Stereoselective Synthesis of Medium-sized Cyclic Compounds through the Intramolecular Michael-type Reaction Utilizing Alkyne–Hexacarbonyldicobalt Complex Formation

Kennichi Inaba, Jun Takaya, and Nobuharu Iwasawa*
Department of Chemistry, Tokyo Institute of Technology, 2-12-1-E1-2 Ookayama, Meguro-ku, Tokyo 152-8551

(Received January 15, 2007; CL-070053; E-mail: niwasawa@chem.titech.ac.jp)

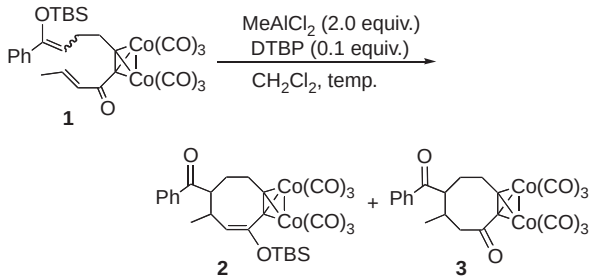
Alkyne–hexacarbonyldicobalt complexes having silyl enol ether and electron-deficient alkene moieties on opposite ends were treated with $MeAlCl_2$ in the presence of 2,6-di-*t*-butylpyridine in CH_2Cl_2 to give synthetically useful medium-sized cyclic products as a single stereoisomer in good yield.

Stereoselective formation of medium-sized ring compounds is still a formidable challenge due to the difficulty both in the medium-sized ring closure and in controlling the stereochemistry of the products.[1,2] We previously reported a novel bridged-type [4 + 2]-cycloaddition reaction of alkyne–hexacarbonyldicobalt complexes containing siloxydiene and electron-deficient alkene moieties, where the reaction was found to proceed stereoselectively through double-Michael type reaction with formation of medium-sized ring.[3] From the synthetic point of view, it is highly desirable to establish an efficient method for the stereoselective construction of medium-sized monocyclic carbon skeleton with multi-functional groups, which would enable further useful transformations. In this paper, we would like to report the stereoselective preparation of such compounds through the Michael-type ring closure, where perfect selectivity was realized by the geometry of the silyl enol ether moiety and the presence of alkyne–hexacarbonyldicobalt moiety.[4]

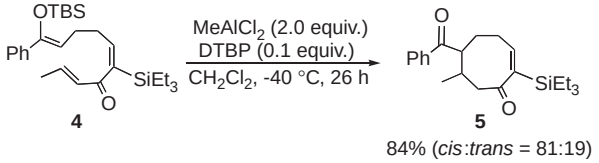
When an alkyne–hexacarbonyldicobalt complex **1** containing (*Z*)-silyl enol ether and electron-deficient alkene moieties was treated with 2 equiv. of $MeAlCl_2$ in the presence of DTBP (2,6-(di-*t*-butyl)pyridine)[5] at −78 °C in CH_2Cl_2, the desired cyclized products were obtained as a mixture of silyl enol ether **2**[6] and its hydrolyzed ketone **3** in the combined yield of 70% (Table 1, Entry 1). Both of the products were obtained as a single stereoisomer with the same relative stereochemistry,[7] whose structure was determined based on the X-ray crystal structure analysis of a compound derived from **3**. Longer reaction time increased the amount of the silyl enol ether **2**, while the reaction at −40 °C gave the hydrolyzed ketone **3** as the major product.[8] In both cases, the products were obtained as a single *cis* isomer (Table 1, Entries 2 and 3). Interestingly, when a mixture (80:20) of (*Z*)- and (*E*)-silyl enol ether **1** was subjected to the same reaction conditions, the product **2** was obtained as a diastereomeric mixture (*cis*:*trans* = 76:24) (Table 1, Entry 4). These results suggest that the stereoselectivity of this reaction is dependent on the geometry of the silyl enol ether part.[9]

To confirm the role of the alkyne–hexacarbonyldicobalt moiety for this reaction, the reaction of a corresponding olefinic substrate was examined. The substrate (*Z*)-**1** was transformed into its silylated alkene derivative (*Z*)-**4** according to the Isobe's protocol for this purpose.[10] Although the reaction of the alkene derivative (*Z*)-**4** did not proceed to an appreciable amount at −78 °C (2 equiv. $MeAlCl_2$, 0.1 equiv. DTBP, CH_2Cl_2), the reaction at −40 °C proceeded to give the cyclized product **5** in good yield but as a mixture of diastereoisomers (Scheme 1).[11] As the reaction of the corresponding alkyne–hexacarbonyldicobalt complex (*Z*)-**1** at −40 °C still gave a single stereoisomer of products **2** and **3** (Table 1, Entry 3), there is apparent difference of stereoselectivity between the alkyne–hexacarbonyldicobalt complex **1** and its alkene derivative **4**. Thus, it was confirmed that the alkyne–hexacarbonyldicobalt moiety has both accelerating effect on the reaction rate and higher control over the stereoselectivity of the reaction. As (*Z*)-silyl enol ether moiety could be easily prepared with more than 95:5 selectivity using TBSOTf in the presence of 2,6-lutidine as a base, this protocol would be a useful method for the stereoselective preparation of medium-sized compounds.

Table 1. Intramolecular Michael addition reaction of alkyne–$Co_2(CO)_6$ complex **1**



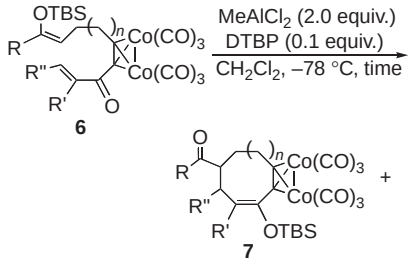
Entry	(*Z*)-**1**:(*E*)-**1**	Conditions	Product **2** (*cis*:*trans*)	Product **3** (*cis*:*trans*)
1	>95:5	−78 °C, 14.5 h	33%(>95:5)	37%(>95:5)
2	>95:5	−78 °C, 43.5 h	73%(>95:5)	6%(>95:5)
3	>95:5	−40 °C, 16.5 h	8%(>95:5)	61%(>95:5)
4	80:20	−78 °C, 24.5 h	68%(76:24)	trace



Scheme 1. Intramolecular Michael addition reaction of olefinic substrate **4**.

We next examined the generality of this stereoselective preparation of medium-sized alkyne–hexacarbonyldicobalt complex. As summarized in Table 2, this reaction showed good generality and not only β-methyl-substituted derivative, but also β-ethyl-substituted and α-methyl-substituted derivatives **6a** and **6b** gave the corresponding products in good yield stereoselectively (Entries 1 and 2).[12] Furthermore, the silyl enol ether **6c** derived from isopropyl ketone could also be applied to this reaction without problem (Entry 3).[12] Related 7 and 9-membered prod-

Table 2. Generality of the reaction

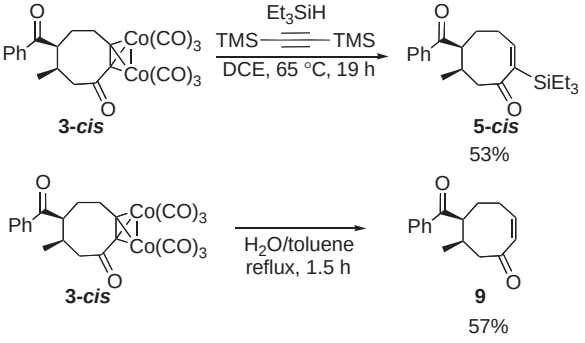


Entry	Substrate **6**					Time/h	Product **7**		Product **8**	
		R	R′	R″	*n*		Yield/%		Yield/%	
1	**6a**	Ph	H	Et	1	35.3	**7a**	69	**8a**	10
2[a]	**6b**	Ph	Me	H	1	11.5	**7b**	41	**8b**	0
3	**6c**	*i*-Pr	H	Me	1	48	**7c**	61	**8c**	0
4[a]	**6d**	Ph	H	Me	0	44	**7d**	30	**8d**	43
5	**6e**	Ph	H	Me	2	16.5	**7e**	29	**8e**	47

[a]This reaction was carried out at −40 °C.

ucts were obtained in good yield as a single diastereoisomer[12] (Entries 4 and 5). It should be noted that 9-membered ring product, which belongs to the most difficult ring size to prepare, could be obtained in good yield stereoselectively by this method.

Finally, the demetallation reaction of the cyclized product **3** was examined. Although the reaction was not fully optimized, treatment of the product **3** with Et_3SiH (10 equiv. Et_3SiH, 5 equiv. bis(trimethylsilyl)acetylene, 65 °C, $ClCH_2CH_2Cl$)[10] gave the silylated cyclooctenone derivative **5**, while simple heating of **3** in toluene–H_2O[3] gave the cyclooctenone derivative **9** in reasonable yield (Scheme 2). Thus, this cyclization–demetallation reaction would be a useful method for the stereoselective synthesis of these medium-sized cyclic compounds.



Scheme 2. Demetallation reactions of cycloadduct **3**.

In conclusion, we have developed a concise method for the stereoselective preparation of the medium-sized cyclic compounds utilizing alkyne–hexacarbonyldicobalt complex formation. Synthetically useful medium-sized ring skeletons with multiple functionalities could be prepared stereoselectively by this procedure.

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References and Notes

1 For a review on medium-sized ring formation, see: a) L. Yet, *Chem. Rev.* **2000**, *100*, 2963. b) G. Mehta, V. Singh, *Chem. Rev.* **1999**, *99*, 881. c) L. Yet, *Tetrahedron* **1999**, *55*, 9349.

2 There are only a few reports on the intramolecular Michael reaction, in particular, *endo*-mode of cyclization, to give medium-sized products. See for examples: a) G. Berthiaume, J.-F. Lavallée, P. Deslongchamps, *Tetrahedron Lett.* **1986**, *27*, 5451. b) J. Christoffers, H. Oertling, *Tetrahedron* **2000**, *56*, 1339. c) T. J. Greshock, R. L. Funk, *J. Am. Chem. Soc.* **2002**, *124*, 754. d) T. J. Greshock, R. L. Funk, *Tetrahedron Lett.* **2006**, *47*, 5437.

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5 P. V. Bonnesen, C. L. Puckett, R. V. Honeychuck, W. H. Hersh, *J. Am. Chem. Soc.* **1989**, *111*, 6070.

6 Geometry of the silyl enol ether part was determined to be (*E*) by the NOE experiment.

7 Mild acid treatment of **2** gave **3** in good yield.

8 It is likely that the aluminum enolate produced by the Michael addition was slowly silylated at −78 °C, but we are not certain why the hydrolyzed ketone **3** was obtained as the major product at −40 °C.

9 In the Lewis acid promoted intermolecular Michael addition reaction of silyl enol ethers, both (*E*)- and (*Z*)-isomers usually give the same *syn* isomer through open-transition structure.

10 S. Takai, P. Ploypradith, A. Hamajima, K. Kira, M. Isobe, *Synlett* **2002**, 588.

11 These compounds coincided with those derived from **3** by the Isobe's protocol.[10]

12 All the products obtained here are single diastereoisomers. Stereochemistry of **8e** was determined to be *cis* based on X-ray analysis of a compound derived from **8e**. **7e** was hydrolyzed to give **8e**. Although obvious determination has not yet been achieved, 8-membered ring products **7a**, **7c** and **8a**, **8c** were thought to have the same *cis* stereochemistry as **2** and **3**. The stereochemistry of the 7-membered ring products **7d** and **8d** has not yet been determined.

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