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Cycloadditions

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Complexation-Initiated Intramolecular [4+2] Cycloaddition: Construction of Bridged-Type Cycloadducts**

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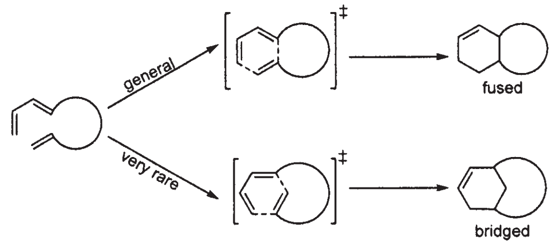
Intramolecular cycloaddition reactions of linear substrates generally give fused-type adducts selectively, owing to the favorable straight alignment of the two reacting sites (Scheme 1). There have been many examples of fused-type intramolecular Diels–Alder reactions, but very few are known for the corresponding bridged-type Diels–Alder reaction.[1,2] Even in these cases, the bridged-type adducts were obtained as minor products along with the major fused-type products.[3,4]



Scheme 1. The regioselectivity in the intramolecular [4+2] cycloaddition reaction.

We previously reported that alkynes bearing a furan diene and a dienophile unit on opposite ends, when complexed with $[Co_2(CO)_8]$, shift from a straight structure to a bent one (that is, the angle changes from 180° to around 140°). A subsequent intramolecular Diels–Alder reaction provides a mixture of the starting alkyne–$Co_2(CO)_6$ complex and the desired cyclized alkyne–$Co_2(CO)_6$ complex in equilibrium.[5] The important feature of this reaction is the ready formation of a seven-membered ring by the carbon tether. This is probably due to the rigid and planar structure of the alkyne–$Co_2(CO)_6$ moiety, compelling the two substituents at the alkyne to form an angle of about 140°,[6] which facilitates formation of the seven-membered ring.[7] We expected that this structural

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feature of the alkyne–$Co_2(CO)_6$ moiety—namely, the wider angle of alkyne substituents compared to alkene substituents—might lessen the steric congestion in the transition state and allow formation of the bridged-type adduct. Thus, by the appropriate design of substrates in which orbital or electronic control favors the formation of bridged-type products, we could carry out a bridged-type cycloaddition reaction selectively, even with simple linear substrates. Here we describe the successful development of this novel bridged-type [4+2] cycloaddition reaction of silyloxydiene derivatives[8] utilizing alkyne–$Co_2(CO)_6$ complex formation.

First, the reaction was examined using the alkyne–$Co_2(CO)_6$ complex **1**, which contains a silyloxydiene and an electron-deficient dienophile [Eq. (1); TBS = *tert*-butyldimethylsilyl]. When the reaction was carried out in the presence of 2 equivalents of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C, the desired [4+2]-cycloadduct was not obtained; instead **4**, the hydrolyzed product of the starting material, was isolated in 34 % yield (Table 1, entry 1). In contrast, when $AlCl_3$ was employed as a Lewis acid, the starting material disappeared at −78 °C, and the cycloadduct was isolated in 34 % yield along with the Michael-type adduct **3** and the hydrolyzed ketone **4** in 12 % and 26 % yields, respectively (entry 2). Among several aluminum-containing Lewis acids examined, $MeAlCl_2$ gave the best results (entry 4).[9]

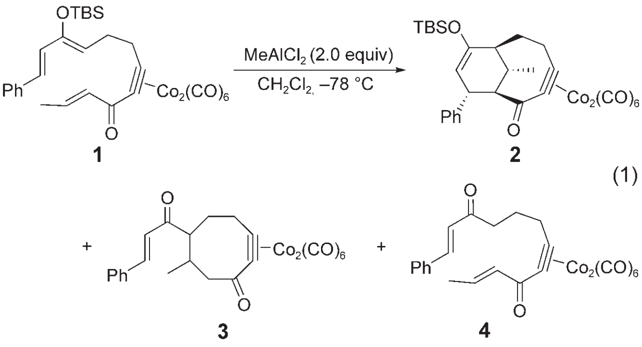


Table 1: Results of the intramolecular [4+2]-cycloaddition reaction in the presence of a Lewis acid [see Eq. (1)].

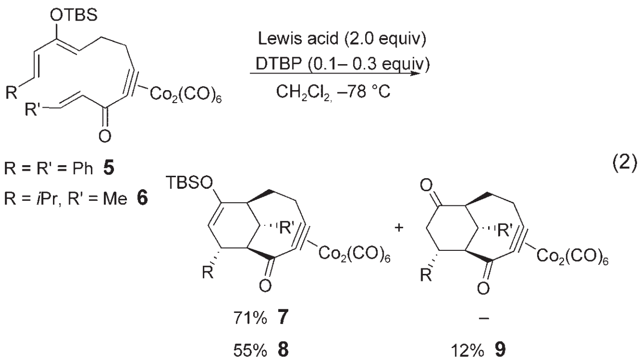
Entry	Lewis acid	*t* [h]	**2** [%]	**3** [%]	**4** [%]
1	$BF_3{\cdot}OEt_2$	0.5	0	0	34
2[a]	$AlCl_3$	25	34	12	26
3	Et_2AlCl	3.5	27	0	0
4[a]	$MeAlCl_2$	3.0	40	30	17
5[a,b]	$MeAlCl_2$	0.33	75	1	2

[a] Products **3** and **4** were obtained as an inseparable mixture. The yields were determined by ^{1}H NMR spectroscopy. [b] For this reaction 0.1 equivalent of DTBP was added.

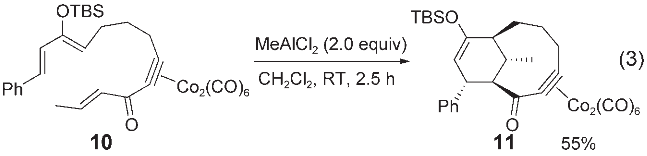
Analysis of the NMR spectra of the cycloadduct obtained demonstrated that the product was not a normal fused-type adduct, but rather the bridged-type adduct **2** having a bicyclo[5.3.1]undec-3-yn-2-one skeleton. The product was isolated as a single stereoisomer, and the structure of the adduct was confirmed by X-ray crystal structure analysis of the corresponding hydrolyzed ketone.[10] This result proves that the cycloaddition is not a concerted Diels–Alder reaction, but a stepwise, double-Michael-type reaction giving the bridged-type [4+2]-cycloadduct.[11]

To prevent hydrolysis, we further examined the reaction in the presence of 2,6-di-*tert*-butylpyridine (DTBP), which is a well-known proton scavenger.[12] When the reaction was carried out employing 2 equivalents of $MeAlCl_2$ in the presence of 0.1 equivalents of DTBP in CH_2Cl_2 at −78 °C, formation of the hydrolyzed products was efficiently suppressed and the desired product **2** was obtained in 75 % yield (Table 1, entry 5).

We then extended the scope of the reaction using several substrates. As shown in Equation (2), the same type of substrates **5** and **6** gave the corresponding bridged-type [4+2] cycloadducts in good yield as a single stereoisomer when the reaction was carried with 2 equivalents of $MeAlCl_2$ in the presence of 0.1–0.3 equivalents of DTBP in CH_2Cl_2 at −78 °C. For the reaction with substrate **6**, the [4+2]-cycloadduct **8** was accompanied by a small amount of its hydrolyzed cycloadduct **9**. The configuration of the products were determined based on the analogy of the coupling pattern of their ^{1}H NMR spectra with that of **2**.



The reaction of substrate **10**, having an additional carbon atom in the tether, also gave the desired bridged-type adduct **11** with a bicyclo[6.3.1]dodec-3-yn-2-one skeleton as a single stereoisomer in reasonable yield [Eq. (3)]. The structure was again confirmed by X-ray crystal structure analysis of the corresponding hydrolyzed ketone.[10] Furthermore, the reac-



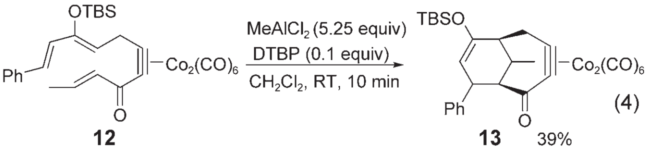
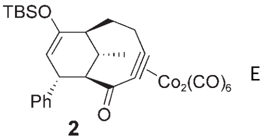
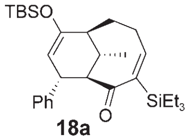
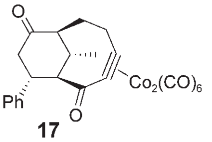
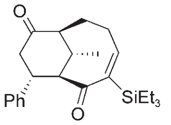
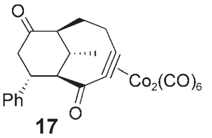
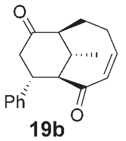
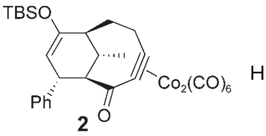
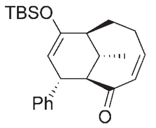


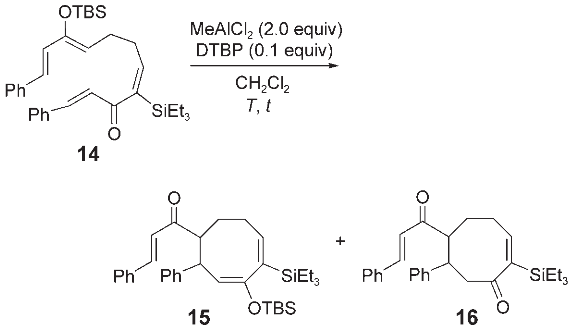
Table 3: Results of the demetalation reaction of bridged-type alkyne–$Co_2(CO)_6$ cycloadducts.[a]

Entry	Substrate	Reaction conditions	Product	Yield [%]
1	 **2**	Et_3SiH, BTMSA, DCE, 65 °C, 6.5 h	 **18a**	68
2	 **17**	Et_3SiH, BTMSA, DCE, 65 °C, 24 h	 **19a**	77
3	 **17**	$NaH_2PO_2{\cdot}H_2O$, 2-methoxyethanol, 65 °C, 2 h	 **19b**	72
4	 **2**	H_2O, toluene, reflux, 2 h	 **18b**	66

[a] BTMSA = bis(trimethylsilyl)acetylene, DCE = 1,2-dichloroethane.

tion of substrate **12**, which has one less carbon atom in the tether than **1**, also proceeded albeit in moderate yield, probably due to the severe strain of the system. The desired adduct **13**, with the bicyclo[4.3.1]dec-3-yn-2-one skeleton, was obtained in 39 % yield by carrying out the reaction with 5.25 equivalents of $MeAlCl_2$ in CH_2Cl_2 at room temperature [Eq. (4)].[13] Thus, this bridged-type [4 + 2] cycloaddition reaction shows reasonable generality with respect to the substituents and the number of carbon atoms in the tether.

We then examined the reaction of the corresponding olefinic substrate **14** to confirm the importance of the alkyne–$Co_2(CO)_6$ moiety for the formation of the bridged-type products. The vinylsilane substrate **14** was obtained in 63 % yield by reduction of **5** with triethylsilane.[14] Treatment of **14** under several typical cycloaddition reaction conditions did not give the corresponding bridged-type cycloadduct, but instead the monocyclic Michael addition products **15** and **16** in high yield [Eq. (5), Table 2]. We believe that the wider bent angle of the alkyne–$Co_2(CO)_6$ complexes releases the steric congestion of the transition state and enables the smooth formation of the bridged-type cycloadduct. However, further examination is necessary to clarify the exact role of the alkyne–$Co_2(CO)_6$ moiety.



(5)

Table 2: Results of the reactions with the olefinic substrate **14** [see Eq. (5)].

Entry	*T*	*t* [min]	**15** [%]	**16** [%]
1	−78 °C	115	65	33
2[a]	−78 °C	50	45	44
3	RT	10	trace	80

[a] DTBP was not added.

Finally, we investigated the decomplexation of the alkyne–$Co_2(CO)_6$ moiety from the bridged-type cycloadducts (Table 3). The cycloadduct **2** and its hydrolyzed ketone **17** both underwent smooth hydrosilylation of the alkyne–$Co_2(CO)_6$ moiety to give vinylsilanes **18a** and **19a** in good yields upon heating of the complexes in the presence of triethylsilane (entries 1 and 2).[15] Furthermore, the reaction of **17** with sodium hypophosphite[16] proceeded smoothly to give enone **19b** (entry 3), while the same reaction using silyl enol ether **2** resulted in a complex mixture of products. To our surprise, simple heating of complex **2** in toluene/H_2O (5/1) with vigorous stirring gave the desired decomplexed enone **18b** in good yield without hydrolyzing the silyl enol ether moiety (entry 4). Although details of this demetalation reaction remain to be explored, this method affords a simple conversion of alkyne–$Co_2(CO)_6$ complexes into the corresponding alkenes.[17]

In conclusion, we have developed a method for the preparation of bridged-type [4+2]-cycloadducts utilizing alkyne–$Co_2(CO)_6$ complex formation. Synthetically useful bicyclo[*n*.3.1] skeletons with multiple functionalities could be prepared stereoselectively by this procedure.

Experimental Section

Cyclization of **1**: The alkyne–cobalt complex **1** was purified by PTLC (hexane/CH_2Cl_2 1/1) just before use. 2,6-Di-*tert*-butylpyridine (4.20 μL, 18.4 μmol) was added to a solution of **1** (125 mg, 0.187 mmol) in CH_2Cl_2 (19 mL) at −78 °C. After 5 min a solution of $MeAlCl_2$ (0.370 mL, 0.370 mmol) in hexane (1.0 M) was added, and the mixture was stirred for 20 min at −78 °C. Then the reaction was quenched with saturate aqueous $NaHCO_3$, and the product was extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by PTLC (hexane/CH_2Cl_2 1/1) to give **2** (93.0 mg, 0.140 mmol) in 75 % yield as a dark red oil. Compounds **3** and **4** were obtained as an inseparable mixture in a 1:2 ratio (3.10 mg, 5.60 μmol) in 3% yield as a dark red oil.

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[1] a) E. Ciganek, *Org. React.* **1984**, *19*, 1; b) L. A. Paquette, *Comprehensive Organic Synthesis, Vol. 5*, Pergamon, Oxford, **1991**; c) F. Fringuelli, A. Taticchi, *The Diels–Alder Reaction: Selected Practical Methods*, Wiley, New York, **2002**.

[2] For type II intramolecular Diels–Alder reactions, see B. R. Bear, S. M. Sparks, K. J. Shea, *Angew. Chem.* **2001**, *113*, 864–894; *Angew. Chem. Int. Ed.* **2001**, *40*, 820–849.

[3] Examples for the bridged-type intramolecular Diels–Alder reaction were reported using cyclohexadienone as a dienophile unit. The *Z*-configuration of the diene part facilitates a suitable transition state for the bridged-type reaction. a) H. Greuter, G. Fráter, H. Schmid, *Helv. Chim. Acta* **1972**, *55*, 526–531; b) H. Greuter, H. Schmid, *Helv. Chim. Acta* **1972**, *55*, 2382–2400; c) G. Fráter, *Helv. Chim. Acta* **1974**, *57*, 172–179; d) H. Greuter, H. Schmid, G. Fráter, *Helv. Chim. Acta* **1977**, *60*, 1701–1729; see also G. Fráter, J. Wenger, *Helv. Chim. Acta* **1984**, *67*, 1702–1706.

[4] For the formation of the bridged-type Diels–Alder product as a minor product, see a) E. J. Corey, M. Petrzilka, *Tetrahedron Lett.* **1975**, 2537–2540; b) S. J. Bailey, E. J. Thomas, *J. Chem. Soc. Chem. Commun.* **1978**, 474–475; c) B. B. Snider, J. V. Dunćia, *J. Org. Chem.* **1980**, *45*, 3461–3464; d) A. Deagostino, J. Maddaluno, C. Prandi, P. Venturello, *J. Org. Chem.* **1996**, *61*, 7597–7599; e) D. Craig, M. J. Ford, R. S. Gordon, J. A. Stones, A. J. P. White, D. J. Williams, *Tetrahedron* **1999**, *55*, 15045–15066.

[5] N. Iwasawa, F. Sakurada, M. Iwamoto, *Org. Lett.* **2000**, *2*, 871–873.

[6] W. G. Sly, *J. Am. Chem. Soc.* **1959**, *81*, 18–20.

[7] For example, see a) N. Iwasawa, H. Satoh, *J. Am. Chem. Soc.* **1999**, *121*, 7951–7952; b) K. Tanino, F. Kondo, T. Shimizu, M. Miyashita, *Org. Lett.* **2002**, *4*, 2217–2219; c) D. G. J. Young, J. A. Burlison, U. Peters, *J. Org. Chem.* **2003**, *68*, 3494–3497; d) T. Baba, S. Takai, N. Sawada, M. Isobe, *Synlett* **2004**, 603–608.

[8] A related intramolecular Diels–Alder reaction of a siloxydiene derivative, which gave a fused-type product selectively in spite of its electronic bias, was reported: K. Takasu, S. Mizutani, M. Ihara, *J. Org. Chem.* **2002**, *67*, 2881–2884.

[9] C. Rogers, B. A. Keay, *Can. J. Chem.* **1992**, *70*, 2929–2947.

[10] CCDC-276360 (for adduct **2**) and CCDC-276361 (for adduct **11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] There have been no reports on bridged-type intramolecular [4+2]-cycloaddition reactions of silyloxydiene derivatives.[8] For examples of fused-type cycloadditions, see a) M. Ihara, K. Makita, K. Takasu, *J. Org. Chem.* **1999**, *64*, 1259–1264; b) M. Ihara, K. Fukumoto, *Angew. Chem.* **1993**, *105*, 1059–1071; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1010–1022, and references therein.

[12] P. V. Bonnesen, C. L. Puckett, R. V. Honeychuck, W. H. Hersh, *J. Am. Chem. Soc.* **1989**, *111*, 6070–6081.

[13] Product **13** was obtained as a single stereoisomer; the relative configuration has not yet been determined.

[14] S. Hosokawa, M. Isobe, *Tetrahedron Lett.* **1998**, *39*, 2609–2612.

[15] S. Tojo, M. Isobe, *Tetrahedron Lett.* **2005**, *46*, 381–384.

[16] S. Takai, P. Ploypradith, A. Hamajima, K. Kira, M. Isobe, *Synlett* **2002**, 588–592.

[17] This demetalation reaction is general for medium-sized cyclic alkynone–$Co_2(CO)_6$ complexes. A $[HCo(CO)_3(L)]$ species, generated by decomposition of the alkyne–$Co_2(CO)_6$ complex, might be acting as a reductant; see R. W. Goetz, M. Orchin, *J. Org. Chem.* **1962**, *27*, 3698.