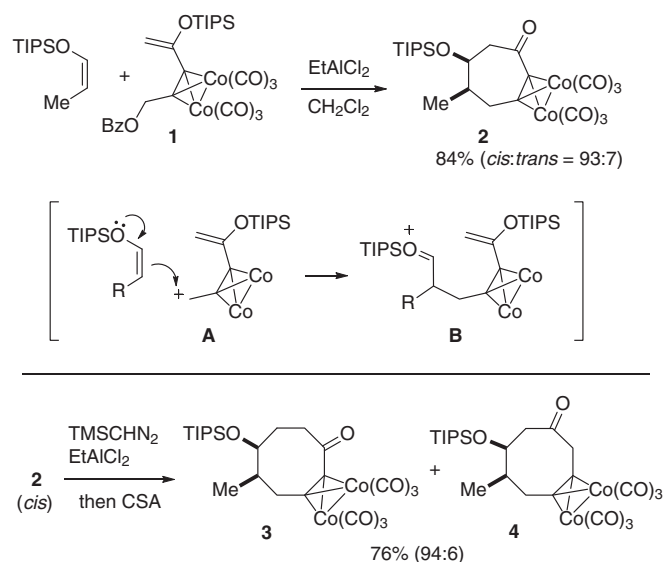
The development of an efficient synthetic method for medium-sized alicyclic compounds has been one of the most challenging subjects in organic chemistry. It has been well recognized that construction of eight-membered rings,¹ which are found as the core skeleton of many biologically active compounds, is much more difficult than that of five-, six-, or seven-membered rings. Thus, both nonbonding interactions and the entropic effects impede closure of an eight-membered ring and promote intermolecular reactions.

On the other hand, we reported a novel method for the stereoselective synthesis of cycloheptanones via a formal [5+2] cycloaddition reaction using dicobalt acetylene complex² **1** as a five-carbon unit (Scheme 1).³ The reaction proceeds through intermolecular addition of enol triisopropylsilyl (TIPS) ether with the dicobalt propargyl cation **A** (Nicholas reaction)⁴ giving rise to the silyloxonium ion **B** which in turn undergoes an intramolecular addition reaction. In this transformation, the large bond angles⁵ of the dicobalt acetylene complex moiety were essential to avoid the formation of a five-membered ring via an intramolecular cyclization reaction of the cation intermediate **A**. In addition, the rigid conformation of the dicobalt acetylene complex moiety may play an important role to control the stereochemistry in the cyclization step of the intermediate **B**.

While cycloheptanone **2** could be transformed into cyclooctanone **3** via the one-carbon ring expansion protocol of Shioiri,⁶ we became intrigued with the possibility of a formal [6+2] cycloaddition reaction for the direct synthesis of cyclooctanone derivatives (Scheme 2).

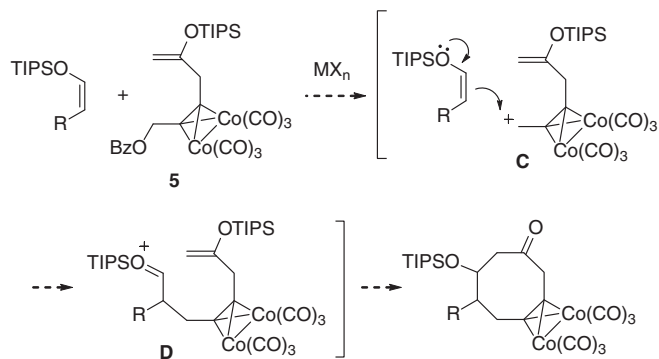
There has been few examples of [6+2] cycloaddition reactions which are applicable for the synthesis of a monocyclic eight-membered compound. While an α -vinylcyclobutanone was used

as a six-carbon unit of an intramolecular formal [6+2] cycloaddition reaction promoted by a Rh(I) catalyst,⁷ the intermolecular version of the cycloaddition reaction has not been reported. On the other hand, 1,3,5-cycloheptatriene,⁸ tropone,⁹ and 1,3,5-cyclooctatriene¹⁰ serve as a useful six-carbon unit of intermolecular cycloaddition reactions, but the products arising from the [6+2] cycloaddition reaction with an olefin or an acetylene always possess a bicyclo[4.2.1]nonane or a bicyclo[4.2.2]decane carbon framework.



Scheme 1. Synthesis of cyclooctanone derivatives via a formal [5+2] cycloaddition reaction and one-carbon ring expansion.

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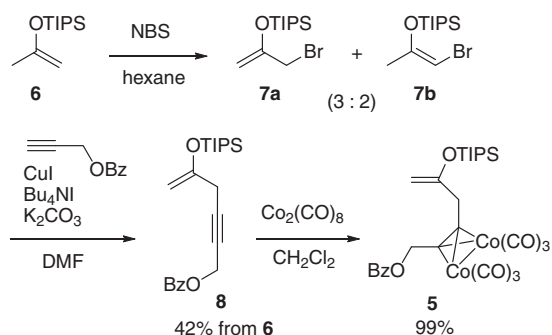
Scheme 2. The formal [6+2] cycloaddition reaction of enol silyl ether and dicobalt acetylene complex **5**.

We herein report that the use of the hexacarbonyl dicobalt acetylene complex **5** as a six-carbon unit opens the door to the stereoselective synthesis of both mono- and bicyclic cyclooctanone derivatives via an intermolecular formal [6+2] cycloaddition reaction. The six-carbon unit **5** was prepared as shown in Scheme 3.¹¹ Treatment of enol silyl ether **6** with NBS afforded an inseparable mixture of allyl bromide **7a** and vinyl bromide **7b** in a 3:2 ratio. The mixture was subjected to the copper-catalyzed cross-coupling reaction¹² with propargyl benzoate, resulting in the selective consumption of **7a**. The six-carbon unit **5** was obtained in quantitative yield by the reaction of the coupling product **8** with $\text{Co}_2(\text{CO})_8$.

The formal [6+2] cycloaddition reactions of **5** 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).¹³ It is noteworthy that no by-product arising from intramolecular cyclization or homo-coupling of the cobalt complex was detected, which allowed us to perform the reaction with 1.1 equiv of the six-carbon unit. In addition, the present reactions afforded satisfactory results without using a high dilution technique, which is often employed to decrease the probability of an encounter between the reactive centers of two different molecules.

Stereochemical features of the formal [6+2] cycloaddition reactions are similar to those of the previously described formal [5+2] cycloaddition reactions.^{3,14} Thus, acyclic enol silyl ethers mainly afforded the products **9c**, **9d**, and **9e** in which the silyloxy group and the alkyl substituent on the neighboring carbon atom are arranged *cis* to each other (entries 3–5). On the other hand, trans-fused bicyclic compound **9f** was obtained from a cyclic enol silyl ether as a single isomer (entry 6).

These results can be rationalized by the transition state models which correspond to the intramolecular cyclization step of a silyloxonium ion intermediate **D** in Scheme 2. Taking into account the rigidity as well as the bulkiness of the dicobalt hexacarbonyl



Scheme 3. Preparation of the six-carbon unit.

Table 1
Stereoselective synthesis of cyclooctanone derivatives by formal [6+2] cycloaddition reactions^a

Entry	Enol silyl ether	Product ^b	Yield ^c (<i>cis:trans</i>)
1			9a 91% (–)
2			9b 96% (–)
3			9c 73% (88:12)
4			9d 68% (single ^d)
5			9e 83% (86:14)
6			9f 81% (single ^d)

^a The typical procedure is described in Ref. 13.

^b Structures of major diastereomers are depicted.

^c Diastereomeric ratio determined by proton NMR spectra.

^d Minor diastereomers were not detected by proton NMR spectra.

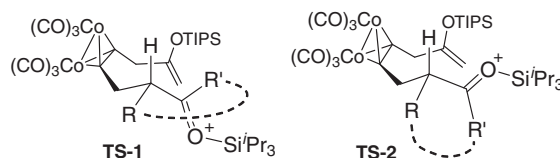
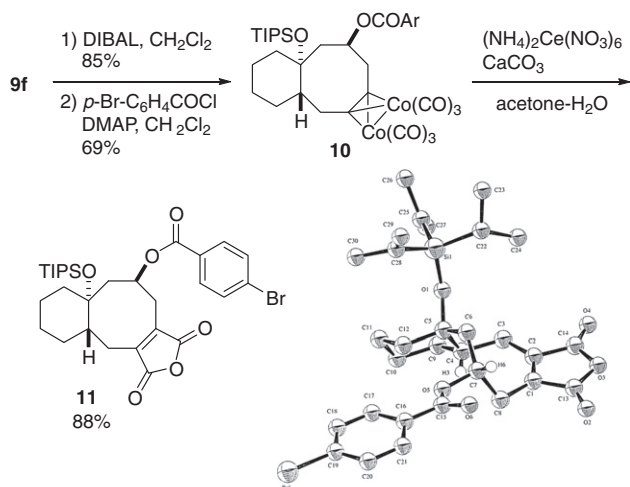


Figure 1. Transition state models of the cyclization reactions.

acetylene moiety, two transition state models in which the R group occupies an equatorial position can be depicted (Fig. 1). In these models, the antiperiplanar transition state **TS-1** may be favored over the synclinal transition state **TS-2** because of the greater $\pi^*-\pi$ orbital overlap between the oxonium ion and the enol silyl ether moiety.¹⁵

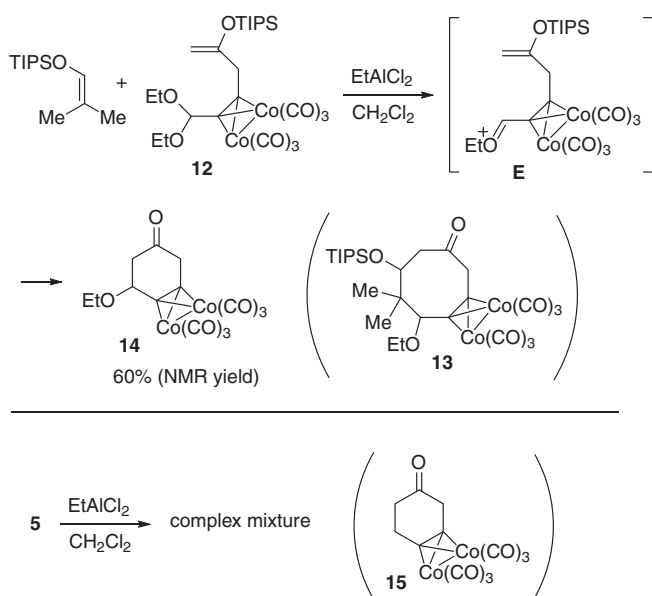
The configurations of the cyclooctanones were determined as follows. Since the major diastereomer of adduct **9c** was identical with cyclooctanone **4**³ in Scheme 1, the *cis* relationship between the methyl group and the silyloxy group was confirmed, which also suggested the preferential formation of the *cis* isomer of **9d** and **9e**. The stereostructure of bicyclic product **9f** was unambiguously established by X-ray crystallographic analysis after transformation



Scheme 4. Determination of the configuration of **9f**.

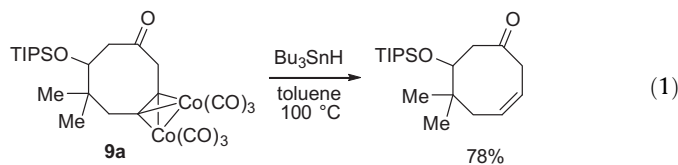
into maleic anhydride **11** (Scheme 4). Reduction of ketone **9f** with DIBAL afforded a secondary alcohol as a single isomer which in turn was acylated with *p*-bromobenzoyl chloride. Maleic anhydride **11** was obtained by treating dicobalt acetylene complex **10** with an excess amount of ceric ammonium nitrate (CAN).^{3,14,16}

In connection with application to the total synthesis of natural products having an eight-membered ring, we next explored the cycloaddition reaction using six-carbon unit **12** which was prepared in a similar manner from 3,3-diethoxy-1-propyne. Surprisingly, the reaction of **12** with enol silyl ether failed to give cyclooctanone **13**, and cyclohexanone **14** was obtained through intramolecular cyclization of the cationic intermediate **E** (Scheme 5). The result indicates that the bond angles of the dicobalt acetylene complex moiety are not large enough to prevent the formation of a six-membered ring.¹⁷ On the other hand, six-carbon unit **5** did not give the corresponding product **15** even in the absence of enol silyl ether. Although the origin of the different behavior between **12** and **5** is not clear at this point, it is important to design a six-carbon unit which does not undergo intramolecular cyclization.



Scheme 5. The different behavior of cobalt complexes **12** and **5**.

In conclusion, a new method for the stereoselective synthesis of cyclooctanone derivatives was developed on the basis of a formal [6+2] cycloaddition reaction using a dicobalt acetylene complex **5**. The cobalt complex moiety of the products can be transformed into a maleic anhydride by treating with CAN (Scheme 4), while the corresponding olefin is obtained by the decomplexation protocol of *Isobe*¹⁸ (Eq. 1). Synthetic studies on natural products having an eight-membered ring are under progress in our laboratory.



Acknowledgments

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unit **5** (0.33 g, 0.50 mmol) in CH_2Cl_2 (0.50 mL) was added a 0.96 M hexane solution of EtAlCl_2 (1.2 mL, 1.1 mmol) at -78°C . After stirring the reaction mixture at -23°C for 20 min, a saturated aq. potassium sodium tartrate was added. The mixture was stirred vigorously at rt under argon atmosphere for 30 min and separated. The aqueous layer was extracted with ether, and the combined organic layer was dried over MgSO_4 . Concentration under reduced pressure followed by purification by silica gel column chromatography (hexane then hexane/ether = 20:1) afforded 0.26 g (91%) of cycloadduct **9a**. IR (neat) 3076, 2947, 2892, 2868, 2091, 2050, 2016, 1971, 1713, 1464, 1387, 1217, 1195, 1110, 1088, 1067, 1015, 883 cm^{-1} ; ^1H NMR (CDCl_3 , 270 MHz) δ 1.06 (s, 3H), 1.08 (br s, 21H), 1.17 (s, 3H), 2.63 (dd, $J = 3.0$ and 16.2 Hz, 1H), 2.96 (dd, $J = 8.9$ and 16.2 Hz, 1H), 3.02 (s, 2H), 3.87 (d $J = 16.5$ Hz, 1H), 4.04 (d, $J = 16.5$ Hz, 1H), 4.19 (dd, $J = 3.0$ and 8.9 Hz, 1H); ^{13}C NMR (CDCl_3 , 67.5 MHz) δ

- 13.03 (3C), 18.31 (3C), 18.35 (3C), 23.73, 27.31, 42.10, 45.32, 48.03, 49.27, 75.61, 87.53, 93.67, 112.07, 199.17 (6C), 202.98; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{34}\text{O}_8\text{SiCo}_2$: 608.0687, found: 608.0710.
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