Pauson–Khand Reaction

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Rhodium-Catalyzed Pauson–Khand-Type Reaction Using Alcohol as a Source of Carbon Monoxide**

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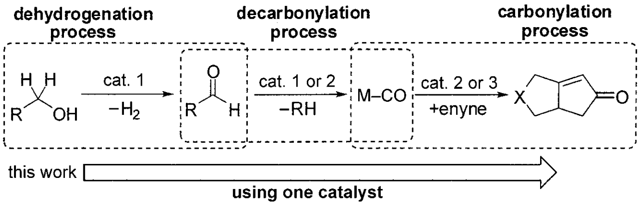
The invention of increasingly rapid, efficient, and convenient strategies to obtain valuable compounds from readily available starting materials is one of the primary objectives of modern chemistry. To this end, chemists have long been interested in tandem or cascade reactions, whereby one catalyst promotes two or more distinct chemical transformations in a single flask without the need for intermediate workup procedures or purification.[1] When considering these sequential reactions, one often needs to consider the compatibility of a catalyst with the residual material derived from the proceeding steps.

Owing to the recent attention given to green chemistry, gaseous carbon monoxide used in carbonylation reactions has been replaced by organic and inorganic carbonyl compounds.[2] In many cases, the substitute for carbon monoxide was an aldehyde,[3] which is normally prepared from the corresponding alcohol. We envisioned the use of alcohols as a carbon monoxide source in the presence of a catalyst (Scheme 1) and supposed that the ability to use the alcohol itself would be highly beneficial.

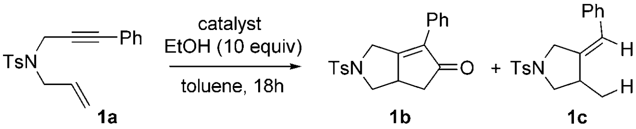


Scheme 1. Hypothesis of the cascade reaction.

Because of the unfavorable thermodynamic nature of the dehydrogenation reaction of alcohols to yield the corresponding aldehydes, the yield of aldehyde and hydrogen in a closed system is low. However, if the aldehyde produced from the alcohol is continually removed from the system through a decarbonylation reaction as a second process,[4] and the thus generated metal carbonyl complex is used in a successive carbonylation reaction, the catalytic system might be effective. To verify our assumption, we explored rhodium complexes, which are known catalysts for the transformation of alcohols into aldehydes,[5] for the decarbonylation of aldehyde[6] and for the Pauson–Khand reaction.[7] Normally, three kinds of rhodium compounds might be needed to catalyze these three conceptually different reactions. However, we wanted to develop a catalytic one-pot reaction using just one rhodium compound as a catalyst. Herein we report our preliminary results for the rhodium-catalyzed intramolecular Pauson–Khand-type reaction using an alcohol as the source of carbon monoxide.

Initially we studied an intramolecular Pauson–Khand-type reaction using allyl propargyl tosylamide (**1a**) as a model substrate using ethanol as a CO source (Table 1). As shown in Table 1, we screened a variety of rhodium complexes that are known as effective catalysts in decarbonylation of aldehydes and Pauson–Khand-type reactions. To our delight, the Pauson–Khand-type product **1b** was obtained in reasonable yields with the concomitant formation of the reductive cyclization compound **1c**.[8] Compound **1c** was derived from

Table 1: Catalytic Pauson–Khand-type reaction of **1a** with ethanol.[a]



Entry	Catalyst	mol%	T [°C]	**1b** [%][b]	**1c** [%][b]
1	$[\{Rh(CO)Cl(dppp)\}_2]$	8	120	61	36
2	$[\{Rh(CO)Cl(dppp)\}_2]$	8	70	66	33
3	$[\{Rh(CO)Cl(dppp)\}_2]$	8	40	31 (45)[c]	22
4	[Rh(CO)Cl(dppe)]	16	70	trace	trace
5	$[\{Rh(CO)Cl(dppb)\}_2]$	8	70	18 (65)[c]	16
6	$[Rh(dppp)_2Cl]$	16	70	24 (32)[c]	34
7	$[\{Rh(cod)Cl\}_2]$ /binap	8 (16)[d]	70	n.r.	
8	$[\{Rh(cod)Cl\}_2]$ /dppp	8 (16)[d]	70	48	49
9	$[RhCl(PPh_3)_3]$	16	70	n.r.	
10[e]	$[\{Rh(CO)Cl(dppp)\}_2]$	8	70	n.r.	
11	$[\{Rh(CO)Cl(dppp)\}_2]$	4	70	58	37
12	$[\{Rh(CO)Cl(dppp)\}_2]$	2	70	41	53

[a] Reaction conditions: **1a** (0.15 mmol), ethanol (10 equiv), toluene (2 mL), and 18 h. [b] Yield of isolated product. [c] The numbers in parenthesis represent the amount of recovered starting materials. [d] Amount of phosphine used. [e] 5 mol% of NaOH was added. cod = cycloocta-l,5-diene, dppb = butane-l,4-diylbis(diphenylphosphane), dppe = ethane-l,2-diylbis(diphenylphosphane), dppp = propane-l,3-diylbis(diphenylphosphane), Ts = 4-toluenesulfonyl, n.r. = no reaction.

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the reaction of **1a** with the generated hydrogen or rhodium hydride intermediate.[9] The yield of **1b** was highly sensitive to the rhodium complexes that were used. The best yield (66%; Table 1, entry 2) was observed with [{Rh(CO)Cl(dppp)}$_2$] at 70°C. Indeed, the reaction could even be conducted at much lower temperature (40°C; Table 1, entry 3).[10] The formation of **1b** was observed with [{Rh(CO)Cl(dppb)}$_2$] (18% yield; Table 1, entry 5) and [Rh(dppp)$_2$Cl] (24% yield; Table 1, entry 6). Strangely, complexes [Rh(CO)Cl(dppe)] and [{Rh(cod)Cl}$_2$] with binap were inactive (Table 1, entries 4 and 7). As expected, no reaction was observed with a monophosphine rhodium complex (Table 1, entry 9).[6b] Remarkably, [{Rh(CO)Cl(dppp)}$_2$] uniquely showed its effectiveness in the oxidation of ethanol to acetaldehyde, in the decarbonylation of acetaldehyde to carbon monoxide and methane, and in the Pauson–Khand-type reaction. To enhance the oxidative dehydrogenation of ethanol, a base such as NaOH was added, but turned out to be detrimental and no reaction occurred (Table 1, entry 10).[4a] When the amount of [{Rh(CO)Cl(dppp)}$_2$] used was lowered to 4 mol% and 2 mol% (Table 1, entries 11 and 12), the catalytic system was still quite effective and the corresponding product **1b** was isolated in 58% and 41% yield, respectively.

To lower the amount of **1c** formed, we screened a variety of hydrogen acceptors including methyl methacrylate, 2-cyclohexenone, diphenylacetylene, and styrene. However, they were ineffective and sometimes no reaction was observed.

By using [{Rh(CO)Cl(dppp)}$_2$] as a catalyst in the intramolecular Pauson–Khand-type reaction of **1a**, we screened diverse alcohols that could be easily dehydrogenated and decarbonylated to give a high yield of cyclopentenone. Primary mono alcohols such as *n*-propanol, *n*-pentanol, and *n*-octanol gave reasonable to high yields (61–81%; Table 2, entries 2–4) of the product. On the other hand, methanol gave a lower yield (22%; Table 2, entry 1), presumably because of its low boiling point. Ethylene glycol was quite efficient (Table 2, entry 6). Olefinic alcohols such as allyl alcohol and cinnamyl alcohol also gave high yields of the product (Table 2, entries 7–11). For unsaturated alcohols, it was expected that the yield of a reductive cyclization product should be decreased.[11] The best yield (95%; Table 2, entry 9) was observed when 10 equivalents of cinnamyl alcohol were used in 2.0 mL of xylene at 130°C for 18 hours.[12] When the amount of cinnamyl alcohol used was lowered to 1.2 equivalents with 4 mol% of the catalyst, the yield was still 91% after 2 hours of reaction time (Table 2, entries 7–11). An aryl group and a carbon–carbon double bond are important characteristics of a good CO donor.[13] Moreover, better yields were observed at 130°C than at 70°C, presumably as a result of the enhancement of both the decarbonylation reaction and the subsequent carbonylative cycloaddition at high temperature.

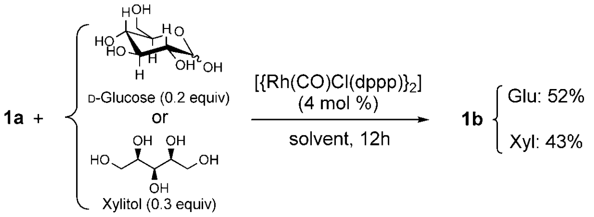
Table 2: Pauson–Khand-type reaction of **1a** with various alcohols catalyzed by [{Rh(CO)Cl(dppp)}$_2$].[a]

$$\mathbf{1a} \quad + \quad \text{alcohol} \quad \xrightarrow[\text{solvent}]{[\{\text{Rh(CO)Cl(dppp)}\}_2]} \quad \mathbf{1b}$$

Entry	Alcohol (equiv)	Cat. [mol%]	*T* [°C]	*t* [h]	Yield [%][b]
1	methanol (10)	8	70	18	22(26)[c]
2	*n*-propanol (10)	8	70	18	63(37)[c]
3	*n*-pentanol (10)	8	130	18	73(25)[c]
4	*n*-octanol (10)	8	70	18	62(36)[c]
5	*n*-octanol (10)	8	130	18	81(12)[c]
6	ethylene glycol (5)	8	130	18	69(29)[c]
7	allyl alcohol (10)	8	70	18	60(32)[c]
8	allyl alcohol (10)	8	130	18	67(18)[c]
9	cinnamyl alcohol (10)	8	130	18	95
10[d]	cinnamyl alcohol (10)	4	130	18	90
11[e]	cinnamyl alcohol (4)	4	130	2	91(4)[c]
12[d]	phenethyl alcohol (4)	4	130	2	69(24)[c]

[a] Reaction conditions: **1a** (0.15 mmol), alcohol, toluene (2 mL, 70°C) or xylene (2 mL, 130°C). [b] Yield of isolated product. [c] The numbers in parenthesis represent the yield of reductive cyclized product. [d] The reaction was conducted without solvent. [e] The reaction was carried out in xylene (0.5 mL).

As an alternative source of carbon monoxide, carbohydrates such as glucose[14] and xylitol were also exploited. In principle, they can donate six or five carbon monoxide groups, but they are almost insoluble in organic solvents. However, when 0.2 equivalents of glucose and 0.3 equivalents of xylitol were used as a CO source, 52% and 43% of the corresponding products were isolated with a concomitant formation of an enyne-dimerized product (Scheme 2).[15]

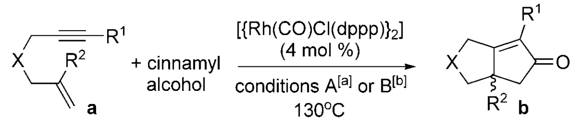


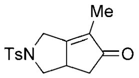
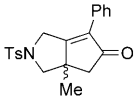
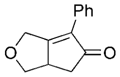
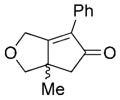
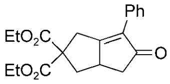
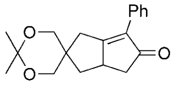
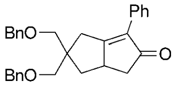
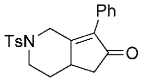
Scheme 2. Using carbohydrates as multiple CO sources. Reaction conditions: in 2 mL of diglyme at 160°C (glucose); in 2 mL of toluene at 110°C (xylitol).

We next screened various enyne substrates for the intramoleular Pauson–Khand-type reaction under optimized reaction conditions. As shown in Table 3, the catalytic system is quite effective for giving high yields (53–99%) of the intramolecular Pauson–Khand-type products. In the cases of Table 3, entries 1, 3, and 6, a considerable amount (12–24% yields) of a reductive cyclization was observed. For entries 7 and 8, an intricate mixture of byproducts was formed. The highest yield (99%) was obtained for the substrate that could be hardly reductively cyclized under the given reaction conditions (Table 3, entry 2).[16] Also, a 1,7-enyne compound was transformed into bicyclo[4.3.0]nonenone in high yield (74%; Table 3, entry 8).

We then conducted a preliminary mechanistic investigation. When a Pauson–Khand reaction was carried out in the presence of ethanol, we could confirm the formation of methane by GC (see the Supporting Information) in addition to the Pauson–Khand product and a reductive cyclization product. As we expected, hydrogen is transferred from the alcohol to the enyne, and the aldehyde formed is decarbonylated to afford methane by the rhodium catalyst. The evolved

Table 3: Scope of the rhodium-catalyzed Pauson–Khand-type reaction with cinnamyl alcohol.



Entry	Product		Reaction conditions	*t* [h]	Yield [%][c]
1	**2b**		A	2	57(21)
2	**3b**		B	2	99
3[d]	**4b**		B	2	68(24)
4[d]	**5b**		A	4	90
5	**6b**		B	12	93
6	**7b**		A	18	77(12)
7	**8b**		A	2	53
8	**9b**		B	4	74

[a] Reaction conditions A: enyne (**a**, 0.15 mmol), cinnamyl alcohol (1.2 equiv), xylene (0.5 mL). [b] Reaction conditions B: enyne (0.15 mmol), cinnamyl alcohol (4 equiv), no solvent. [c] Yield of isolated product. [d] 0.3 mmol of enyne was used. Bn = benzyl.

CO reacts with the enyne in the presence of the rhodium catalyst.

To follow high-temperature reactions, a high-temperature NMR experiment was performed (see the Supporting Information). Enyne **1a** was heated with cinnamyl alcohol in the presence of a catalytic amount of [{Rh(CO)Cl(dppp)}$_2$] in [D$_8$]toluene at 130 °C. From the beginning, the signal corresponding to the aldehyde was observed. The signals corresponding to the Pauson–Khand-type reaction product were also observed in the early stage of heating. Thus, the observations suggested that the dehydrogenation of cinnamyl alcohol and the decarbonylation of cinnamaldehyde occur almost at the same time. As the processes are not sequential, the precise mechanism by which a catalyst influences the three processes is difficult to elucidate. Based on the above observation and on other previous studies,[6e] a plausible mechanism for the rhodium-catalyzed tandem transformation is proposed (see the Supporting Information).

In conclusion, we have developed a new version of an auto-tandem catalytic intramolecular Pauson–Khand-type reaction in a one-pot reaction procedure, which is an inexpensive, safe, and environmentally benign carbonylation method that uses alcohols as a CO source in the presence of the catalyst [{Rh(CO)Cl(dppp)}$_2$]. Any primary alcohol can be directly used as a CO source. The carbonylation method developed in this study is more reliable and accessible than other currently available methods and should promote further advances in this area. More detailed studies are required to fully understand the mechanism of these sequential reactions.

Experimental Section

Preparation of **1b** using ethanol in toluene: [{Rh(CO)Cl(dppp)}$_2$] (7.0 mg, 6 μmol) and toluene (1 mL) were added to a flame-dried Schlenk tube equipped with a stirring bar. The mixture was stirred at RT for 5 min before enyne **1a** (0.15 mmol, 48 mg) in toluene (1 mL) and ethanol (10 equiv, 1.5 mmol) were added. After the reaction mixture had been stirred for 18 h at 70 °C the mixture was purified by flash chromatography on silica gel (eluent: *n*-hexane/EtOAc 5:2 v/v) to afford **1b** as a white solid.

Preparation of **1b** using cinnamyl alcohol without solvent: [{Rh(CO)Cl(dppp)}$_2$] (7.0 mg, 6 μmol), enyne **1a** (0.15 mmol, 48 mg), and cinnamyl alcohol (0.6 mmol, 80 mg) were added to a flame-dried Schlenk tube equipped with a stirring bar. After the reaction mixture had been stirred for 2 h at 130 °C, the reaction mixture was purified by flash chromatography on silica gel (eluent: *n*-hexane/EtOAc 5:2 v/v) to afford **1b** as a white solid.

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[10] When the same reaction was carried out under bubbling N_2, a trace amount of **1c** was formed but formation of **1b** was not observed.

[11] For unsaturated alcohols, an aldehyde species could be generated without the generation of hydrogen or a metal hydride species through an allylic isomerization through coordination of the π C–C bond followed by hydrogenation, see: A. Emery, A. C. Oehlschlager, A. M. Unrau, *Tetrahedron Lett.* **1970**, *11*, 4401.

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[15] According to the mass spectrometric investigation, the molecular weight of the product was twice that of **1a**, but its NMR spectrum was too complicated to assign. Thus, we temporary call the product an enyne-dimerized product.

[16] When the same substrate was reacted in ethanol under the optimized reaction conditions, the yield of the Pauson–Khand-type product decreased to 43% and an alkyne hydrogenated product instead of a reductive cyclized product was obtained in 35% yield.