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Rh(I)-Catalyzed Carbonylative Carbocyclization of Tethered Ene− and Yne−cyclopropenes

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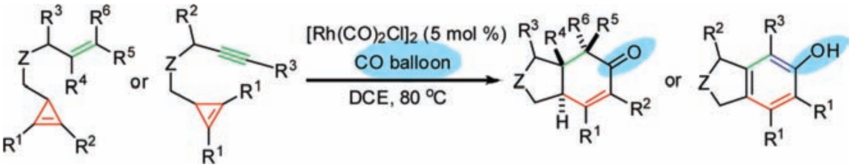
ABSTRACT



Rh(I)-catalyzed carbonylative carbocyclization of ene− and yne−cyclopropene systems provides cyclohexenones and phenols with high efficiency, respectively.

Transition-metal-catalyzed carbocyclization of the polyunsaturated system has attracted significant attention.[1] In particular, carbonylative carbocyclization is a powerful tool to construct ring systems possessing carbonyl functional groups, as represented by carbonylative alkyne−alkene [2 + 2 + 1] carbocyclization (Pauson−Khand reaction), which has been widely used in the synthesis of cyclopentenones.[2] Pioneering work by Narasaka and Jeong demonstrated that rhodium complexes were efficient catalysts in the Pauson−Khand reaction.[3,4] Wender and co-workers have expanded metal-catalyzed [2 + 2 + 1] carbocyclization into diene−yne, diene−ene, and diene−allene systems and observed a remarkable rate-accelerating effect of the diene moiety.[5] Furthermore, Wender and co-workers in 2002 reported the first Rh(I)-catalyzed intermolecular [5 + 2 + 1] carbocyclization, in which vinylcyclopropene provides the five-carbon component.[6] Intramolecular Rh(I)-catalyzed [5 + 2 + 1] cycloaddition of the ene−vinylcyclopropane system has been developed recently by Yu and co-workers, which is an efficient method to construct bicyclooctenones.[7]

In contrast to these remarkable developments, the formation of a six-membered ring through [3 + 2 + 1] carbonylative carbocyclization has been much less developed, presumably due to the difficulty of introducing the required three-carbon component. An obvious source of a three-carbon component would be cyclopropane. Although cyclopropane has been utilized in metal-catalyzed carbocyclization reactions, the presence of a neighboring

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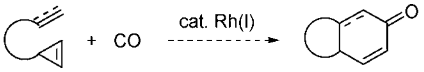
double bond is necessary for metal coordination, which results in the participation of five-carbon component in the reaction in most cases.[1,6−8] Koga and Narasaka have examined the Rh-catalyzed carbonylative carbocyclization of the tethered yne−cyclopropane system, in which the cyclopropane moiety does not bear a neighboring double bond.[9] The cyclopropane did participate in the reaction as a three-carbon component, giving [3 + 2 + 1] carbocyclization products. However, the catalytic efficiency is not high, apparently due to the difficulty of ring-opening of an isolated cyclopropane moiety under the reaction conditions of Rh(I) catalysis.

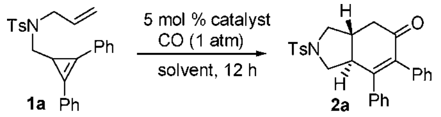
We envisage that cyclopropene, which has a double bond in the three-membered ring for metal coordination and has much higher strain energy than cyclopropane or methylenecyclopropane, will show high reactivity in the carbocyclization reaction (eq 1).[10−12] Indeed, it has been well documented that ring-opening and/or metallocyclobutene formation occurs easily when cyclopropene reacts with transition metals.[13−16] In particular, Pd(II)- or Rh(I)-catalyzed intermolecular [3 + 2] carbocyclization reactions of cyclopropenone acetal or cyclopropenone with alkyne have been reported.[16] We communicate herein the Rh(I)-catalyzed [3 + 2 + 1] carbonylative carbocyclization of ene− and yne−cyclopropene systems, which provides bicyclohexenones and phenols, respectively.



(1)

At the outset, nitrogen-tethered ene−cyclopropene substrate **1a** was used to examine the Rh(I)-catalyzed cycloaddition with CO (Table 1). The Wilkinson catalyst alone or its combination with $AgSbF_6$ at 80 °C in DCE afforded only a trace amount of the desired bicyclohexenone **2a**, with most of the starting material recovered (entries 1 and 2). To our delight, $[Rh(COD)Cl]_2$ under the same conditions gave much higher yield (entry 3). Compound **2a** was obtained in 89% yield with $[Rh(CO)_2Cl]_2$ (entry 5). Addition of Ag(I) salt had negative effects (entries 4 and 6), presumably due to the side reaction catalyzed by $AgSbF_6$. Reaction in toluene and *p*-xylene at high temperature with $[Rh(CO)_2Cl]_2$ gave only moderate yields with recovery of starting materials (entries 7 and 8). The structure of **2a** was confirmed by X-ray crystallographic analysis (Figure 1). It is noteworthy that **2a** has a *trans* configuration for the fused rings.

Table 1. Optimization for Rh(I)-Catalyzed Carbonylative Cycloaddition[a]



entry	catalyst (5 mol %)	solvent	temp (°C)	yield[b] (%)
1	$Rh(PPh_3)_3Cl$	DCE	80	<5[c]
2	$Rh(PPh_3)_3Cl+AgSbF_6$	DCE	80	<5[c]
3	$[Rh(COD)Cl]_2$	DCE	80	74
4	$[Rh(COD)Cl]_2+AgSbF_6$	DCE	80	42
5	$[Rh(CO)_2Cl]_2$	DCE	80	89
6	$[Rh(CO)_2Cl]_2+AgSbF_6$	DCE	80	57
7	$[Rh(CO)_2Cl]_2$	toluene	100	58
8	$[Rh(CO)_2Cl]_2$	*p*-xylene	130	71

[a] Reaction conditions: **1a** (50 mg, 0.12 mmol) in 5 mL of solvent. [b] Isolated yield. [c] **1a** was recovered.

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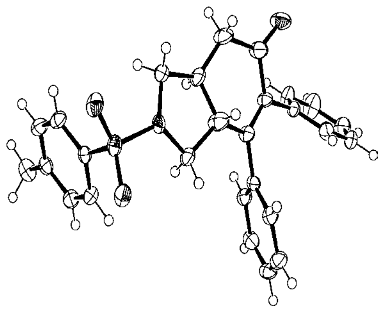
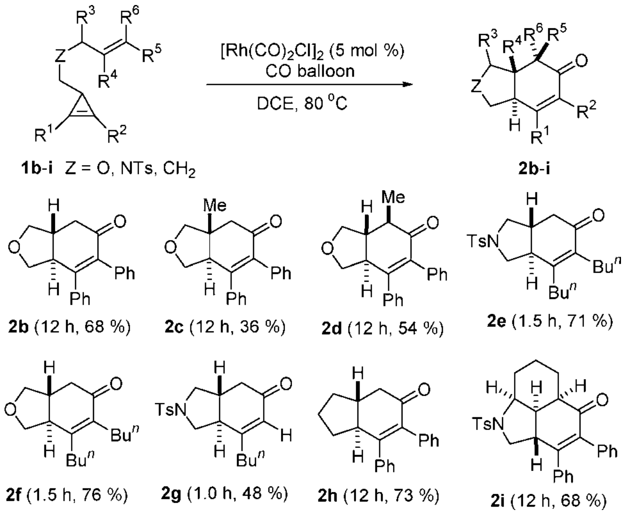


Figure 1. X-ray structure of **2a**.

Scheme 1. Rh(I)-Catalyzed Carbonylative Cycloaddition of **1a-i**



The generality of this reaction was then examined under the optimized conditions. As summarized in Scheme 1, the reaction with a series of ene−cyclopropene substrates **1b**−**i** provided the expected bicyclohexenone derivatives as single diastereomers in all cases. The reaction works well with the oxygen- (**1b**−**d**,**f**) and carbon-tethered substrates (**1h**). The substituent on the alkene moiety has an effect on the yield (**1c**,**d**). In the case of **1c**, the significant drop of yield may be attributed to the methyl substituent in the double bond, impeding the step of alkene insertion in the reaction mechanism. The stereochemistry of **2c** is confirmed by NOESY experiments, which demonstrates that the fused two rings also have a *trans* configuration. When the two substituents on cyclopropene were alkyl groups, the reaction was found to proceed much faster as compared to their phenyl-substituted counterparts (**1e**−**g**). In the case of **1g** (cyclopropene is unsymmetrically substituted), the Rh selectively inserts into the less substituted C−C bond of cyclopropene, affording **2g** as the only carbocyclization product. When the substrate bearing a cyclohexenyl moiety was subjected to the reaction, tricyclic cyclohexenone product **2i** was obtained in 68% yield. The structure of **2i** was confirmed by X-ray crystallographic analysis (Figure 2).

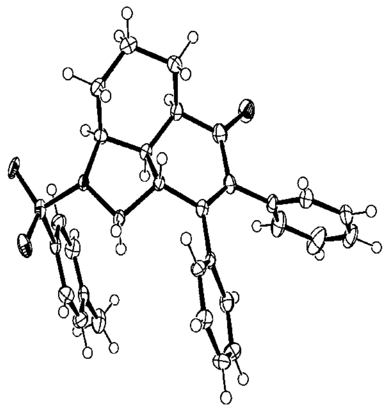
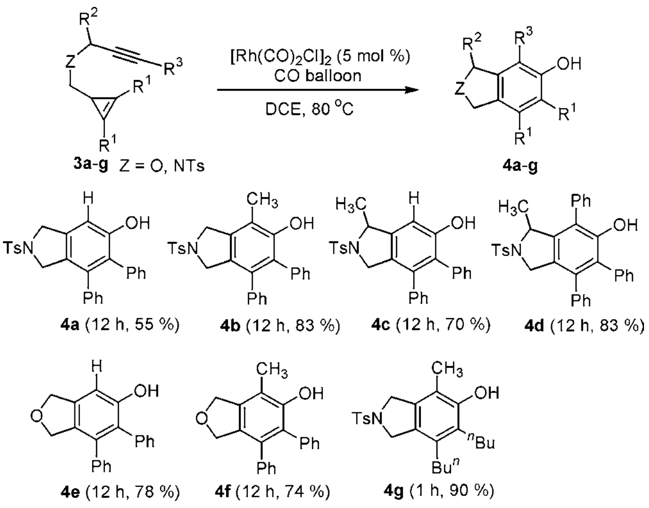


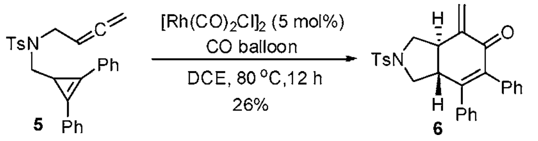
Figure 2. X-ray structure of **2i**.

Scheme 2. Rh(I)−Catalyzed Carbonylative Cycloaddition of **3a-g**



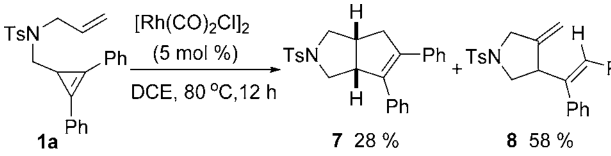
Next, we examined the reactions of tethered yne−cyclopropene systems under the same reaction conditions. As shown in Scheme 2, the reaction provides bicyclic phenols in moderate to good yields. The reaction gave slightly higher yield when there was a substituent in the terminal carbon of alkyne (**3b**,**d**,**f**,**g**), while a substituent in the propargylic position (R^2) did not significantly affect the yields (**3c**,**d**). Similar to the reaction of ene−cyclopropenes, the reaction of the substrate **3g**, which bears an alkyl-substituted cyclopropenyl moiety, proceeded faster compared with its phenyl-substituted counterpart.

To further expand the scope of this reaction, we investigated the reaction of a tethered allene−cyclopropene system (eq 2). The allene moiety did participate in the reaction, and the expected [3 + 2 + 1] carbocyclization product was obtained in 26% yield, with most of the starting material recovered.



(2)

To gain insight into the mechanism, the Rh(I)-catalyzed reaction of **1a** was carried out in the absence of CO. The [3 + 2] carbocyclization product **7** was isolated in 28% yield, together with **8** in 58% yield (eq 3). The structure of bicyclic product **7** was confirmed by X-ray crystallographic analysis (Figure 3). Interestingly, the fused bicyclic structure in product **7** has a *cis* configuration.



(3)

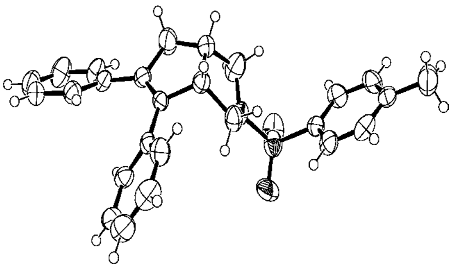
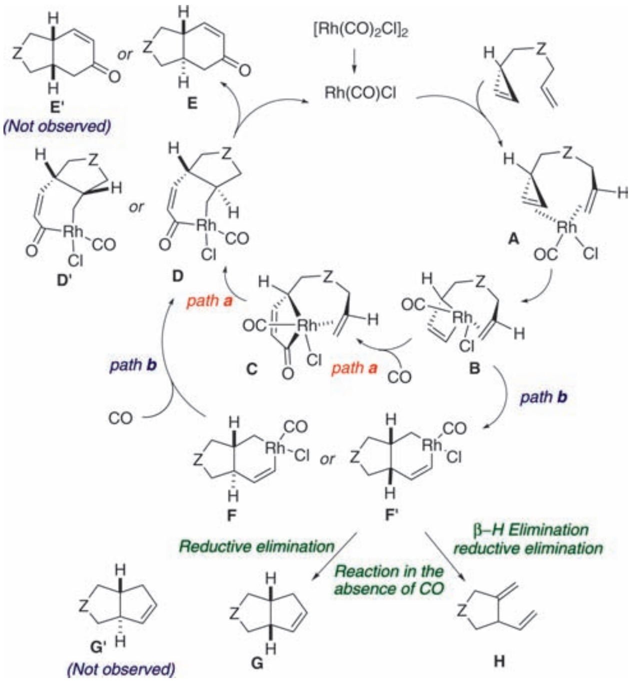


Figure 3. X-ray structure of **7**.

A mechanistic rationale is proposed in Scheme 3.[17] Complexation of the dissociated Rh(I) catalyst with substrate forms intermediate **A**. Direct oxidative addition of the Rh(I) to the σ-bond of the cyclopropene moiety generates rhodacyclobutene intermediate **B**.[13] From intermediate **B**, there are two possible pathways: path a and path b. In path a, CO insertion occurs first to give **C**, from which insertion of alkene leads to intermediate **D**, which undergoes reductive elimination to provide the final product **E**. In path b, alkene insertion occurs first to generate **F** or **F′**, followed by CO insertion and reductive elimination to give final product **E** or **E′**. In the absence of CO as shown in eq 3, **G** and **H** are obtained from **F′** through reductive elimination or β-hydride elimination/reductive elimination. Since the possible *cis*-fused cycloadduct **E′** was not observed in the carbonylative reaction and the reaction in the absence of CO only afforded *cis*-fused cycloadduct **G**, it can be deduced that the carbonylative carbocyclization follows path a rather than path b. However, more rigorous study is needed to confirm the mechanism.

Scheme 3. Proposed Reaction Mechanism



In conclusion, we have developed the first Rh(I)-catalyzed [3 + 2 + 1] carbonylative carbocyclization reactions of ene– and yne–cyclopropene systems. The results demonstrate that the highly strained cyclopropene structure can be used as an excellent three-carbon component in a transition-metal-catalyzed carbocyclization reaction of polyunsaturated systems.

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Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for all new compounds, and X-ray crystallography data (CIF) for **2a**, **2i**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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