DOI: 10.1002/ange.200800432

Cycloaddition

Rhodium-Catalyzed Carbonylative [3+3+1] Cycloaddition of Biscyclopropanes with a Vinyl Substituent To Form Seven-Membered Rings**

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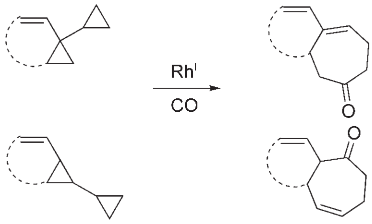
The synthesis of highly substituted carbocyclic seven-membered rings, which are found frequently in natural products, is a significant challenge for the synthetic chemist.[1] Many useful cycloaddition reactions for the synthesis of such rings have been discovered; for example, [4+3],[2] [5+2],[3] [6+1],[4] [4+2+1],[5] [3+2+2],[6] and [2+2+2+1] cycloaddition reactions[7] have been studied in some detail. However, there has been no report of a [3+3+1] cycloaddition reaction, which can be regarded as the combination of two three-carbon-atom donors and carbon monoxide.

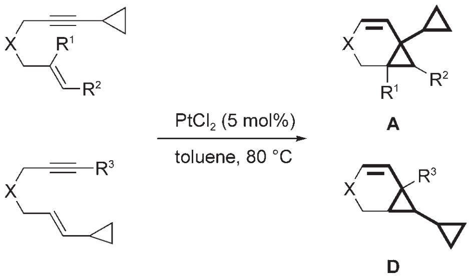
Cyclopropane derivatives[8] are particularly attractive building blocks for organic chemistry.[9] Their unique structural and electronic properties give rise to an array of very interesting, characteristic transformations. Various cyclopropane derivatives have been used in the synthesis of carbocyclic ring systems, such as five- and six-membered ring systems.[10] Among the transformations of cyclopropanes, rhodium-catalyzed ring-opening cycloaddition reactions of vinyl cyclopropanes with π systems to form seven-membered rings are of particular interest.[3a,b,c,e] In these reactions, a rhodium catalyst coordinates to the vinyl group of the vinyl cyclopropane, and the cleavage of the cyclopropyl ring results in the formation of a (π-allyl)(σ-alkyl)Rh^{III} intermediate that can react with π systems.[11] Thus, the presence of a double bond in the substrate is a prerequisite for the transition-metal-catalyzed cycloaddition of cyclopropanes.

We envisioned that biscyclopropanes with a vinyl substituent would be useful substrates in a carbonylative [3+3+1] cycloaddition reaction: Two cyclopropyl groups in a molecule could act as two three-carbon-atom donors, and a carbonylative cycloaddition of the two three-carbon-atom donors would lead to the formation of a seven-membered-ring compound. Herein, we show that certain catalytic systems promote the carbonylative [3+3+1] cycloaddition of biscyclopropanes with a vinyl group under an atmosphere of carbon monoxide (Scheme 1).



Scheme 1. Rh^I-catalyzed carbonylative [3+3+1] cycloaddition.

Biscyclopropane derivatives with a vinyl substituent were obtained readily from cyclopropylenynes by transition-metal-catalyzed cycloisomerization reactions.[12,13] The 1-cyclopropylbicyclo[4.1.0]hept-2-ene derivatives **A** and 7-cyclopropylbicyclo[4.1.0]hept-2-ene derivatives **D** used in this study were obtained readily by $PtCl_2$-catalyzed cycloisomerization of the corresponding enynes (Scheme 2).[13]



Scheme 2. Synthesis of the substrates.

We studied the carbonylative [3+3+1] cycloaddition of the biscyclopropane **1A** (X = NTs, R^1,R^2 = H) as a model substrate in the presence of a rhodium compound as a catalyst under carbon monoxide at atmospheric pressure. When a cationic rhodium catalyst system, such as $[Rh(PPh_3)_2(CO)Cl]$/AgX, was used, no reaction was observed. However, when a neutral rhodium compound was used as the catalyst, the product **1B** of carbonylative cycloaddition was obtained. We therefore screened a number of neutral rhodium compounds, such as $[\{RhCl(cod)\}_2]$, $[RhCl(PPh_3)_3]$, and $[RhCl(CO)(PPh_3)_2]$, as catalysts. $[\{RhCl(cod)\}_2]$ was found to be the best catalyst with respect to the yield of **1B**. Thus, the

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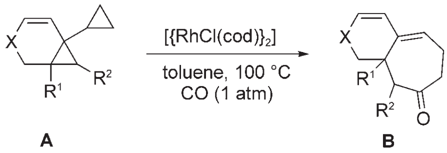
[**] This research was supported by a Korea Research Foundation grant funded by the Korean Government (MOEHRD) (KRF-2008-341-C00022 and KRF-2005-070-C00072) and the SRC/ERC program of MOST/KOSEF (R11-2005-065). S.Y.K. and S.Y.C. are grateful for Brain Korea 21 Fellowships and Seoul Science Fellowships.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200800432.

treatment of **1A** in the presence of a catalytic amount of [{RhCl(cod)}$_2$] (10 mol%) in toluene at 100 °C for 18 h gave the [3+3+1] cycloadduct **1B** in 91% yield (Table 1).[13] The formation of **1B** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic investigations (COSY, HMQC, and HMBC) and high-resolution mass spectrometry. Compound **1B** derives from the ring opening of the two cyclopropane rings followed by carbonylation. We investigated the Rh^I-catalyzed carbonylative cycloaddition of various 1-cyclopropylbicyclo[4.1.0]hept-2-ene compounds with the catalyst [{RhCl(cod)}$_2$] (Table 1). As expected, no reaction was observed in the absence of CO.

Table 1: Rh^I-catalyzed carbonylation reaction.[a]



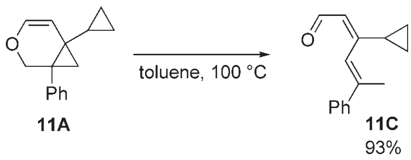
Entry	A	X	R^1	R^2	Yield [%]
1	**1A**	NTs	H	H	91
2	**2A**	NTs	Me	H	46 (51)[b]
3	**3A**	NTs	H	Me	55 (38)[b]
4	**4A**	NMts	H	H	61
5	**5A**	NSO$_2$Ph	H	H	83
6	**6A**	NNaph	H	H	83
7	**7A**	O	H	H	98
8	**8A**	O	Me	H	61 (36)[b]
9	**9A**	O	H	Ph	61 (19)[b]
10	**10A**	NTs	Ph	H	n.r.

[a] Reaction conditions: **A** (0.33 mmol), [{RhCl(cod)}$_2$] (10 mol%), toluene (6 mL), CO (1 atm), 100 °C, 18 h. [b] The amount of **A** recovered is given in parentheses. cod = 1,5-cyclooctadiene, Mts = 2,4,6-trimethylbenzenesulfonyl, Naph = 2-naphthalenesulfonyl, n.r. = no reaction, Ts = *p*-toluenesulfonyl.

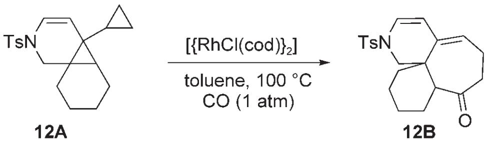
Compounds with an O atom or substituted N atom attached to the double bond of the vinyl substituent in the tether to the substituted cyclopropane ring were useful substrates. The corresponding products **B** of carbonylative cycloaddition were obtained in high yields (up to 98%; Table 1, entry 7). In cases in which the product was formed in lower yield, some of the reactant was recovered intact (Table 1, entries 2, 3, 8, and 9).

Interestingly, substrate **10A**, with a phenyl substituent R^1 and an NTs tether, did not undergo the desired reaction (Table 1, entry 10). In the case of the analogous O-tethered substrate **11A**, thermal opening of the fused cyclopropane in the absence of a catalyst led to the dienyl aldehyde **11C** as the sole product [Eq. (1)].

This carbonylative [3+3+1] cycloaddition facilitates the construction of polycyclic systems containing seven-membered rings. When the 4a-cyclopropylbenzo[1,3]cyclopropa[1,2-*c*]pyridine **12A** was subjected to the standard reaction conditions, the 6,6,7-tricyclic dienone **12B** was obtained in 44% yield with the recovery of **12A** in 42% yield [Eq. (2)].



(1)



(2)

Encouraged by these results, we next investigated the rhodium-catalyzed [3+3+1] cycloaddition of 7-cyclopropylbicyclo[4.1.0]hept-2-ene derivatives **D**. We used **1D** (X = NTs, R^3 = Me) as a model substrate and studied the carbonylative [3+3+1] cycloaddition in the presence of a rhodium catalyst under carbon monoxide at atmospheric pressure. No reaction was observed when [{RhCl(cod)}$_2$] was used without an additive. However, the treatment of **1D** with a catalytic amount of [RhCl(CO)(PPh$_3$)$_2$] (5 mol%)/AgSbF$_6$ (7 mol%) in dichloroethane at 80 °C for 4 h gave the [3+3+1] cycloadduct **1E** and the monocyclic triene **1F** in 32 and 18% yield, respectively.[13] The formation of **1E** and **1F** was confirmed by ^{1}H NMR spectroscopy, high-resolution mass spectrometry, and X-ray diffraction (Figure 1). The structural framework of **E** has not been described previously. Both products result from ring opening of the two cyclopropane rings.

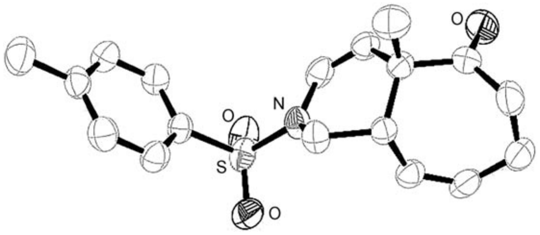
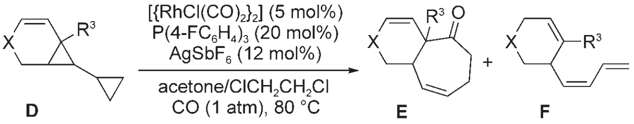


Figure 1. X-ray crystal structure of **1E**.

We screened catalyst systems to find the optimum conditions for the formation of **1E** as the sole product (see the Supporting Information). However, we always obtained a mixture of **1E** and **1F** in varying ratios. The yield of the product mixture varied greatly. Although our endeavor to avoid the formation of **1F** was unsuccessful, the two products can be separated readily by column chromatography. The most efficient catalytic system studied was a mixture of [{RhCl(CO)$_2$}$_2$] (5 mol%), P(4-FC$_6$H$_4$)$_3$ (20 mol%), and AgSbF$_6$ (12 mol%) under 1 atm of CO. We studied the Rh^I-catalyzed carbonylative cycloaddition of various compounds **D** under these reaction conditions (Table 2).[13] Substrates **D** were transformed into **E** and **F** in high overall yields (78–95%); however, the **E**/**F** ratio varied greatly depending on the tether group. In contrast with the results in Table 1, our catalytic system was ineffective when the substrate contained an O atom in the tether. As expected, **1F** was obtained as the only product in the absence of CO.

Table 2: Rh^I-catalyzed transformation of **D** into **E** and **F**.[a]



Entry	D	X	R^3	Yield (**E**/**F**) [%][b]
1	**1D**	NTs	Me	95 (71/24)
2	**2D**	NTs	Et	90 (79/11)
3	**3D**	N−*o*-Ts	Me	85 (51/34)
4	**4D**	NSO$_2$Ph	Me	92 (64/28)
5	**5D**	NMts	Me	90 (62/28)
6	**6D**	NNaph	Me	78 (44/34)

[a] Reaction conditions: **D** (0.33 mmol), [{RhCl(CO)$_2$}$_2$] (5 mol%), P(4-FC$_6$H$_4$)$_3$ (20 mol%), AgSbF$_6$ (12 mol%), acetone (2 mL), ClCH$_2$CH$_2$Cl (4 mL), CO (1 atm), 80°C, 4 h. [b] The yields of the isolated products **E** and **F** are given in parentheses along with the combined yield. *o*-Ts = *o*-toluenesulfonyl.

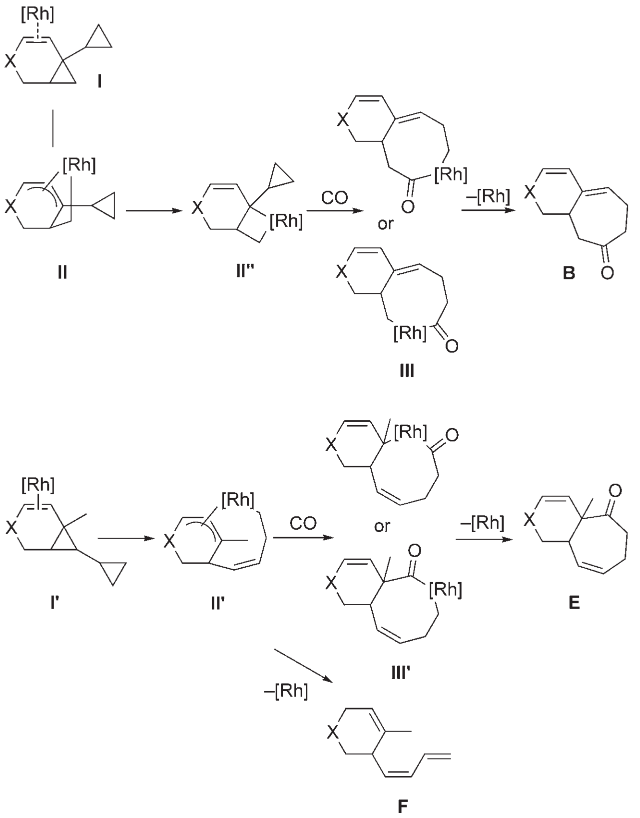
Although the double bond in **D** is in a different position to that in **A** with respect to the two cyclopropane rings, and although the carbonyl group is not in the same position in the two product types, the two transformations are very similar. In both cases, the carbonylative [3+3+1] cycloaddition facilitates the construction of a seven-membered ring. Thus, substantial structural variation can be accommodated. It seems that this Rh^I-catalyzed intramolecular carbonylative [3+3+1] cycloaddition of two cyclopropyl groups in biscyclopropanes may be a general process, although the reaction is somewhat sensitive to the substrate.

All substrates used in this study have a common backbone. The following mechanism is proposed on the basis of our results and previous studies (Scheme 3).[11,14] The precoordination of the Rh^I center to the double bond (in **I**, **I′**) leads to the formation of a (π-allyl)(σ-alkyl)Rh^{III} intermediate **II**, **II′**. The strain-driven cleavage of the cyclopropane in the intermediate **II** would produce metallacycle **II″**. A CO-insertion step to give **III**, **III′**, followed by the elimination of the metal fragment, provides the [3+3+1] cycloadduct **B**, **E**. The formation of **F** appears to result from the facile ring opening of the two cyclopropane rings before the insertion of CO.

In summary, we have demonstrated that judicious selection of the rhodium catalyst system enables the carbonylative [3+3+1] cycloaddition of biscyclopropanes to give the corresponding seven-membered-ring products in reasonable to high yields. Recently, transition-metal-catalyzed cyclopropanation has been developed considerably. Thus, the unprecedented Rh^I-catalyzed cycloisomerization of enynes bearing a cyclopropyl group could become a highly versatile tool for obtaining [3+3+1] cycloaddition products that can not be attained readily by other methods. Further efforts to elucidate the mechanism of the reaction are in progress.

Experimental Section

General procedure for substrates **A**: [{RhCl(cod)}$_2$] (0.033 mmol) and toluene (4 mL) were placed in a Schlenk flask equipped with a stirring bar and capped with a rubber septum. The substrate (0.33 mmol) was added as a solution in toluene (2 mL), and the resulting mixture was stirred at 100°C under a balloon of CO for 18 h. The product was isolated by flash column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate 2:1).



Scheme 3. Proposed mechanism.

General procedure for substrates **D**: [{RhCl(CO)$_2$}$_2$] (0.0165 mmol), P(4-FC$_6$H$_4$)$_3$ (0.066 mmol), and acetone (2 mL) were placed in a Schlenk flask equipped with a stirring bar and capped with a rubber septum, and the resulting mixture was stirred at room temperature for 10 min. AgSbF$_6$ (0.0396 mmol) and 1,2-dichloroethane (2 mL) were then added, and the resulting suspension was stirred for 30 min under a balloon of CO. The substrate (0.33 mmol) was added as a solution in 1,2-dichloroethane (2 mL), and the reaction mixture was stirred at 80°C under a balloon of CO for 4 h. The products were isolated by flash column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate 2:1).

Received: January 28, 2008

Keywords: carbonylation · cycloaddition · cyclopropanes · rhodium · seven-membered rings

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[13] The synthetic procedures and spectroscopic data of new compounds are summarized in the Supporting Information. CCDC 655707 (**1E**) contains 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.

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