Cycloaddition Reactions

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[4+2] Cycloaddition Reaction of Cyclic Alkyne–{$Co_2(CO)_6$} Complexes with Dienes**

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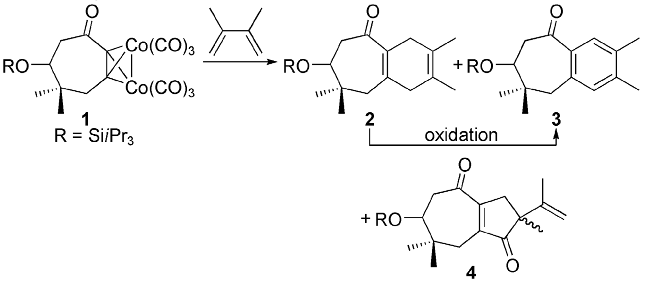
Utility of alkyne—{$Co_2(CO)_6$} complexes in synthetic organic chemistry is widely recognized, however, it is mostly limited to the Pauson–Khand reaction[1] and the Nicholas reaction.[2] There have been few reported examples of [4+2] cycloaddition reaction of alkyne—{$Co_2(CO)_6$} complexes,[3,4] partly because the Pauson–Khand reaction proceeds even when dienes were employed as a reactant.[5] Such a reaction would make it possible to annulate a six-membered ring onto cycloalkynes such as cycloheptynes or cyclooctynes, which are usually inaccessible owing to their highly strained bond angles. Herein, we report a general protocol for the [4+2] cycloaddition reaction of cyclic alkyne—{$Co_2(CO)_6$} complexes[6] with dienes to give benzene derivatives after oxidation. This approach is another utilization of alkyne—{$Co_2(CO)_6$} complexes for carbocycle formation.

The reaction conditions were optimized for the reaction of cycloheptynone—{$Co_2(CO)_6$} **1** and 2,3-dimethyl-1,3-butadiene (Table 1). Heating a mixture of these reactants in toluene at 60 °C for 62 hours gave 47 % yield of a mixture of the dihydrobenzene derivative **2** and its oxidized, benzene derivative **3** along with 6 % yield of the Pauson–Khand product **4** (Table 1, entry 1). Direct treatment of the reaction mixture with DDQ cleanly converted the products into the benzene derivative **3** in good yield (Table 1, entry 2). Use of dimethylbutadiene as the solvent somewhat improved the yield of the product, and furthermore, addition of about 10 equivalents of CH_3CN to the reaction in toluene shortened the reaction time and increased the yield of the product considerably (Table 1, entry 3).[7] On the other hand, commonly employed promoters for the Pauson–Khand reaction such as NMO and $O=PPh_3$ were not effective (Table 1, entries 4 and 5). Thus, **3** was obtained in 74 % yield by heating a mixture of **1** and an excess amount of dimethylbutadiene in toluene in the presence of 10 equivalents of CH_3CN at 60 °C for 11 hours followed by oxidation of the crude products with DDQ. In all cases, formation of a small amount (ca. 5 %) of Pauson–Khand product was observed.

Table 1: Optimization of reaction conditions.[a]



Entry	Reaction conditions	Yield [%] 3	Yield [%] 4
1[b]	toluene, 60 °C, 62 h	47[c]	6
2[d]	60 °C, 21 h	56	ca. 6
3[d]	CH_3CN (10 equiv), toluene, 60 °C, 11 h	74	n.d.
4[d]	NMO (10 equiv), toluene, RT, 1 h	17	2[e]
5[d]	$O=PPh_3$ (10 equiv), toluene, 60 °C, 10 h	46[e]	ca. 7

[a] All reactions were performed with 60 equivalents of dimethylbutadiene. [b] Work-up was done under air. [c] Obtained as a mixture of **2** and **3** (**2**/**3** = 1:2). [d] Oxidized with 3 equivalents of DDQ in toluene at room temperature for 3 h. [e] Based on ^1H NMR spectroscopy. n.d. = not determined, NMO = 4-methylmorpholine *N*-oxide.

Notably, not only the addition of CH_3CN but also the presence of the diene considerably accelerated the rate of consumption of **1** in toluene at 60 °C. For example, after 10 hours of heating at 60 °C, the amount of complex **1** recovered was as follows: 87 % (without the diene in toluene), 65 % (with the diene in toluene), 27 % (without the diene in toluene/CH_3CN (20:1); 10 equiv of CH_3CN based on **1**), 0 % (with the diene in toluene/CH_3CN (20:1); 10 equiv of CH_3CN based on **1**).[8] We believe that CH_3CN would facilitate liberation of CO as a Lewis base,[9] and π complexation of the diene with the coordinatively unsaturated alkyne–$Co(CO)_5$ complex generated under the reaction conditions plays an important role in promoting the reaction. From these results along with the reversal of regioselectivity of the reaction with siloxydiene (as will be described in Table 2, entry 6),[10] it is likely that liberation of a noncomplexed cycloheptynone derivative through decomposition of the cyclic alkyne—{$Co_2(CO)_6$} complex **1** did not occur as the major reaction pathway under the reaction conditions, and the reaction proceeded through the Pauson–Khand-like pathway as shown in Scheme 1. Thus, by heating the complex at 60 °C, a coordinatively unsaturated cobalt species was generated and the diene coordinated to the cobalt (**B**), followed by insertion of the diene into the Co–C bond to give metallacyclic intermediate **C**. Instead of undergoing CO insertion leading to a cyclopentenone derivative (Pauson–Khand product), this intermediate undergoes a 1,3-allylic shift to give another metallacyclic intermediate **D**,[11] which finally underwent reductive elimination to give the product **E**.

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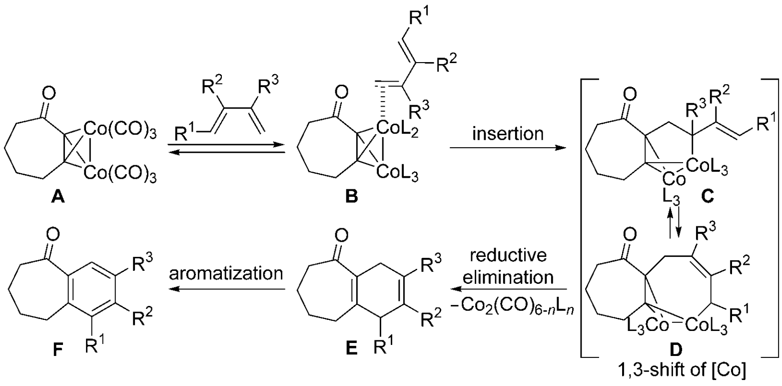


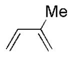
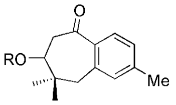
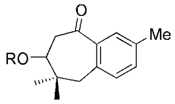
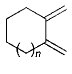
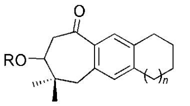
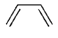
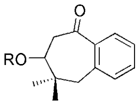
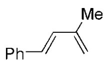
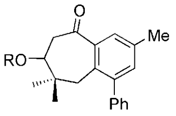
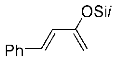
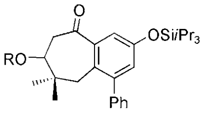
Scheme 1. Proposed reaction mechanism.

Next, we examined the generality of the reaction and we first examined various diene derivatives. As shown in Table 2, the reaction is applicable to acyclic dienes, in particular, 2-substituted or 2,3-disubstituted dienes and gave the corresponding fused benzene derivatives in good yields after DDQ oxidation. Isoprene gave a 3:2 mixture of the regioisomers (Table 2, entry 1). Exocyclic dienes **8** and **10** gave the corresponding tricyclic products **9** and **11** in good yields (Table 2, entries 2 and 3). Butadiene itself was employed for this reaction and gave nonsubstituted benzannulated product in reasonable yield (Table 2, entry 4). Other acyclic dienes such as 1,3-disubstituted diene was employed for this reaction, although the yield decreased (Table 2, entry 5). Importantly a siloxy diene also reacted and gave a phenol derivative in a regioselective manner with acceptable yield (Table 2, entry 6). Interestingly, the regioselectivity of the reaction was contrary to the one expected for the Diels–Alder-type reaction employing α,β-unsaturated ketones and 2-siloxydienes. The selectivity could be explained by assuming that the terminally nonsubstituted side of the diene first inserts into the C−Co bond neighboring the carbonyl group.[12,13]

Then we examined the generality of cyclic alkyne—$\{Co_2(CO)_6\}$ complexes employing 2,3-dimethylbutadiene as the diene component. As summarized in Table 3, this reaction is general for a wide variety of cyclic alkyne—$\{Co_2(CO)_6\}$ complexes. Seven- to nine-membered alkyne—$\{Co_2(CO)_6\}$ complexes reacted smoothly and the corresponding benzannulated products were obtained in good yields (Table 3, entries 1–3). With respect to the functional groups neighboring the alkyne—$\{Co_2(CO)_6\}$ moiety, somewhat higher reactivity was observed for the carbonyl group (Table 3, entry 4) and the reaction proceeded without problem for the acetoxy group, silyloxy group (Table 3, entries 5 and 6), and even the simple methylene group (Table 3, entry 10). Cyclic lactones **30** and **32** could also be employed for this reaction (Table 3, entries 7 and 8). The reaction of **34** gave a product related to taxol. (Table 3, entry 9). Notably, cycloheptynes or cyclooctynes are usually unstable, and thus, the present reaction would be an appropriate substitute for the Diels–Alder of cycloalkynes, which are not available under the standard conditions.[14]

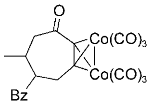
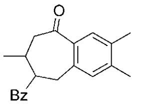
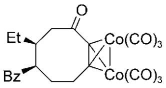
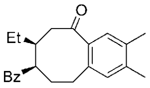
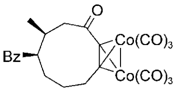
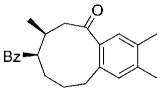
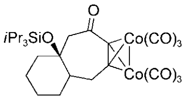
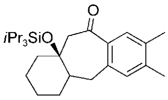
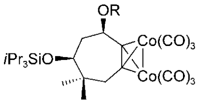
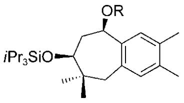
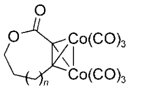
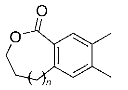
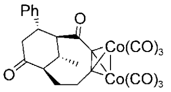
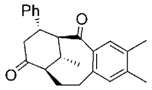
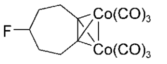
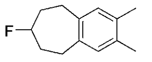
In summary, we have succeeded in realizing a [4+2] cycloaddition reaction of cyclic alkyne—$\{Co_2(CO)_6\}$ complexes with acyclic dienes. As this reaction is applicable to cyclic alkyne—$\{Co_2(CO)_6\}$ complexes in general and various methods for the preparation of cyclic alkyne—$\{Co_2(CO)_6\}$ complexes are now available, this approach should afford a concise method for the preparation of a variety of benzannulated polycyclic compounds.

Table 2: Generality of diene derivatives ($OR = OSi\mathit{i}Pr_3$).[a,b]

Entry	Diene	T [°C]	t [h]	Products		Yield [%]
1[c]	 **5** (30 equiv)	60	10.4	 **6**	 **7**	65
2	 **8** (10 equiv), *n* = 1	110	3	 **9**, *n* = 1		70
3	**10** (30 equiv), *n* = 2	60	12	**11**, *n* = 2		71
4[c]	 **12** (370 equiv)	60	9.3	 **13**		47
5[c]	 **14** (10 equiv)	110	2	 **15**		41
6[c]	 **16** (5 equiv)	110	5	 **17**		49

[a] All reactions were performed at 0.1 M in toluene with substrate **1** and 10 equivalents of CH_3CN. [b] R = TIPS. [c] The crude product was oxidized with 3 equivalents of DDQ in toluene for 3 hours. [d] Obtained as a mixture of **6** and **7** (**6**/**7** = 3:2). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TIPS = triisopropylsilyl.

Table 3: Generality of cyclic alkyne—$\{\mathrm{Co_2(CO)_6}\}$ complexes.[a]

Entry		Substrate	T [°C]	t [h]		Product	Yield [%]
1	**18**		60	23	**19**		45
2	**20**		60	27	**21**		81
3	**22**		60	32	**23**		86
4	**24**		110	3.5	**25**		77
5	**26**, R = Ac		60	14	**27**		85
6	**28**, R = TBS		60	20	**29**		52
7	**30**, n = 1		110	2	**31**		75
8	**32**, n = 2		60	15	**33**		76
9	**34**		60	23	**35**		60
10	**36**		60	25	**37**		88

[a] All reactions were performed at 0.1 M in toluene with 30 equivalents of dimethylbutadiene and 10 equivalents of $\mathrm{CH_3CN}$. The crude product was oxidized with 3 equivalents of DDQ in toluene for 3 hours. TBS = *tert*-butyldimethylsilyl. Bz = benzoyl.

Experimental Section

Typical procedure (synthesis of **3**): A dried two-necked flask with a magnetic stirring bar was charged with alkyne—$\{\mathrm{Co_2(CO)_6}\}$ complex **1** (38.2 mg, 0.064 mmol), toluene (640 μL), 2,3-dimethylbutadiene (436 μL, 3.86 mmol), acetonitrile (33.6 μL, 0.643 mmol) and the mixture was heated at 60 °C for 11 h. The reaction mixture was filtered through a column of silica gel, and the filtrate was concentrated under reduced pressure. To the residue in toluene (2 mL) was added DDQ (43.8 mg, 0.193 mmol) and the mixture was stirred for 3 h at RT. Then the reaction mixture was concentrated under reduced pressure, and the residue was purified by PTLC (ethyl acetate/hexanes = 1:9) to give the compound **3** (18.4 mg, 0.047 mmol) in 74 % yield.

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[2] a) K. M. Nicholas, *Acc. Chem. Res.* **1987**, *20*, 207–214; b) B. J. Teobald, *Tetrahedron* **2002**, *58*, 4133–4170.

[3] To our knowledge, two papers describe [4+2] cycloaddition reaction of alkyne—$\{\mathrm{Co_2(CO)_6}\}$ complexes with dienes. The first one by Khand, Pauson, et al. describes the reaction of alkyne—$\{\mathrm{Co_2(CO)_6}\}$ complexes and 1,3-cyclohexadiene to give consecutive [4+2] and [2+2+1] cycloadducts. The second one by Chung and co-workers describes a $\{\mathrm{Co_2(CO)_8}\}$-catalyzed intramolecular Pauson–Khand reaction of diene-ynes that accompanied [4+2] cycloadditions, however, it seems that the reaction proceeded thermally; a) I. U. Khand, P. L. Pauson, M. J. A. Habib, *J. Chem. Res. Synop.* **1978**, 346–347; b) K. H. Park, S. Y. Choi, S. Y. Kim, Y. K. Chung, *Synlett* **2006**, 527–532.

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[5] I. U. Khand, P. L. Pauson, M. J. A. Habib, *J. Chem. Res. Miniprint* **1978**, 4401–4417.

[6] Our reports on the preparation of cyclic alkyne—$\{\mathrm{Co_2(CO)_6}\}$ complexes: a) N. Iwasawa, K. Inaba, S. Nakayama, M. Aoki, *Angew. Chem.* **2005**, *117*, 7613–7616; *Angew. Chem. Int. Ed.* **2005**, *44*, 7447–7450; b) K. Inaba, J. Takaya, N. Iwasawa, *Chem. Lett.* **2007**, *36*, 474–475.

[7] For examples of promoters of the Pauson–Khand reaction, see: a) D. C. Billington, I. M. Helps, P. L. Pauson, W. Thomson, D. Willison, *J. Organomet. Chem.* **1988**, *354*, 233–242; b) S. Shambayai, W. E. Crowe, S. L. Schreiber, *Tetrahedron Lett.* **1990**, *31*, 5289–5292; c) T. Sugihara, M. Yamada, H. Ban, M. Yamaguchi, C. Kaneko, *Angew. Chem.* **1997**, *109*, 2884–2886; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2801–2804; d) C. Perez del Valle, A. Milet, Y. Gimbert, A. E. Greene, *Angew. Chem.* **2005**, *117*, 5863–5865; *Angew. Chem. Int. Ed.* **2005**, *44*, 5717–5719, and references therein.

[8] For the use of $\mathrm{CH_3CN}$ as an additive in the Pauson–Khand reaction, see: a) Y. K. Chung, B. Y. Lee, N. Jeong, M. Hudecek, P. L. Pauson, *Organometallics* **1993**, *12*, 220–223; for the Lewis base promoted Pauson–Khand reaction, see: b) T. Sugihara, M. Yamaguchi, M. Nishizawa, *Chem. Eur. J.* **2001**, *7*, 1589–1595.

[9] For details, see the Supporting Information. We have not been successful in obtaining any obvious decomposition products derived from **1** when the reaction was carried out in the absence of the diene.

[10] The similar activity of α-oxy and α-methylene substrates (Table 3, entries 5, 6; and 10) compared to that of the α-keto substrate also supports this mechanism.

[11] It is likely that a π-allyl intermediate actually exists and retards insertion of CO.

[12] The regioselectivity of the Pauson–Khand reaction using alkynones or alkynoates as an alkyne component has been examined both experimentally and theoretically to reveal that insertion reaction occurs at the C–Co bond adjacent to the carbonyl group first, see: a) T. J. M. de Bruin, C. Michel, K. Vekey, A. E. Greene, Y. Gimbert, A. Milet, *J. Organomet. Chem.* **2006**, *691*, 4281; b) F. Robert, A. Milet, Y. Gimbert, D. Konya, A. E. Greene, *J. Am. Chem. Soc.* **2001**, *123*, 5396–5400; c) M. E. Krafft, R. H. Romero, J. L. Scott, *J. Org. Chem.* **1992**, *57*, 5277–5278; d) T. R. Hoye, A. J. Suriano, *J. Org. Chem.* **1993**, *58*, 1659–1660.

[13] This reversal of regioselectivity was also observed in the reaction of acyclic alkyne—{$Co_2(CO)_6$} complex although the yield was low.

[14] This [4+2] cycloaddition reaction of alkyne—{$Co_2(CO)_6$} complexes with dienes is applicable to acyclic substrates, however, the reaction did not proceed efficiently and the yield was not very good. For example, the following reaction did not proceed even at 100°C without complexation, but the corresponding alkyne—{$Co_2(CO)_6$} complex gave benzene derivative in moderate yield.