

Rh-Catalyzed [7 + 1] Cycloaddition of Buta-1,3-dienylcyclopropanes and CO for the Synthesis of Cyclooctadienones

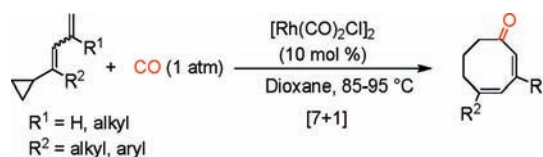
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ABSTRACT



Discovering new carbon building blocks is very significant to advance transition-metal-catalyzed cycloadditions for the synthesis of various-sized ring compounds. A new seven-carbon building block from buta-1,3-dienylcyclopropanes (BDCPs) has been developed, showing that, under the catalysis of $[\text{Rh}(\text{CO})_2\text{Cl}]_2$, BDCPs react with CO to give [7 + 1] cycloaddition products, cyclooctadienones. The present [7 + 1] reaction provides an efficient entry to the synthetically challenging eight-membered carbocyclic skeleton, which is present in many natural products of medicinal and biological significance.

Discovering and developing transition-metal-catalyzed $[m + n]$, $[m + n + o]$, and $[m + n + o + x]$ cycloadditions, where the m , n , o , and x refer to various atom building blocks ultimately incorporated in the final cycloadducts, is very important in today's science of synthesis.¹ This is because the newly discovered cycloadditions are expected to provide new and efficient approaches and strategies to synthesize ring compounds of various sizes, which are building blocks and/or skeletons of natural products, drugs, materials, etc.² Today many scientists are endeavoring to discover and develop new transition-metal-catalyzed cycloadditions by designing and screening various combinations of transition metals and the existing atom building blocks. To further advance this

research field, it is very significant to discover new building blocks that can be used in cycloadditions. If a new building block is found, it could have various combinations with the known building blocks and transition metals to reach ring compounds of various sizes and substitutions.

Today many carbon building blocks from one to six (referred to as the C_x building blocks, $x = 1, 2, 3, 4, 5, 6$) have been discovered and used in transition-metal-catalyzed cycloadditions. However, discovering a seven-carbon building block (C_7) and larger carbon building blocks is still a formidable challenge.³ We regard the discovery and development of such large building blocks as significant toward the synthesis of medium- and large-sized ring compounds, which can be only reached by a limited number of reactions today. Here we report for the first time a rhodium-catalyzed [7 +

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(2) (a) Nicolaou, K. C.; Vourloumis, D.; Wissinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44. (b) Maimone, T. J.; Baran, P. S. *Nat. Chem. Biol.* **2007**, *3*, 396. (c) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197.

(3) The only known building block larger than a C_6 building block, to the best of our knowledge, is a C_7 building block of divinyl cyclopropane, which undergoes a [7 + 1] cycloaddition with CO of $\text{Fe}(\text{CO})_5$ and a [7 + 2] cycloaddition with tetracyanoethene. However, this [7 + 1] cycloaddition requires excess $\text{Fe}(\text{CO})_5$ (3 equiv) and light irradiation. See: (a) Sarel, S.; Langbeim, M. *J. Chem. Soc., Chem. Commun.* **1977**, 593. (b) Sarel, S.; Langbeim, M. *J. Chem. Soc., Chem. Commun.* **1977**, 827.

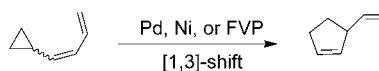
1] cycloaddition of buta-1,3-dienylcyclopropanes (BDCPs) and CO for the synthesis of cyclooctadienones, where BDCPs act as a C₇ building block. This new [7 + 1] reaction complements the known transition-metal-catalyzed cycloadditions^{4,5} to the synthetically challenging eight-membered carbocyclic skeleton, which is present in many natural products of medicinal and biological significance.⁶ Of the same importance, the discovery of this new C₇ building block expands the existing set of building blocks and would create opportunities to develop other transition-metal-catalyzed [7 + x], [7 + x + y] cycloadditions.

BDCPs usually undergo [1,3]-shift reactions to give 3-vinyl-cyclopentene derivatives, either by the catalysis of transition metals^{7a,b} or flash vacuum pyrolysis, as the vinyl cyclopropanes do (Scheme 1a).^{7c} We reasoned that, under the catalysis of Rh complex, BDCP could become a C₇ building block and take part in [7 + 1] cycloaddition with CO (Scheme 1b). In the presence of a Rh complex, BDCP could form an η^4 -complex **A** with Rh. Then cyclopropane cleavage gives intermediate **B** or **C**. Reductive elimination from **B** to give a seven-membered carbocyclic product is expected to be difficult since this step involves the formation of a C(sp³)–C(sp³) bond.⁸ However, once CO is present, through coordination and insertion processes, complex **D** or **E** will be generated. Finally a migratory reductive elimination from **D** or **E** to generate a C(sp²)–C(sp³) bond is much easier than the reductive elimination step from **B**, leading to the [7 + 1] cycloadduct **F**.⁹

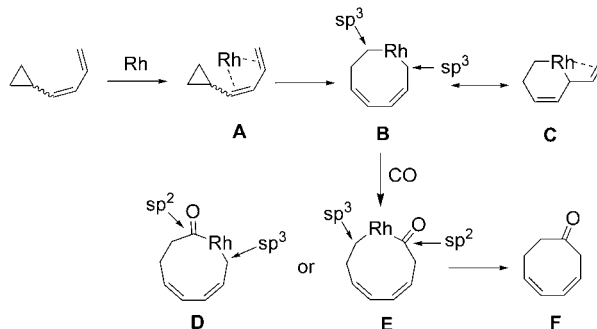
We started our test of the proposed [7 + 1] reaction by subjecting **1a** and CO (balloon pressured mixed gas of CO

Scheme 1. Previous [1,3]-Shift and Our Proposed [7 + 1] Reaction of Buta-1,3-dienylcyclopropanes

a) Previous reports



b) Our proposed [7+1] reaction



and Ar (CO/Ar = 1:9 V/V)) to 10 mol % catalyst of [Rh(CO)₂Cl]₂ in dioxane.¹⁰ To our delight, this reaction really gave the [7 + 1] cycloadduct **2a** with a reaction yield of 22% (Table 1, entry 1). **2a** is a conjugated cyclooctadienone¹¹ and is probably generated from a nonconjugated cyclooctadienone, **3a**, which is the expected [7 + 1] cycloadduct according to the proposed mechanism shown in Scheme 1b. This hypothesis was proved to be true by the following experiments. First, when the partial pressure of CO was increased to 0.5 atm, both **2a** and **3a** were obtained with **3a** as the minor product (Table 1, entry 2). Second, **3a** can be isomerized to **2a** under the catalysis of [Rh(CO)₂Cl]₂ in dioxane (Scheme 2).

To improve the [7 + 1] reaction yield, we further screened the reaction conditions. When the CO pressure was 1.0 atm, the [7 + 1] reaction yield was 74% with a conversion of 81% (entry 3). Further increasing the CO pressure did not improve the reaction yield. For example, the [7 + 1] reaction yield decreased to 57% and 45% when CO pressure was 2.0 and 4.0 atm, respectively (entries 4 and 5, Table 1). Reducing the load of catalyst resulted in low yield (entry 6). The best solvent for the present [7 + 1] reaction is dioxane since reactions carried out in DCE and toluene gave lower yields (entries 7 and 8). In all cases, conjugated cycloocta-2,4-dienone **2a** is the main product, accompanied by the minor product **3a**.

Substrate **1a**, which is a mixture of the *Z* (**1a-Z**) and *E* (**1a-E**) isomers, could not be consumed in all of the

(4) For Rh-catalyzed cycloadditions to eight-membered rings, see: (a) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815. (b) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876. (c) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782. (d) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784. (e) Evans, P. A.; Baum, E. W. *N. J. Am. Chem. Soc.* **2004**, *126*, 11150. (f) Hermann, A. W.; de Merjere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530. (g) Evans, P. A.; Baum, E. W.; Fazal, A. N.; Pink, M. *Chem. Commun.* **2005**, 63. (h) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 5354. (i) Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 10060. (j) DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799. (k) Huang, F.; Yao, Z.-K.; Wang, Y.; Wang, Y.; Zhang, J.; Yu, Z.-X. *Chem.-Asian J.* **2010**, *5*, 1555.

(5) For recent other transition metal-catalyzed cycloadditions to eight-membered rings, see: (a) Wender, P. A.; Ihle, N. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (c) Rigby, J. H.; Kirova-Snover, M. *Tetrahedron Lett.* **1997**, *38*, 8153. (d) Varela, J. A.; Castedo, L.; Saa, C. *Org. Lett.* **2003**, *5*, 2841. (e) Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* **2005**, *7*, 2353. (f) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2006**, *128*, 2166. (g) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 13402. (h) Tenaglia, A.; Gaillard, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2454. (i) Hilt, G.; Paul, A.; Hengst, C. *Synthesis* **2009**, 3305. (j) For other reactions, see citations in ref 1f.

(6) (a) Faulkner, D. *J. Nat. Prod. Rep.* **1988**, *5*, 613. (b) Daum, R. S.; Kar, S.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2007**, *6*, 865. (c) Kingston, D. G. I. *J. Org. Chem.* **2008**, *73*, 3975.

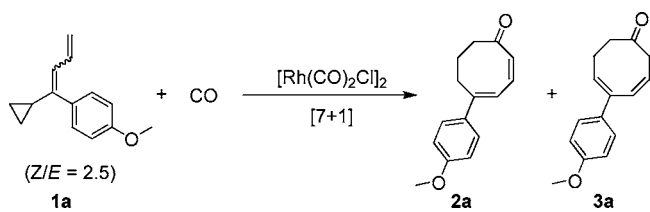
(7) (a) Murakami, M.; Nishida, S. *Chem. Lett.* **1979**, 927. (b) Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 2871. (c) See a recent review about the chemistry of vinylcyclopropane to cyclopentene chemistry: Hudlicky, T.; Reed, J. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 4864.

(8) (a) Yu, Z.-X.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154. (b) Yu, Z.-X.; Cheong, P. H.-Y.; Liu, P.; Legault, C. Y.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 2378.

(9) Similar intermediates were involved in [6 + 2], [5 + 2 + 1] reactions; see refs 4a,i, and k.

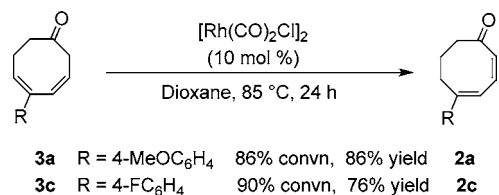
(10) Low pressure of CO was found to be beneficial for some [Rh(CO)₂Cl]₂-catalyzed cycloadditions such as [(5 + 2) + 1], [(3 + 2) + 1], and [(2 + 2) + 1] cycloadditions. See: (a) Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem.* **2001**, *624*, 73. (b) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 2528. (c) See refs 4i and 4k.

(11) The structure of **2a** was identified by ¹H and ¹³C NMR of **2a** and confirmed by the crystallographic data of the hydrazone derivative of **2a** (see the Supporting Information).

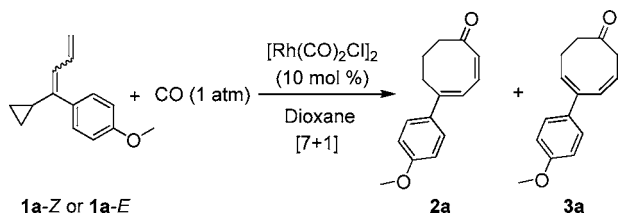
Table 1. Screening of the [7 + 1] Reaction Conditions^a

entry	CO(atm)	solvent	time(h)	convn(%) ^b	yield (%) ^c (2a:3a)
1	0.1 ^d	Dioxane	48	80	22 (-) ^e
2	0.5 ^f	Dioxane	48	80	35 (13:1)
3	1.0	Dioxane	48	81	74 (6:1)
4	2.0	Dioxane	48	83	57 (10:1)
5	4.0	Dioxane	48	78	45 (2:1)
6 ^g	1.0	Dioxane	60	81	32 (-) ^e
7 ^h	1.0	DCE	56	64	33 (3:1)
8	1.0	Toluene	48	80	60 (6:1)

^a General conditions: **1a** (0.2 mmol), [Rh(CO)₂Cl]₂ (10 mol %), solvent (4 mL), 90 °C. ^b Based on recovered starting material. ^c Combined isolated yield. ^d Balloon pressured mixed gas of CO and Ar (1:9, V/V). ^e Only **2a** was isolated. ^f Balloon pressured mixed gas of CO and Ar (1:1, V/V). ^g Reaction run with 5 mol % [Rh(CO)₂Cl]₂. ^h Reaction run at 80 °C.

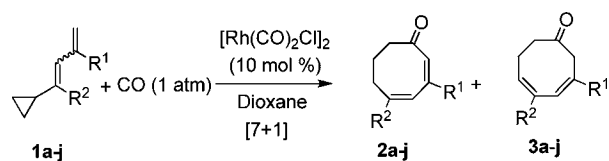
Scheme 2. Rhodium-Catalyzed Isomerizations of Cycloocta-3,5-dienones to Cycloocta-2,4-dienones

described reaction conditions shown in Table 1. To understand the reasons behind this, we studied the

Table 2. Reactivity Comparison of Z and E Isomers of BDCP^a

entry	substrate	time(h)	temp(°C)	convn(%) ^b	yield (%) ^c (2a:3a)
1	1a-Z	70	60	32	20 (1:2)
2	1a-Z	70	80	66 ^d	58 (3:1)
3	1a-Z	58	95	100	62 (11:1)
4	1a-E	58	95	41	38 (7:1)

^a General conditions: **1a-Z** or **1a-E** (0.2 mmol), [Rh(CO)₂Cl]₂ (10 mol %), dioxane (4 mL). ^b Based on recovered starting material. ^c Combined isolated yield. ^d 30% of E isomer (**1a-E**) was isolated.

Table 3. Scope of the [7 + 1] Reaction^a

entry	1a-j	temp (°C)	time (h)	convn (%) ^b	yield (%) ^c (2:3)
1	1a (Z/E=2.5)	90	48	81	74 (6:1)
2	1b (Z/E=2.9)	85	36	85	77 (6:1)
3	1c (Z/E=3.0)	85	46	86	55 (6:1) ^d
4	1d (Z/E=1.9)	85	36	83	59 (6:1)
5	1e (Z/E=2.0)	95	46	76	55 (10:1)
6	1f (Z/E=4.0)	85	46	77	47 (8:1)
7	1g (Z/E=2.2)	85	46	72	70 (19:1)
8	1h (Z/E=0.8)	85	46	96	85 (15:1)
9	1i	85	36	94	63 (4:1)
10	1j (Z/E=0.3)	90	48	90	12 (-) ^e

^a General conditions: **1** (0.2 mmol), [Rh(CO)₂Cl]₂ (10 mol %), solvent (4 mL). ^b Based on recovered starting material. ^c Combined isolated yield. ^d Isomerization was shown in Scheme 2. ^e Only **2j** was isolated.

individual reactions of the pure Z (**1a-Z**) and E (**1a-E**) isomers of **1a** (Table 2). It was found that both isomers could undergo [7 + 1] cycloaddition, but with different reactivities. The Z isomer gave products in yield of 20% at 60 °C, with a conversion of 32% (68% of the starting **1a-Z** was recovered) (entry 1). By increasing the reaction

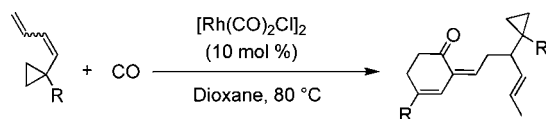
temperature to 80 °C, the *Z* isomer gave a reaction yield of 58% with a conversion of 66% (entry 2). Notably, the *E* isomer, **1a-E**, was obtained in 30% in this case, indicating that the *Z* isomer can isomerize to its *E* isomer at this relatively high temperature (e.g., 80 °C). By a further increase in the reaction temperature to 95 °C, the *Z* isomer could be consumed in 58 h, with a yield of 62% (entry 3). Unlike the *Z* isomer, the *E* isomer behaved more sluggishly in the [7 + 1] cycloaddition: even at 95 °C, it gave cycloadducts in yield of 38%, with a conversion of only 41% (entry 4). About 59% of **1a-E** was recovered in this reaction, suggesting that **1a-E** is much more stable than **1a-Z** in the present reaction system. To summarize, data in Table 2 demonstrate that both *E* and *Z* isomers of BDCPs can take part in the [7 + 1] reaction, but BDCP with the cyclopropyl and terminal alkene in a *trans* configuration (**1a-Z**) is more reactive than BDCP with the cyclopropyl and terminal alkene in a *cis* configuration (**1a-E**) in the [7 + 1] cycloaddition. The reasons behind these differences are the subject of future mechanistic investigation.

With the new discovered reaction in hand, we further studied the scope of this [7 + 1] reaction. It was found that BDCPs with various substituents could undergo the [7 + 1] cycloaddition to give eight-membered carbocycles in moderate to good yields (Table 3, entries 1–9). The substituents could be electron-neutral aryl (entries 2, 4, and 7), electron-rich aryl (entries 1 and 5), electron-poor aryl (entry 3), heterocyclic aryl (entry 6), and alkyl (entries 8 and 9) groups. Electron-rich and -neutral substituents gave good reaction yields (entries 1, 2, 4, and 7–9). Electron-poor and heterocyclic aryl substituents gave moderate reaction yields (entries 3 and 6). BDCP with a trisubstituted diene moiety could also undergo [7 + 1] cycloaddition smoothly and gave a moderate yield (entry 5). A methyl substituent gave a low yield of 12% (entry 10). When R² = H in **1**, no [7 + 1] cycloadducts but cyclohex-3-enone derivatives **4k** and **4l** were obtained in yields of 66% and 69%, respectively (Scheme 3). The proposed mechanism of the formation of **4k** and **4l** was given in the Supporting Information.

Unfortunately, an aryl substitution (Scheme 4, **1m**) or a fused six-membered ring (**1p** and **1q**) on the cyclopropane totally retarded the target [7 + 1] reactions. Alkynyl substrate **1n** or enolate **1o** could not undergo the [7 + 1] reactions either. In all these unsuccessful cases, only starting materials were recovered under the standard reaction conditions.

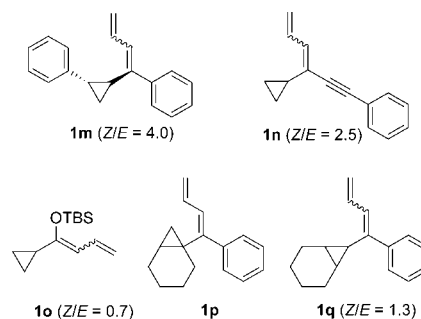
In summary, we have shown, for the first time, a Rh-catalyzed [7 + 1] cycloaddition of BDCPs and CO. This reaction provides a new strategy for the assembly of eight-

Scheme 3. Unexpected Reactions of BDCPs and CO



1k R = Ph (*Z/E*=3.0) 100% convn, 66% yield **4k**
1l R = 4-MeOC₆H₄ (*Z/E*=5.4) 100% convn, 69% yield **4l**

Scheme 4. Unsuccessful Substrates for the [7 + 1] Reaction



membered carbocycles. This is the first report of BDCPs acting as a C₇ building block and is expected to bring opportunities to develop other transition-metal-catalyzed cycloadditions. Further work to study the scope and detailed reaction mechanism of this [7 + 1] reaction and explore this C₇ building block in transition-metal-catalyzed cycloadditions is underway.

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Supporting Information Available: Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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