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Pauson–Khand-type reaction mediated by Rh(I) catalysts*

Nakcheol Jeong‡, Byung Ki Sung, Jin Sung Kim, Soon Bong Park, Sung Deok Seo, Jin Young Shin, Kyu Yeol In, and Yoon Kyung Choi

Department of Chemistry and Division of Chemistry and Molecular Engineering, Korea University, Seoul, 136-701, Korea

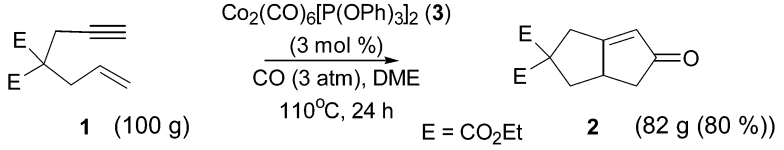
Abstract: Cocyclization of alkynes, alkenes, and carbon monoxide by transition metals (known as Pauson–Khand reaction when dicobalt octacarbonyl complexes are used) has been accepted as one of the most powerful tools in the synthesis of cyclopentenones. Despite significant progress in the various aspects of the reaction, we still needed new catalysts to expand the scope of the reaction further.

We found rhodium (I) catalysts, e.g., $RhCl(PPh_3)_3$, *trans*-$RhCl(CO)(PPh_3)_2$, RhCl(CO)(dppe), and *trans*-$[RhCl(CO)(dppp)]_2$, were also effective for this transformation. The scope and the efficiencies of the reaction could be tuned and expanded by the choice of catalysts. For example, we were able to devise an enantioselective PK-type reaction and a tandem strategy employing two catalysts in one pot. These results will be presented.

INTRODUCTION

The preparation of 5-membered rings has been a subject of intensive research for organic chemists. Of the many reported methods, transition metal-mediated coupling of three components, alkyne, alkene, and carbon monoxide, is a unique synthetic arsenal in the preparation of cyclopentenones. Since the very first report mediated by cobalt carbonyls by Pauson and Khand in 1973 (hereafter, PKR or PK-type reaction), numerous improvements of the prototype of the reaction and the variations employing other metals have been reported [1].

In 1994, we made the original stoichiometric reaction catalytic in terms of cobalt metal by introduction of an additive such as triphenylphosphite [2]. After optimization, we showed that the premade bis(triphenylphosphite)dicobalthexacarbonyl can catalyze the reaction efficiently under mild pressure of carbon monoxide (1–3 atm). This catalyst is so practical that we are able to run the reaction up to 100 g of the substrate (Scheme 1) [3].



Scheme 1 A practical catalytic PKR.

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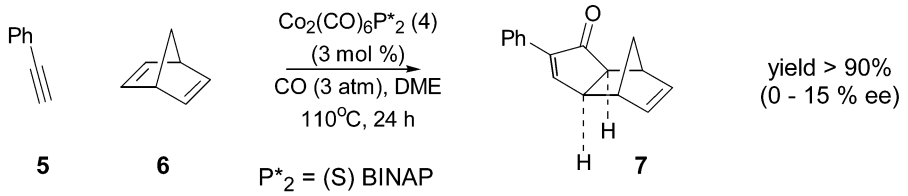
‡Corresponding author

Next, we turn our attention to develop enantioselective PKR—especially in intermolecular PKR—by introduction of chiral phosphines or phosphites [4]. The results in our hand were disappointing (Scheme 2). We never had significant enantioselectivities in this study. This failure may be accounted by a couple of reasons: (1) The PKR is actually promoted by the multitudes of cobalt carbonyls species in the reaction mixture. There must be more than a structurally well-defined catalyst. (2) The rate of PKRs by phosphine or phosphite ligand-modified catalysts is substantially slower than that by cobalt carbonyls. Thus, they are in competition with various structurally ill-defined cobalt species to give low ee. And we thought it was impossible to make enantioselective PKR by cobalt because of such inherent problems. Thus, we decided to look for the other possibility.



Scheme 2 Trials for the enanatioselective PKR with cobalt.

RHODIUM (I) CATALYSTS IN PKR

Before this work, Rh(I) has been used for the cycloaddition to give 6- and 7- membered rings from acetylene-butadiene and acetylene-vinylcyclopropane, respectively [5]. Metallacyclo-pentenes were presumed as transient intermediates in these transformations. We envision that if carbon monoxide is inserted into these intermediates, a new catalytic version of the PK-type reaction can be achieved. We found that all catalysts we tested, including even a zwitterionic catalyst, $RhCl(PPh_3)_3$, *trans*-$RhCl(CO)(PPh_3)_2$, RhCl(CO)(dppe), *trans*-$[RhCl(CO)(dppp)]_2$ [6], and $(n^6\text{-}PhBPh_3)^-Rh^+(COD)$ (Fig. 1) [7], are effective for the PK-type transformation as long as the right reaction condition is applied for each catalyst [8].

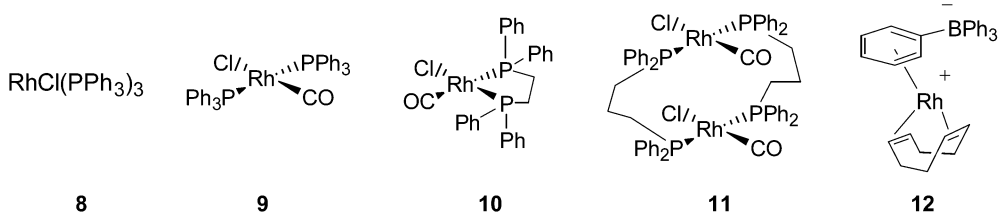
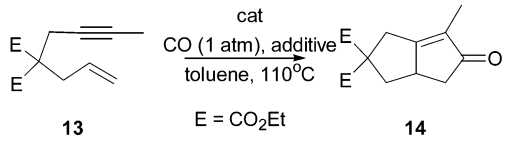


Fig. 1 Rhodium catalysts tested in this study.

Wilkinson catalyst and *trans*-$RhCl(CO)(PPh_3)_2$ requires an additive such as AgOTf to be properly activated to give the products in a reasonable time. The reactions were carried out at refluxing temperature under 1 atm of carbon monoxide. In the case of mononuclear catalyst with bidentate ligand (e.g., dppe) the presence of silver triflate is not essential but desirable (Scheme 3).

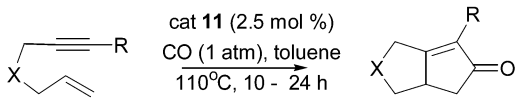
The best reaction condition was obtained by using a dinuclear rhodium catalyst, *trans*-$[RhCl(CO)(dppp)]_2$ (Scheme 4).

With these catalysts in our hands, we now can explore the potential of the PKR further. The first is to devise the enantioselective PKR.



cat (mol %)	additive (mol %)	reaction time (h)	conversion (%)	yield (%)
8 (5)	none	12	0	0
8 (5)	AgOTf (10)	18	100	89
9 (5)	none	12	0	0
9 (5)	AgOTf (10)	18	100	90
10 (5)	none	18	60	58
10 (5)	AgOTf (10)	24	90	82
11 (5)	none	24	100	96
12 (5)	none	24	100	90

Scheme 3 Rhodium-catalyzed cocyclization of enynes and CO.



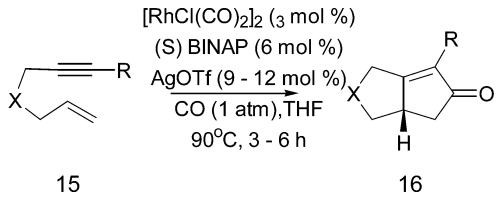
X	R	yield (%)
$(EtO_2C)_2C$	Me	95
$(EtO_2C)_2C$	Ph	99
O	Me	60
O	Ph	82
TsN	Me	94
TsN	Ph	97

Scheme 4 PKR catalyzed by *trans*-$[RhCl(CO)(dppp)]_2$.

ENANTIOSELECTIVE PKR BY Rh(I)

Among the rhodium (I) catalysts previously examined by us, RhCl(CO)(dppe) was selected and modified for the enantioselective version [9]. In a control experiment, we confirmed that the reaction with a catalyst bearing a phosphine ligand, e.g., RhCl(CO)(dppe), was also significantly decelerated compared to the reaction with $[RhCl(CO)_2]_2$ [10]. It might be attributed to the diminished Lewis acidity of the phosphine-bound catalyst, and this was also true for Co catalyst [4]. It implied that catalysts with strongly bound phosphine ligand were desirable to suppress the unwanted competition arising from the phosphine-free catalyst, which might be in equilibrium with the phosphine-bound catalyst at high temperature under CO atmosphere.

After extensive study to identify the optimum reaction conditions, we were able to figure out the following features in this transformation: (1) The catalysts prepared *in situ* by mixing of slightly excess of chiral bisphosphine ligands and $[RhCl(CO)_2]_2$ were effective for this cyclization. (2) Choice of solvent is important. Although the reaction proceeded more efficiently in toluene than in a coordinating solvent such as THF, it has to be run in THF for the high enantioselectivity. (3) Silver salt (e.g., AgOTf) is required for the proper initiation of the reaction in THF. (4) Among a number of ligands we have screened, (*S*)-BINAP turned out to be the best. (5) Balancing of CO pressure from case to case is quite critical for the high enantioslectivity as well as the chemical yield because there is a trade-off between the chemical yield and enantioselectivity of PKR product. More PKR products tend to occur under higher CO pressure, but better enantioselectivities might be obtained under lower CO pressure because the unfavorable equilibrium between potential catalysts is suppressed (Scheme 5) [11].

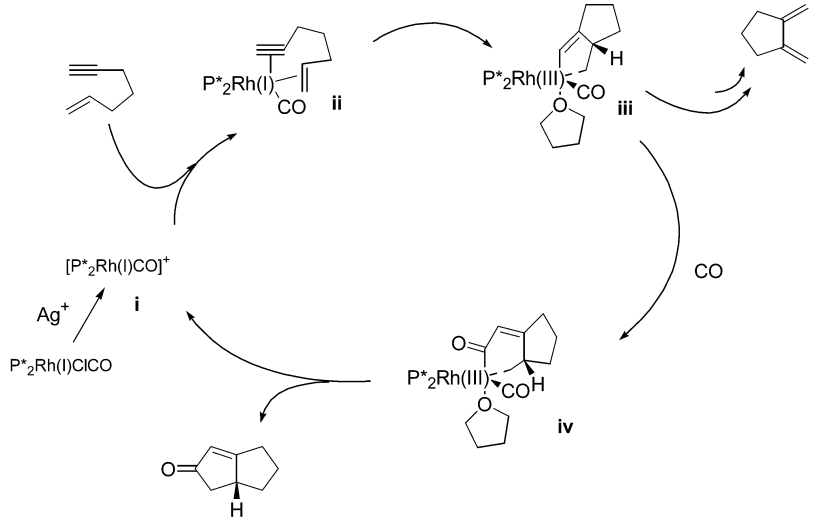


X	R	yield (%)	ee (%)	abs. confg.
$(EtO_2C)_2C$	Me	95	70	*S*
$(EtO_2C)_2C$	Ph	80	60	*S*
O	Me	85	90	
O	Ph	88	81	*R*
TsN	Me	80	84	
TsN	Ph	93	74	

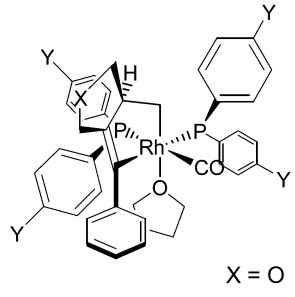
Scheme 5 An enatioselective PK-type reaction.

A reaction pathway based on the previous results is proposed in Scheme 6. The cationic catalytic species $[Rh(CO)(S)\text{-}BINAP]^+$ binds to 1,6-enyne first. This intermediate (**ii**) is converted to octahedral Rh(III) metallacyclopentene intermediate (**iii**) by the aid of THF. Subsequent migratory insertion of CO to give **iv** and reductive elimination would eventually yield the PKR product.

The face-selectivity in the first coordinating step may determine the enantioselectivity of the overall reaction. This idea was confirmed by the reactions studied with BINAP analogs having various electronic characters. Electron withdrawer provided better ee, albeit the reaction time was longer (Scheme 7) [12].



Scheme 6 A proposed mechanism of the Rh(I)-catalyzed enantioselective PKR.



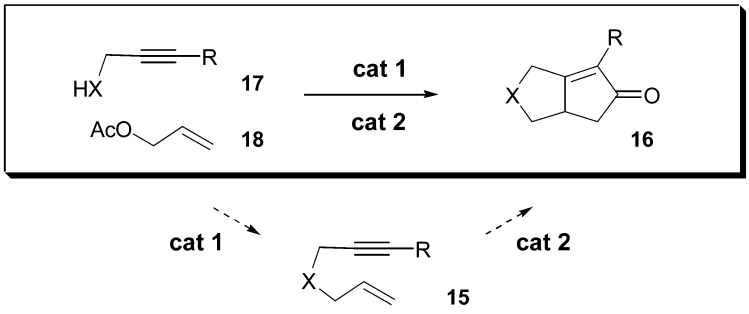
Y	reaction time (h)	yield (%)	ee (%)
OMe	1	62	73
Me	2	77	80
H	2	96	79
CF_3	3	90	90

Scheme 7 Electronic effects on the enantioselectivities.

TANDEM REACTION

One of the most remarkable features in a living organism is the specific synthesis of numerous metabolites [13]. A number of enzymes are involved for a specific metabolite, but every enzyme in a series of reactions shows high specificity to the substrates among many structurally related intermediates. As a result, a transformation including multistep reactions could be carried out in one pot without confusion and difficulties. Mimicking this feature with conventional metallic catalysts would be a great interest among organic chemists. The success of these manipulations would allow not only a conceptual advance in designing new processes, but also an economically useful integrated process, which will minimize the use of chemicals and the production of waste, and save the processing time.

Given the understanding of the state of the art and the need, it seems to be reasonable to devise a one pot multistep transformation, in which the first step catalyzed by one catalyst creates the products to be subjected to the second catalyst of the next step. And that in turn sets up the third reaction, and so on. In this context, we chose the following multiple C–C bond-forming transformation to demonstrate our proposal (Scheme 8).



Scheme 8 A proposed tandem reaction by two catalysts in one pot.

This transformation includes two reactions, e.g., the formation of an enyne intermediate (**15**) via Pd π-allyl complex of **18** and the Pauson–Khand-type cycloaddition of the resultant **15** leading to bicyclopentenones (**16**). The transformations should proceed in order to give the desired product in one pot. Thus, it is required to identify the right combination of catalysts bearing the following features: (1) The catalysts should not interfere each other. (2) All catalysts should be reluctant to induce any reactions with the substrates other than the desired. (3) In addition to those, the reaction condition needs to be normalized by one.

This notion was realized by employing a combination of $Pd_2(dba)_3(CHCl_3)$ (**19**), together with additives for the allylic alkylation and $[RhCl(CO)(dppp)]_2$ (**11**) for the PKR. Key to the success of this idea is the compatibility between $[RhCl(CO)(dppp)]_2$ and Pd(0). In a typical test experiment, substrates **17** (1.0 eq) and **18** (2.0 eq) were added to a solution of the mixture of catalysts $Pd_2(dba)_3(CHCl_3)$ (**19**) together with dppp and BSA, and $[RhCl(CO)(dppp)]_2$ (**11**) in toluene at ambient temperature. The reaction mixture was evacuated and charged with CO (1 atm) and allowed to react at r.t. for a couple of hours first and heated at 110 °C. The results are summarized in Table 1.

We soon realized that the efficiency of this transformation by a given combination of catalysts is heavily dependent on the substrates. The reactions with propargyl malonates proceeded uneventfully when the acetylene are disubstituted, although there is a substantial difference of reaction rate from case to case. While phenyl-substituted substrate gave an excellent yield (91%) of the corresponding bicyclicpentenone, methyl-substituted substrate reacted rather slowly and gave the product in only 72% yield. The reaction of propargylsulfonamides proceeded nicely regardless of the substitution pattern to

Table 1 Tandem reactions by the condition in the text.

X	R	reaction time (h)	yield of **16** (%)
$(EtO_2C)_2C$	Ph	25	92
$(EtO_2C)_2C$	Me	25	73
TsN	Ph	10	90
TsN	Me	10	91
TsN	H	6	92
O	Ph	24	0
O	Me	24	0

give the corresponding cyclopentenones in 90% yield for H, in 92% for Me, and in 90% for Ph, respectively. But the propargyl alcohols were not compatible with this condition.

CONCLUSION

Rh(I) catalysts are found to catalyze the PK-type transformation efficiently. Each catalyst has its own advantages as well as limitations. We took advantages of each catalyst to develop the enantioselective PKR by the modification of RhCl(CO)(dppe) with chiral ligands and the tandem reaction by coupling of $[RhCl(CO)(dppp)]_2$ with Pd(0) catalyst.

ACKNOWLEDGMENTS

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