Rhodium-Catalyzed Carbonylative [3+2+1] Cycloaddition Reaction: Catalytic Formation of Bicyclic Cyclohexenones from Trienes and Carbon Monoxide

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Transition metal-catalyzed cycloaddition reactions are powerful methods for the construction of complex polycyclic systems.[1] Carbonylative coupling, as a tool for the synthesis of cyclic compounds possessing a carbonyl moiety,[2] is especially fascinating. In this respect, the carbonylative alkyne−alkene coupling (Pauson−Khand reaction) has been thoroughly studied.[3] However, no report of carbonylative cycloaddition giving cyclohexenones has been disclosed yet, although cyclohexenones are very useful starting materials in the synthesis of natural products.[4] Recently, lanthanide- and rhodium-catalyzed [4+2] cycloaddition reactions have been used in the synthesis of cyclohexenone derivatives.[5]

Transition metal-catalyzed intramolecular [4+2] cycloisomerization of trienes is quite popular in the synthesis of six-membered ring compounds.[6] However, no reports of a transition metal-catalyzed carbonylative cycloaddition of trienes have been published. In that case, what could be the product(s) in a transition metal-catalyzed reaction of trienes under CO? In view of regiochemical results obtained in previous intramolecular Rh-catalyzed reactions,[1b,6b] we envisaged that trienes such as **1a** might participate in a metal-catalyzed carbonylative [3+2+1] cycloaddition process. We herein communicate the catalytic formation of bicyclic cyclohexenones from trienes and carbon monoxide.

Reaction of triene **1a** with CO in the presence of a catalytic amount of [Rh(cod)Cl]$_2$ in toluene at 130 °C for 4 h resulted in bicyclohexenones **1A** and **1B** as major products and a Diels−Alder reaction product **1C** as a minor product, in a 77% combined yield (**1A**:**1B**:**1C** = 52:20:5) (eq 1).

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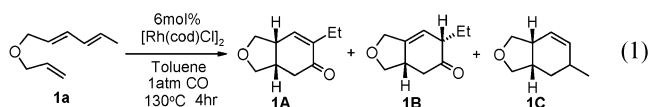
As expected, carbonylated cycloaddition products were isolated with the concomitant formation of [4+2] cycloisomerization products. The carbonylated cycloaddition products were six-membered ring compounds with a high regioselectivity. A *cis*-isomer was exclusively observed. As far as we know, this is the first observation of the catalytic formation of bicyclic cyclohexenones from a triene and carbon monoxide.

To explore this novel reaction in a synthetically useful context, we first screened rhodium catalysts including Rh$_4$(CO)$_{12}$, Rh(acac)(CO)$_2$, Rh$_2$(OAc)$_4$, [Cp*RhCl]$_2$, and [Rh(cod)Cl]$_2$ with dppm (Table 1). All of the rhodium complexes used in this study were active, but the details of their reactivity were quite different depending upon the catalytic system. The relative ratio of the Diels−Alder product increased in the following order: Rh$_4$(CO)$_{12}$ < [Rh(cod)Cl]$_2$ < Rh(acac)(CO)$_2$ < [Cp*RhCl]$_2$ < Rh$_2$(OAc)$_4$. When

Table 1. Transition Metal-Catalyzed Carbonylative Triene Cyclization[a]

entry	catalyst	time (h)	yield (%)[b]		
			1A	1B	1C
1[c]	Rh$_4$(CO)$_{12}$	1	68		trace
2	Rh$_4$(CO)$_{12}$	2	85		trace
3	Rh$_4$(CO)$_{12}$	3	63	24	trace
4	Rh$_4$(CO)$_{12}$	12		88	trace
5	[Rh(cod)Cl]$_2$ + 2dppm[d]	2	70		15
6	Rh(acac)(CO)$_2$	6	40	28	20
7	Rh$_2$(OAc)$_4$	6	20	21	40
8	[Cp*RhCl]$_2$	6	35	10	30
9	Ir$_4$(CO)$_{12}$	6	35	20	22
10[e]	Ru$_3$(CO)$_{12}$	24	10	12	25

[a] 0.7 mmol of substrate and 3 mol % catalyst were used. [b] Isolated yield. [c] 12% reactant recovered. [d] dppm = bis(diphenylphosphino)methane. [e] 40% reactant recovered.

an additive such as dppm was added, the activity increased but the relative ratio of a Diels−Alder product also increased. The iridium complex Ir$_4$(CO)$_{12}$ was quite active and gave a high combined yield with a moderate selectivity. In addition to rhodium and iridium complexes, Ru$_3$(CO)$_{12}$ was also active, but the combined yield and selectivity were quite poor. The best yields for **1A** and **1B** were obtained when Rh$_4$(CO)$_{12}$ was used. Because the one-step formation of **1A** and **1B** was synthetically very attractive, we also investigated the reaction variables to optimize the selectivity for **1A** or **1B** using Rh$_4$(CO)$_{12}$ as a catalyst. When the reaction was shortened to 1 h, the yield for **1A** was 68% and a trace amount of **1C** was formed. As the reaction time was increased, the relative portion of **1B** increased. When the reaction time was increased to 3 h, the yields of **1A** and **1B** were 63% and 24%, respectively. Finally, **1B** was obtained in 88% yield when the reaction time was 12 h. The detailed reaction conditions such as the reaction time are dependent upon the substrate.
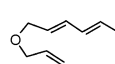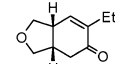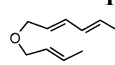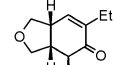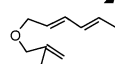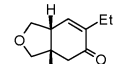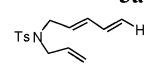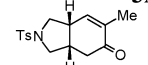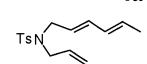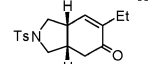
The generality of this present bicyclic cyclohexenone formation was examined with respect to the triene substrates. As summarized in Table 2, the Rh-catalyzed carbonylative cycloaddition i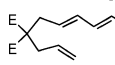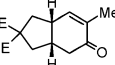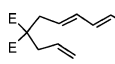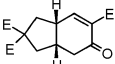s applicable to a range of substrates, allowing the formation of bicyclic cyclohexenone derivatives in moderate to high yields. As compared to the case of **1a**, substrates **2a** and **3a**, having a disubstituted olefin in a tether, afforded somewhat lower yields (57−58%), and a longer reaction time (12 h) was needed.

This result clearly shows some steric effect on the reactivity, but the position of the substituent in the olefin does not make any difference. In the cases of terminal trienes (**4a** and **6a**), the difference between the combined yields (84% for **4** and 93% for
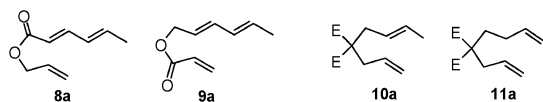
[†] Seoul National University.
[‡] Korea Research Institute of Chemical Technology.

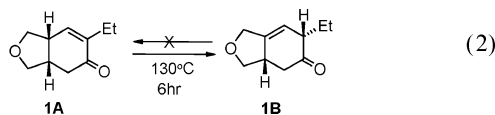**Table 2.** $Rh_4(CO)_{12}$-Catalyzed Carbonylative Triene Cyclization[a]

Entry	Reactant	Product	Time (h)	Yield (%)[b]
1	**1a**	**1A**	2	85
2	**2a**	**2A**	12	45(12)
3	**3a**	**3A**	12	41(17)
4[c]	**4a**	**4A**	6	63(21)
5	**5a**	**5A**	6	65(19)
6[d]	**6a**	**6A**	6	88(5)
7	**7a**	**7A**	6	71(13)

[a] 0.7 mmol of substrate and 3 mol % Rh-catalyst were used. [b] Isolated yield (yield for **B** isomer). [c] Ts = −tosyl. [d] E = −CO₂Et.

Scheme 1. The Proposed Mechanism

After workup, **1A(D)** was obtained as the sole product. From the above observations, a possible mechanism for this novel carbonylative cycloaddition is proposed in Scheme 1.[8]

The reaction begins with the initial generation of rhodium metallacycle (**D**) by an oxidative coupling which could be transformed into **E** by β-hydrogen elimination. Insertion of the double bond of allene into the Rh−H bond should give **F**, which should give cyclohexenone.

In conclusion, the process developed in this study constitutes a previously unknown formal [3+2+1] cycloaddition between a triene and carbon monoxide. Further studies on the scope and limitation of this novel carbonylative cycloaddition process, as well as its application to the synthesis of biologically active compounds, are currently underway.

Supporting Information Available: Full experimental details, copies of ¹H and ¹³C NMR spectra of all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.
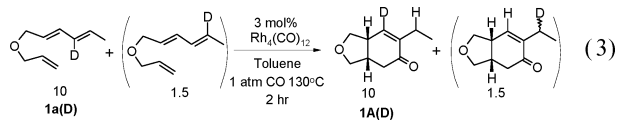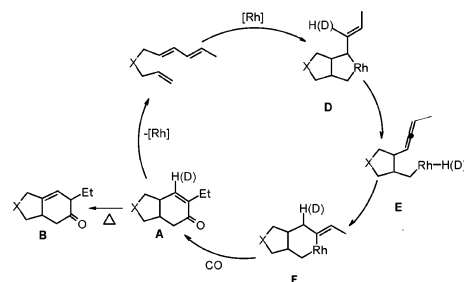
6) was not big, but the yields (63% and 88%) for **4A** and **6A** were quite different and highly varied depending on the bridging atom. A relatively high ratio of **B** was obtained for nitrogen atom-bridged **4**. In the cases of substrates **5a** and **7a** having an internal diene and a monosubstituted olefin in a tether, the combined yields (84%, 84% for **5** and **7**, respectively) were quite close. The present cycloaddition tolerates functionalities including ether, sulfonamide, and ester. These results emphasize the wide functional group compatibility of rhodium catalysis. However, for alkenoates **8a** and **9a**, the corresponding products were not obtained.

8a **9a** **10a** **11a**

The following observations might provide some mechanistic insights into the catalysis. Refluxing **1A** in toluene for 6 h afforded **1B** as the sole product (eq 2). However, no reaction was observed for the thermal treatment of **1B** in toluene. Treatment of dienes **10a** and **11a** under the same reaction conditions as for trienes gave no reaction products.

$$\text{1A} \xrightleftharpoons[\text{6hr}]{130^\circ\text{C}} \text{1B} \qquad (2)$$

Thus, the presence of the diene moiety is critical. Recently, a substrate having a diene moiety has been used in the catalytic addition-cyclization reactions.[7] Reaction of **1a(D)** with CO was also investigated (eq 3).

$$\text{10, 1a(D)} + \text{1.5} \xrightarrow[\substack{\text{Toluene} \\ \text{1 atm CO 130}^\circ\text{C} \\ \text{2 hr}}]{3 \text{ mol}\% \\ Rh_4(CO)_{12}} \text{10, 1A(D)} + \text{1.5} \qquad (3)$$

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