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Rh(I)-catalyzed Pauson-Khand-type cycloaddition reaction of ene-vinylidenecyclopropanes with carbon monoxide (CO)

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Abstract

An intramolecular Pauson-Khand type cycloaddition reaction of ene-vinylidenecyclopropanes with carbon monoxide has been established by using $[\text{Rh}(\text{COD})\text{Cl}]_2$ as the catalyst. The reaction was found to be highly efficient in solvents of 1,2-dichloroethane and 1,1,2,2-tetrachloroethane to give excellent yields of 90 – 99%. The reaction provides easy access to a series of fused 6,5-ring structures containing spiro-cyclopropane units that are useful for drug design and development. A mechanism of this cycloaddition process has been proposed accounting for structures of resulting products that were unambiguously assigned by X-ray diffractive analysis.

The Pauson-Khand reaction has been actively investigated for several decades because it can provide easy access to cyclopentanone derivatives to serve as important structural motifs that exist in a huge number of pharmaceutical substances and biologically active natural products.^{1–3} This reaction occurs through a [2+2+1] cycloaddition mechanism involving alkyne, alkene and CO as reactants. Besides the use of alkyne and alkene as starting materials, allene derivatives including allenynes have also been employed for the Pauson-Khand reaction.² In 1994, Narasaka and coworkers reported the first intramolecular version of the Pauson-Khand reaction by using allenynes as substrates in the presence of an iron complex.³ Later, Brummond's group extensively studied the allene-based Pauson-Khand reaction by using transition metals, molybdenum or rhodium, as the catalysts for highly efficient control of regioselectivity of this cycloaddition reaction.⁴ During our ongoing project on vinylidenecyclopropanes' (VDCPs) chemistry,⁵ we have developed a Rh(I)-catalyzed Pauson-Khand-type [3+2+1] cycloaddition reaction of ene-vinylidenecyclopropanes (ene-VDCPs) with carbon monoxide to generate a series of aza- or

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Supporting Information Available: The reaction procedure for preparation of ene-vinylidenecyclopropanes and spectroscopic data of the compounds shown in Tables 1–2 along with the detailed descriptions of experimental procedures as well as the crystal structures of **2a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

oxa-bicyclic products in moderate to good yields with a highly regio- and diastereoselective fashions (Scheme 1).⁶ In this communication, we would like to report a highly efficient Rh(I)-catalyzed intramolecular Pauson-Khand type cycloaddition reaction of ene-vinylidenecyclopropanes with carbon monoxide for the synthesis of a series of fused 6,5-ring structures containing spiro-cyclopropane motifs, which afforded up to 99% chemical yields (Scheme 1).

Our initial study on this catalytic reaction started with ene-vinylidenecyclopropane **1a** as the substrate. In this substrate alkene and vinylidenecyclopropane moieties are connected by an anchor of "TsN" (Ts = 4-toluenesulfonyl). As shown in Table 1, we found that when the reaction was carried out at 80 °C in toluene under argon atmosphere protection (without the use of CO) in the presence of 5 mol % or 20 mol % of [Rh(CO)₂Cl]₂, the corresponding cycloaddition adduct **2a** was obtained in 9% and 30% yields, respectively (Table 1, entries 1 and 2). The reaction was then conducted under CO atmosphere and in the presence of 10 mol % [Rh(CO)₂Cl]₂ as the catalyst, adduct **2a** was produced in a chemical yield of 54% (Table 1, entry 3). However, a similar catalyst, Rh(CO)Cl(PPh₃)₂, was found to be catalytically inactive under this condition. Pleasingly, [Rh(COD)Cl]₂ was confirmed as more efficient catalyst for this reaction to afford **2a** in 66% yield (Table 1, entries 4 and 5). Our examination of solvent effects revealed that DCE (1,2-dichloroethane) and TCE (1,1,2,2-tetrachloroethane) are suitable solvents together with 10 mol % of [Rh(CO)₂Cl]₂ as the catalyst, giving **2a** in 91% and 99% yields, respectively (Table 1, entries 7 and 8). Decreasing the loading of [Rh(COD)Cl]₂ from 10 mol % to less than 5 mol % can also give product **2a** in 94–99% yields under the above conditions (Table 1, entries 9–11). Using Pd(PPh₃)₂Cl₂ (4 mol %) as the catalyst, no reaction occurred (Table 1, entry 12).

Having identified the optimal conditions, we next examined the scope and limitations of this Rh(I)-catalyzed cycloaddition reaction; the results are summarized in Table 2. Using ene-VDCPs **1b–1k** as the substrates in which R can be various primary or secondary alkyl groups with X as TsN or BsN anchor (Bs = 4-bromobenzenesulfonyl), the desired products **2b–2k** were obtained in excellent yields ranging from 92% to 97% (Table 2, entries 2–11). Moreover, as for substrates **1l** and **1m**, in which alkene and vinylidenecyclopropane moieties are connected by oxygen and carbon anchors, the reactions were performed smoothly to give the corresponding products **2l** and **2m** in 91% and 90% yields, respectively (Table 2, entries 12 and 13). Interestingly, when ene-vinylidenecyclopropane **1n** which contains an additional CH₂ extension was used as the substrate, no reaction was observed under the above conditions (Table 2, entry 14). The substrates with other different R groups are difficult to be prepared.

To our delight, on enlarging the reaction scale to 2.0 mmol by employing **1a** as the substrate, similar results could be obtained, affording **2a** in 82% yield (Scheme 2).

The resulting products have been determined by NMR spectroscopic and HRMS analysis (see SI supplement); and the product of **2a** has been unambiguously assigned by X-ray diffractational analysis. The CIF data of this X-ray analysis are summarized in SI supplement materials and corresponding ORTEP drawing is presented in Figure 1.⁷

A plausible reaction mechanism has been shown in Scheme 3 using **1a** for the model reaction. At first, the coordination of Rh(I) with alkene and allene moieties in VDCP leads to formation of intermediate **A**; this intermediate then undergoes oxidative cyclization to give the rhodacycle intermediate **B**. Insertion of CO into **B** generates two regioisomers **C** and **D** which is subjected to reductive elimination followed by the formation of cycloadduct **2a**. At this last step, the species Rh(I) is regenerated for catalytic cycles.

In conclusion, we have developed a highly efficient Rh(I)-catalyzed intramolecular Pauson-Khand type cycloaddition reaction of ene-vinylidenecyclopropanes with CO, which can efficiently result in fused 6,5-ring structures containing spiro-cyclopropane units with excellent yields (> 90% for all cases). Further work will be devoted toward applications of this new methodology to the synthesis of biologically important targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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7. The crystal data of **2a** have been deposited in CCDC with number 830675.

Figure 1.
X-ray Crystal Structure of Product **2a**

Previous work

(R^1 = aliphatic group)
 (R^3 = H or methyl group)
 (X = NTs, NBs, NNs, O)

yield = 45%-76%
cis:trans = 6.9:1.0-→20.0:1.0

This work

up to 99% yield

Scheme 1.
 Rh(I)-catalyzed Pauson-Khand reaction of Ene-VDCPs

Scheme 2.

Rh(I)-catalyzed Pauson-Khand-type cycloaddition reaction of ene-vinylidenecyclopropane

1a (2 mmol) and CO

Scheme 3.
A Plausible Reaction Mechanism

Table 1

Optimization of Rh(I)-catalyzed Pauson-Khand-type cycloaddition reaction of ene-vinylidenecyclopropane **1a** with CO

entry ^a	catalyst	x ^b	solvent	yield (%) ^c
				2a
1	[Rh(CO) ₂ Cl] ₂	5	toluene	9 ^d
2	[Rh(CO) ₂ Cl] ₂	20	toluene	30 ^d
3	[Rh(CO) ₂ Cl] ₂	10	toluene	54
4	Rh(CO)Cl(PPh ₃) ₂	10	toluene	-
5	[Rh(COD)Cl] ₂	10	toluene	66
6	[Rh(CO) ₂ Cl] ₂	10	DCE	73
7	[Rh(COD)Cl] ₂	10	DCE	91
8	[Rh(COD)Cl] ₂	10	TCE	99
9	[Rh(COD)Cl] ₂	5	TCE	99
10	[Rh(COD)Cl]₂	2	TCE	99
11	[Rh(COD)Cl] ₂	1	TCE	94
12	Pd(PPh ₃) ₂ Cl ₂	4	TCE	-

^aEne-VDCP **1a** (0.2 mmol), catalyst (x mol %) and the solvent (2.0 mL) were added into a reaction tube under argon. Then, the reaction was carried out under CO atmosphere at 80 °C with in 1 h.

^bThe loading of the catalyst.

^cIsolated yields.

^dThe reaction was carried out under argon.

Table 2

Substrate scope of Rh(I)-catalyzed Pauson-Khand-type cycloaddition reaction of ene-vinylidenecyclopropanes and CO

entry ^a	substrate			yield (%) ^b
	X	R	no.	2
1	TsN	Me	1a	2a , 99
2	TsN	Et	1b	2b , 95
3	TsN	<i>c</i> -Hex	1c	2c , 94
4	TsN	Bn	1d	2d , 92
5	BsN	Me	1e	2e , 95
6	BsN	Et	1f	2f , 94
7	BsN	<i>c</i> -Hex	1g	2g , 92
8	BsN	Bn	1h	2h , 92
9	BsN		1i	2i , 97
10	BsN		1j	2j , 95
11	BsN	<i>n</i> -Bu	1k	2k , 97
12	O	Bn	1l	2l , 91
13	CH ₂	Bn	1m	2m , 90
14				1n NR

^a **1** (0.2 mmol), [Rh(COD)Cl]₂ (2 mol %), and TCE (2.0 mL) were added into a schlaker reaction tube under CO (1 atm). The reactions were carried out at 80 °C within 1 h.

^b Isolated yields.