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Rh(I)-catalyzed Pauson-Khand-type Cycloaddition Reaction of Ene-vinylidenecyclopropanes with Carbon Monoxide (CO)

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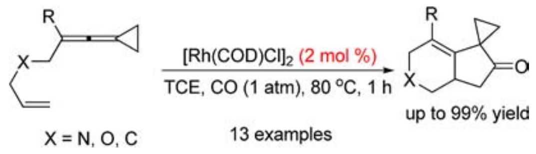
ABSTRACT



An intramolecular Pauson-Khand type cycloaddition reaction of ene-vinylidenecyclopropanes with carbon monoxide has been established by using [Rh(COD)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 diffractional 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 co-workers 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

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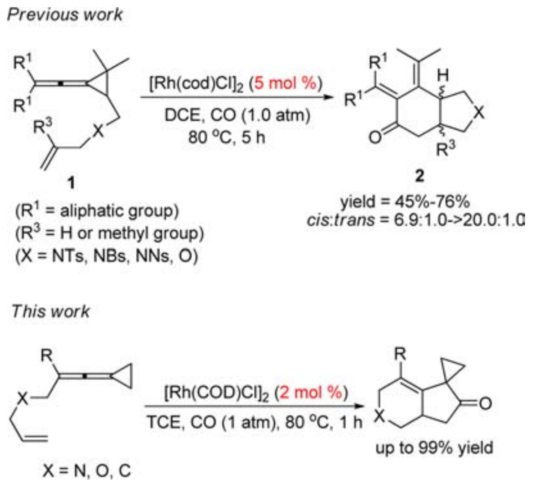
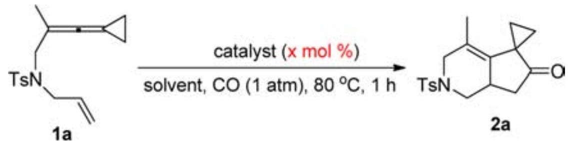
Scheme 1. Rh(I)-catalyzed Pauson-Khand Reaction of Ene-VDCPs



Pauson-Khand-type [3 + 2 + 1] cycloaddition reaction of ene-vinylidenecyclopropanes (ene-VDCPs) with carbon monoxide to generate a series of aza- or 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).

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	$[Rh(CO)_2Cl]_2$	5	toluene	9[d]
2	$[Rh(CO)_2Cl]_2$	20	toluene	30[d]
3	$[Rh(CO)_2Cl]_2$	10	toluene	54
4	$Rh(CO)Cl(PPh_3)_2$	10	toluene	
5	$[Rh(COD)Cl]_2$	10	toluene	66
6	$[Rh(CO)_2Cl]_2$	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	$Pd(PPh_3)_2Cl_2$	4	TCE	

[a] Ene-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 within 1 h. [b] Loading of the catalyst. [c] Isolated yields. [d] Reaction was carried out under argon.

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 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, $Rh(CO)Cl(PPh_3)_2$, 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 $Pd(PPh_3)_2Cl_2$ (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

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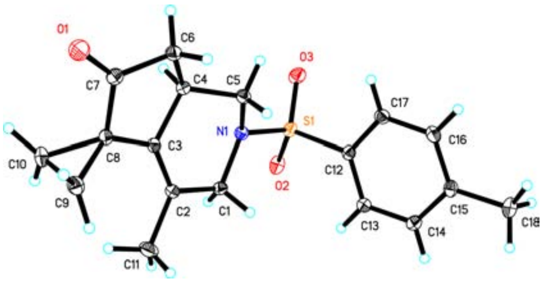
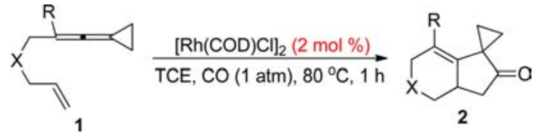
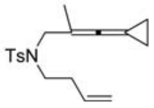


Figure 1. X-ray Crystal Structure of Product **2a**.

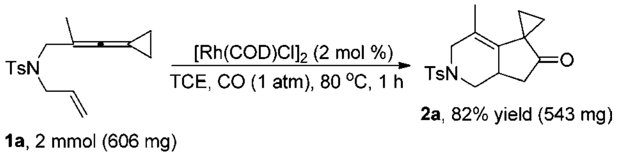
Table 2. Substrate Scope of Rh(I)-catalyzed Pauson-Khand-type Cycloaddition Reaction of Ene-vinylidenecyclopropanes and CO



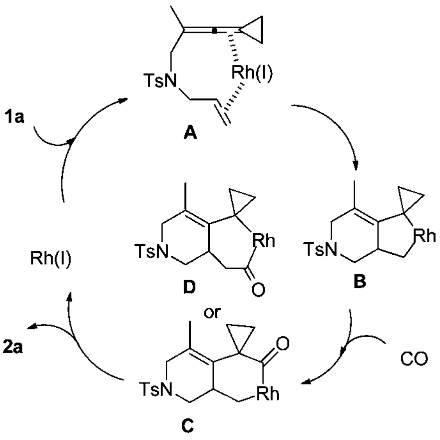
entry[a]	substrate			yield (%)[b]
	X	R	no.	2
1	TsN	Me	**1a**	**2a**, 99
2	TsN	Et	**1b**	**2b**, 95
3	TsN	*c*-Hex	**1c**	**2c**, 94
4	TsN	Bn	**1d**	**2d**, 92
5	BsN	Me	**1e**	**2e**, 95
6	BsN	Et	**1f**	**2f**, 94
7	BsN	*c*-Hex	**1g**	**2g**, 92
8	BsN	Bn	**1h**	**2h**, 92
9	BsN		**1i**	**2i**, 97
10	BsN		**1j**	**2j**, 95
11	BsN	*n*-Bu	**1k**	**2k**, 97
12	O	Bn	**1l**	**2l**, 91
13	CH_2	Bn	**1m**	**2m**, 90
14	 TsN		**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.

Scheme 2. Rh(I)-catalyzed Pauson-Khand-type Cycloaddition Reaction of Ene-vinylidenecyclopropane **1a** (2 mmol) and CO



Scheme 3. Plausible Reaction Mechanism



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 was 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 CH_2 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 Supporting Information); and the product of **2a** has been unambiguously assigned by X-ray diffractional analysis. The CIF data of this X-ray analysis are summarized in Supporting Information 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

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

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.

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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.

The authors declare no competing financial interest.