

The Pauson–Khand Reaction

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Abstract The transition metal mediated conversion of alkynes, alkenes, and carbon monoxide in a formal [2 + 2 + 1] cycloaddition process, commonly known as the Pauson–Khand reaction (PKR), is an elegant method for the construction of cyclopentenone scaffolds. During the last decade, significant improvements have been achieved in this area. For instance, catalytic PKR variants are nowadays possible with different metal sources. In addition, new asymmetric approaches were established and the reaction has been applied as a key step in various total syntheses. Recent work has also focused on the development of CO-free conditions, incorporating transfer carbonylation reactions. This review attempts to cover the most important developments in this area.

Keywords Pauson–Khand reaction · Homogeneous catalysis · Cycloaddition · Transfer carbonylation · Cyclopentenones

Abbreviations

acac	Acetylacetonate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BSA	Bis(trimethylsilyl)acetamide
Bu	Butyl
^t Bu	<i>tert</i> -Butyl
cod	Cyclooctadiene
Cp	Cyclopentadienyl
dba	Dibenzylideneacetone
DMAc	<i>N,N</i> -Dimethylacetamide
DME	1,2-Dimethoxyethane
DMSO	Dimethyl sulfoxide

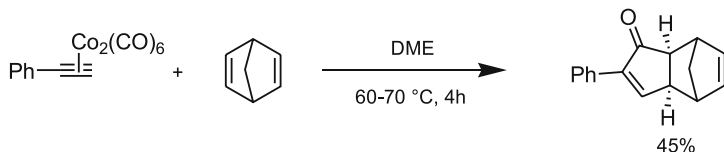
dppb	1,4-Bis(diphenylphosphino)butane
dppp	1,3-Bis(diphenylphosphino)propane
EBTHI	Ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)
ee	Enantiomeric excess
Me	Methyl
Ph	Phenyl
PKR	Pauson–Khand reaction
Py	Pyridine
SDS	Sodium dodecyl sulfate
Tf	Trifluoromethanesulfonyl
TMANO	Trimethylamine <i>N</i> -oxide
tolBINAP	2,2'-Bis(di-4-tolylphosphino)-1,1'-binaphthyl
TPPTS	Triphenylphosphine trisulfonate

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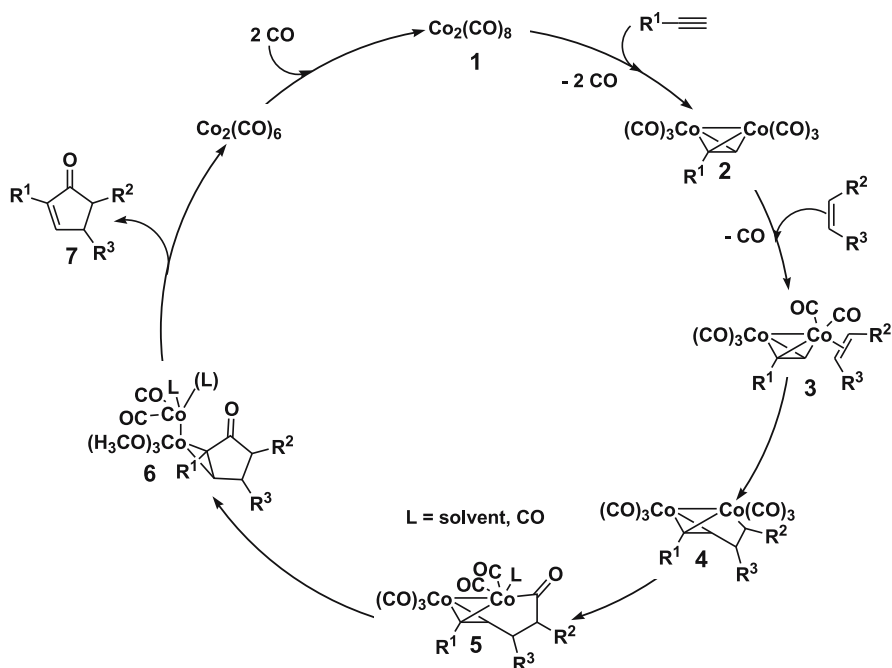
Introduction

An important procedure for the synthesis of cyclopentenones is the so-called Pauson–Khand reaction, which constitutes a formal $[2 + 2 + 1]$ cycloaddition of an alkene, an alkyne, and carbon monoxide. Due to the increase in structural diversity of the available starting materials, the reaction has become an attractive target for scientific investigations [1–8]. The first successful example was reported by Pauson, Khand et al [9] in 1973 for the conversion of norbornene with the phenylacetylene–hexacarbonyldicobalt complex to give the corresponding cyclopentenone in 45% yield (Eq. 1).

A proposed mechanism of this reaction was reported by Magnus and Principle [10], which is nowadays widely accepted (Scheme 1). Recently, negative-ion electrospray collision experiments have confirmed this mechanism in detail [11]. Starting with the formation of the alkyne– $\text{Co}_2(\text{CO})_6$ complex **2**, olefin **3** coordination and subsequent insertion takes place at the less hindered end of the alkyne. The in situ formed metallacycle **4** reacts rapidly under insertion of a CO ligand **5** and reductive elimination of **6** proceeds to liberate the desired cyclopentenone **7**. It is important to note that all the bond-forming steps occur on only one cobalt atom. The other cobalt atom of the complex is presumed to act as an anchor which has additional electronic influences on the bond-forming metal atom via the existing metal–metal bond [12].



Equation 1



Scheme 1 Mechanistic proposal for the Pauson–Khand reaction

After its discovery the method was affected by various problems. For instance, a stoichiometric amount of catalyst and the use of strained olefins were necessary to obtain useful yields. Furthermore, if unsymmetrical alkynes and alkenes were used, the reactions typically gave a mixture of regioisomers. In addition, many early examples reported the need for long reaction times and high temperatures to obtain full conversion.

An important advance was reported by Schore and Croudace [13], who showed for the first time that carbon-tethered enyne precursors undergo an intramolecular Pauson–Khand reaction (PKR) in good yields with complete control of regioselectivity. In this connection, it was not essential to use strained olefins as starting materials.

In addition to $\text{Co}_2(\text{CO})_8$, subsequently other metal complexes such as molybdenum hexacarbonyl [14], iron pentacarbonyl [15, 16], tungsten pentacarbonyl [17], and zirconium [18] or heterobimetallic cobalt/tungsten complexes [19] were reported to facilitate the PKR. Although various metals furnish the stoichiometric PKR, $\text{Co}_2(\text{CO})_8$ has become the catalyst of choice due to its several advantages, e.g., the complex tolerates a broad range of functional groups, reveals activity toward both terminal and internal alkynes, and is relatively cheap. With regard to problems like high temperatures and CO pressures, as well as long reaction times, significant progress was reported independently by the groups of Jeong [20] and Schreiber [21], who reported

the application of *N*-methylmorpholine *N*-oxide and trimethylamine *N*-oxide as PKR accelerating agents. Using *N*-oxides, cyclopentenones were obtained in good yields even at room temperature. It is likely that the promoting effect of *N*-oxides is based on the oxidative liberation of the CO ligands of the metal complex. Therefore, the following oxidative alkene addition, known as the rate-determining step in the PKR, can now proceed very fast.

Other reagents such as silica gel [22, 23], molecular sieves [24, 25], alkyl methyl sulfides [26], or primary amines [27] were also reported to facilitate the reaction, but seem not to work as generally as *N*-oxides.

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The Catalytic Pauson–Khand Reaction

PKR with stoichiometric amounts of $\text{Co}_2(\text{CO})_8$ are still often used as the key step in various total syntheses. However, with regard to environmental friendliness, catalytic procedures are desirable. This chapter will deal with recent approaches in the development of the catalytic PKR.

The first catalytic PKR was reported by Rautenstrauch et al. [28], who described the conversion of heptyne using a mixture of 40 bar ethylene and 100 bar CO to form the resulting cycloaddition adduct in a yield of 48%. A more practicable procedure was later reported by Jeong et al. [29], who realized the PKR in good yields at 3 atm of CO and 110 °C by stabilization of the cobalt catalyst with triphenylphosphite as ligand. Apart from $\text{Co}_2(\text{CO})_8$, other Co sources were also successfully applied within the reaction. For example, Sugihara and Yamaguchi [30] described the employment of methylidyne-tricobalt nonacarbonyl clusters $\text{Co}_3(\text{CO})_9(\mu^3-\text{CH})$, which are advantageous due to the catalyst productivity (1–2 mol %). Furthermore, the system catalyzes both the intra- and intermolecular PKR with remarkably good yields (78–91%). Lee and Chung [31] examined the use of $\text{Co}(\text{acac})_2/\text{NaBH}_4$ as cycloaddition catalyst. In this case, yields were observed in a range of 33–85%. Successful conversions needed high CO pressures (40 atm) and long reaction times (up to several days). The first example of a catalytic conversion under atmospheric pressure of carbon monoxide was reported by Rajesh and Periasamy [32]. Here, a combination of 0.4 eq. CoBr_2 and 0.43 eq. Zn was chosen to facilitate the intermolecular PKR. Isolated yields were obtained in the range of 30–88% at 110 °C. Supplementary to reactions in organic solvents, procedures applying supercritical fluids have become more and more attractive in industry and academic research. So it is not surprising that Jeong's group reported the use of supercritical CO_2 as alternative solvent [33]. Using $\text{Co}_2(\text{CO})_8$ as catalyst, 112 atm of CO_2 and 15–30 atm of CO were required at 37 °C to obtain cyclopentenones in yields up to 91%.

In addition to the accelerating effect of sulfides and amines in the stoichiometric $\text{Co}_2(\text{CO})_8$ -mediated procedure, Hashimoto et al. showed that phos-

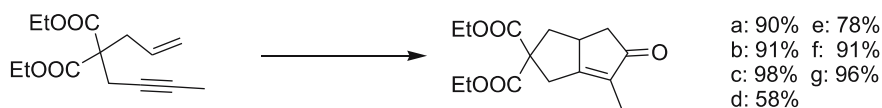
phane sulfides are able to promote the $\text{Co}_2(\text{CO})_8$ -catalyzed reaction [34]. Even at atmospheric CO pressure and moderate temperature of 70°C , the desired products were isolated in almost quantitative yields (ca. 90%).

Due to the easier recycling of heterogeneous catalysts, Chung et al. developed an easy system that is based on the immobilization of 12 wt % metallic cobalt on commercially available charcoal [35]. The resulting yields were obtained in the range of 61–98%. After simple filtration the catalyst was reused up to ten times without significant loss of activity.

Although Co carbonyl complexes have been used most often in catalytic PKR, a variety of other transition metal complexes are able to catalyze this reaction. For instance, $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$ [36] and Ni(0) catalysts [37] have been reported to afford iminocyclopentenones by the use $^t\text{BuMe}_2\text{SiNC}$ instead of CO. Subsequent hydrolysis provides the desired cyclopentenones. Unfavorably, the isolated product yield decreases significantly when applying this reaction sequence.

Buchwald et al. have shown that 5–20 mol % $\text{Cp}_2\text{Ti}(\text{CO})_2$ facilitates the PKR at 18 psi CO and 90°C , giving yields in between 58 and 95% [38]. Moreover, Mitsudo et al. [39] and Murai et al. [40] reported independently on the employment of $\text{Ru}_3(\text{CO})_{12}$ as active catalyst. Cyclopentenones were isolated in moderate to excellent yields (41–95%). In addition, rhodium catalysts were successfully examined for use in the PKR. Narasaka et al. [41] carried out reactions at atmospheric CO pressure using the dimeric $[\text{RhCl}(\text{CO})_2]_2$ complex. Also, in the presence of other rhodium complexes like Wilkinson catalyst $\text{RhCl}(\text{PPh}_3)_3$ and $[\text{RhCl}(\text{CO})(\text{dppp})]_2$ [42] in combination with silver salts, cyclopentenones were obtained in yields in the range of 20–99%. Some representative examples of the catalytic PKR are shown in Eq. 2.

In contrast to the development of general procedures for intramolecular PKR, the realization of comparable intermolecular procedures was afflicted

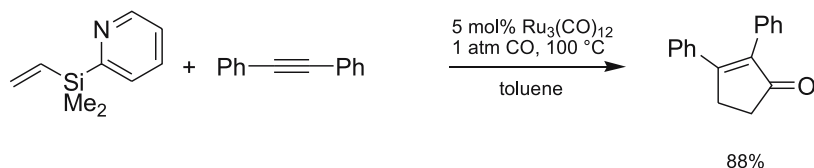


conditions:

- a: 3 mol% $\text{Co}_2(\text{CO})_8$, $\text{P}(\text{OPh})_3$, DME, 3 atm, [29]
- b: 3 mol% $\text{Co}_2(\text{CO})_8$, 11 atm CO_2 at 36°C , 30 atm CO, 94°C , 24 h [33]
- c: 12 wt%Co supported on charcoal, 20 atm CO, THF, 18 h, [35]
- d: 10 mol% $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$, $^t\text{BuMe SiNC}$, additional hydrolysis, [36]
- e: 5 mol% $\text{Ru}_3(\text{CO})_{12}$, DMAc, 15 atm CO, 140°C , 20 h, [39]
- f: 1 mol% $[\text{RhCl}(\text{CO})_2]_2$, 1 atm CO, Bu_2O , 130°C , 18 h, [41]
- g: 2.5 mol% *trans*- $[\text{RhCl}(\text{CO})(\text{dppp})]_2$, 1 atm CO, 110°C , 24 h, toluene, [42]

Equation 2

with various problems. With exception of ethylene and strained alkenes, reactions employing simple olefins gave only poor yields because of their low reactivity. Furthermore, the observed regioselectivities were also disappointing. The pioneering work of Krafft et al. [43–45] revealed that the introduction of coordinating heteroatoms, such as nitrogen or sulfur, attached to the alkene leads to a strong enhancement of reactivity and regioselectivity. Hence, further work was dedicated to developing an easily removable directing group, which would open the way to increasing the synthetic potential of the intermolecular PKR. In this connection, Itami et al. [46, 47] developed an interesting system, which included a 2-pyridyldimethylsilyl group tethered to the alkene part (Eq. 3). As a major advantage, this directing group enabled the regioselective synthesis of cyclopentenones at the 4- and 5-position, respectively. The pyridylsilyl group is removed after product formation caused by residual water. Looking at different catalysts, $\text{Ru}_3(\text{CO})_{12}$ gave the best results even under a remarkably low pressure of 1 atm CO. Here, yields were obtained in the range of 40–91%.



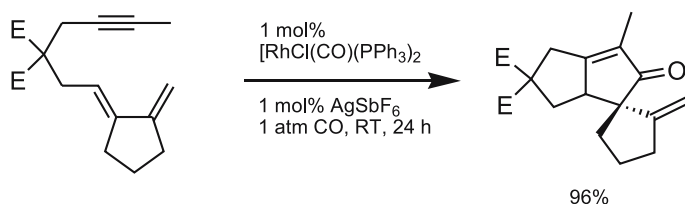
Equation 3

3 Synthetic Applications

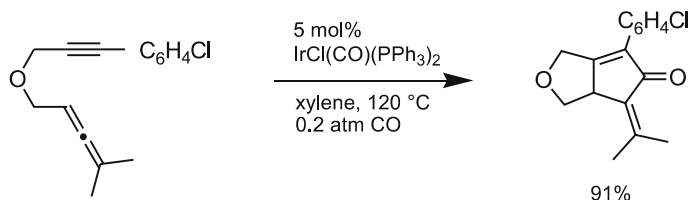
In addition to the use of the simple enyne precursors, several groups examined the PKR of related systems, which would broaden the scope of the method. Pursuing this strategy, Wender et al. elaborated dienyl-type PKR [48]. Conversion proceeded smoothly even at room temperature under an atmospheric pressure of CO by applying $[\text{RhCl}(\text{CO})(\text{PPh}_3)_2]$ as catalyst. Yields ranging from 43 to 96% were obtained. Interestingly, the chosen system tolerates a variety of substitution patterns on the alkyne dienyl moiety (Eq. 4).

Recently, Shibata et al. reported on the successful conversion of alkenynes [49]. By employing $[\text{IrCl}(\text{CO})(\text{PPh}_3)_2]$ as active catalyst (Eq. 5), reactions were carried out under a very low pressure of carbon monoxide affording yields up to 91%.

Without doubt, multicomponent reactions have become an attractive tool for the synthesis of biologically active molecules. In this regard, Jeong et al. reported an interesting domino synthesis of bicyclopentenones [50]. They employed a bimetallic system consisting of $[\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)]$ and

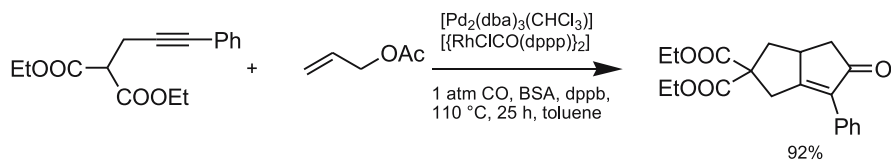


Equation 4



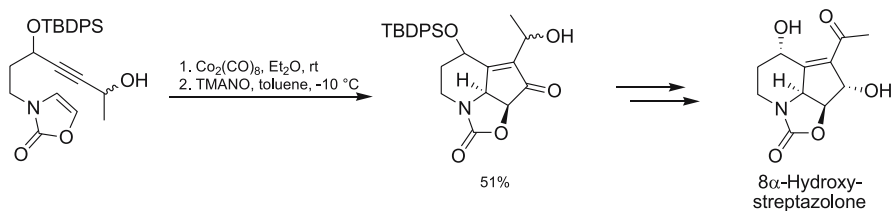
Equation 5

$[\{\text{RhClCO}(\text{dppp})\}_2]$ for the sequential construction of an enyne precursor, starting from a malonic acid derivative and allylic acetate, which was converted in situ to the cycloaddition product with excellent yields. Obviously, the Pd complex catalyzes the allylic substitution reaction, while the rhodium catalyst is responsible for the PKR (Eq. 6).



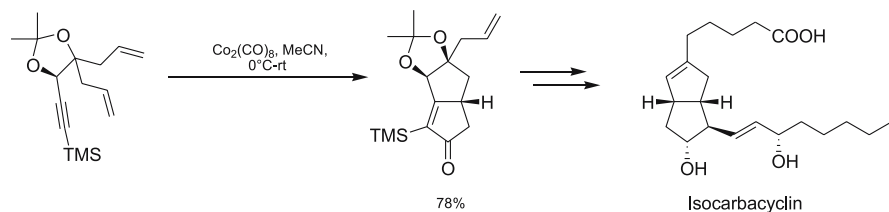
Equation 6

Because of the remarkable increase of molecular complexity, the PKR serves as a useful methodology for various natural product syntheses. Numerous examples of synthetic applications have been reported during the last two decades. For instance, the PKR was successfully employed in the total syntheses of β -cupraenone [51], loganin [52], hirsutene [53], and (+)-epoxydictymene [54]. Just to comment on recently published examples, Nomura and Mukai [55] reported on the total synthesis of (\pm)-8 α -hydroxystreptazolone (Eq. 7). This target molecule achieved attention due its antibiotic and antifungal activity. In this case, the PKR was used to build up the required tricyclic framework. The successful conversion was facilitated by the employment of an equimolar amount of $\text{Co}_2(\text{CO})_8$ and TMANO as promoting reagent. The resulting cyclopentenone derivative was isolated in 51% yield.



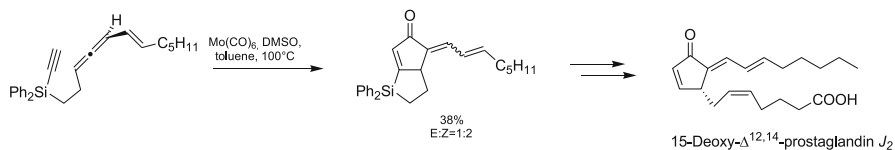
Equation 7

More recently, the total synthesis of iscarbacyclin, a therapeutically useful agent against numerous vascular diseases, was reported by Saito et al. [56]. Again, the crucial cycloaddition step was carried out using a stoichiometric amount of $\text{Co}_2(\text{CO})_8$. The reaction was completed within 3 h and gave 78% yield of the desired cyclopentenone (Eq. 8).



Equation 8

With regard to the known activity of cyclopentenone-containing prostaglandins, which serve, for instance, as anti-inflammatory and antineoplastic ingredients [57], Brummond et al. elaborated the total synthesis of 15-deoxy- $\Delta^{12,14}$ -prostaglandin J_2 by applying an allenic PKR [58]. As a special feature, screening for a suitable catalyst system gave the best results when employing $\text{Mo}(\text{CO})_6$. The reaction was accomplished in a moderate yield of 38%, producing a mixture of *E/Z* isomers in a ratio of 1 : 2 with respect to the unwanted *Z* isomer. Additional reisomerization of the undesired isomer, by photolysis or treatment with boron trifluoride/propanedithiol, increased the yield of the target isomer (Eq. 9).



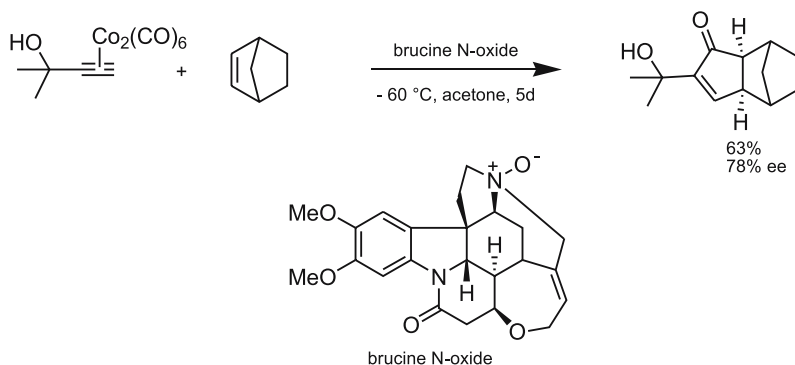
Equation 9

4 Stereoselective Pauson–Khand Reactions

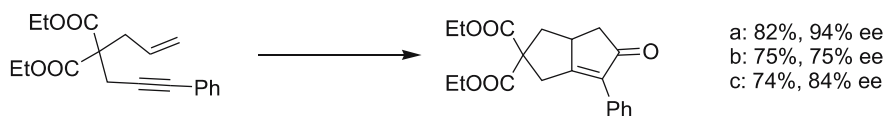
The virtue of performing the PKR in an enantioselective manner has been extensively elaborated during the last decade. As a result, different powerful procedures were developed, spanning both auxiliary-based approaches and catalytic asymmetric reactions. For instance, the use of chiral *N*-oxides was reported by Kerr et al., who examined the effect of the chiral brucine *N*-oxide in the intermolecular PKR of propargylic alcohols and norbornadiene [59]. Under optimized conditions, ee values up to 78% at $-60\text{ }^{\circ}\text{C}$ have been obtained (Eq. 10). Chiral sparteine *N*-oxides are also able to induce chirality, but the observed enantioselectivity was comparatively lower [60].

The application of chiral auxiliaries is an alternative route to obtain enantiomerically pure compounds. This approach has been frequently used in the total syntheses of natural products like hirsutene [53] and (+)-15-norpentalone [61].

Although this procedure often provides excellent diastereoselectivities, a major drawback is the expensive synthesis of the PKR precursor. Hence, the application of chiral transition metal catalysts is a more convenient method for the synthesis of enantiomerically pure cyclopentenones. The first successful results were reported by Buchwald and Hicks, who showed that the chiral titanocene complex (*S,S*)-(EBTHI)Ti(CO)₂ is a useful system for that purpose [62, 63]. Various enynes were converted under 14 psig CO pressure and $90\text{ }^{\circ}\text{C}$ reaction temperature. Yields were often good (72–96%), and the obtained enantioselectivities were also good to excellent (70–94%). In addition, RhCl(CO)₂ in combination with AgOTf and (*S*)-BINAP was reported to facilitate enantioselective PKR [64]. Values of ee were observed in between 22 and 99% and isolated yields were in the range of 22–96%. Moreover, it was shown that chiral iridium diphosphine complexes catalyze such cycloaddition reactions [65]. Using a comparatively large amount of 10 mol %



Equation 10

**conditions:**

a: 7.5 mol% (*S,S*)(EBTHI)Ti(CO)₂, 14 psig CO, toluene, 12h, 90 °C, [62, 63]

b: 6 mol% Co₂(CO)₈, 10 mol% ligand, toluene, 1 atm CO, 24 h, 95 °C, [67]

c: 5 mol% [Ir(cod)Cl]₂ + 10 mol% (*S*)-tolBINAP, 1 atm CO, refluxing xylene, 72h, [65]

Equation 11

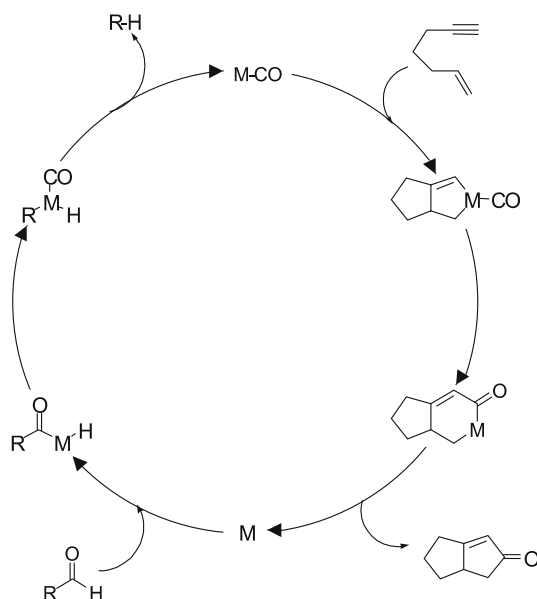
[Ir(cod)Cl]₂, reactions afforded enantiomerically enriched cyclopentenones when (*S*)-tolBINAP was employed as ligand. The corresponding cyclopentenones were obtained in yields up to 85% and ee values ranging from 82 to 98%. Interestingly, Co₂(CO)₈ in combination with a chiral bisphosphite also gives access to chiral Pauson–Khand products [66]. Here, yields were observed up to 97%; however, in most cases the ee was rather low (< 20%). Equation 11 summarizes some representative examples of enantioselective PKR.

5**Pauson–Khand Transfer Carbonylation Reactions**

During the last few years, the PKR has been developed as a straightforward and practicable method for the synthesis of highly substituted cyclopentenones. But for many synthetic chemists, the employment of poisonous CO still represents a disadvantage. Hence, different strategies focused on the replacement of carbon monoxide within the reaction sequence. Recent successful examples are based on results from the early 1960s, which dealt with the transition metal catalyzed decarbonylation of organic oxo compounds [67].

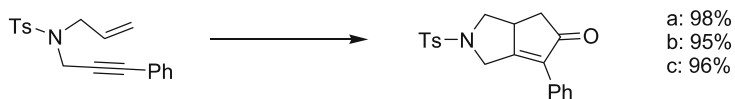
In Scheme 2 the general mechanism of this transformation is shown. Clearly, the in situ formation of CO by a decarbonylation process takes advantage of the formation of metal carbonyls, which are known to be the key intermediates in the PKR.

Morimoto, Kakiuchi, and co-workers were the first to show that aldehydes are a useful source of CO in the catalytic PKR [68]. Based on ¹³C-labeling experiments, it was proposed that after decarbonylation of the aldehyde, an active metal catalyst is formed. This was proven by the absence of free carbon monoxide. As a consequence CO, which is directly generated by previous aldehyde decarbonylation, is incorporated in situ into the carbonylative coupling. The best results were obtained using C₅F₅CHO and cinnamaldehyde as CO source in combination with [RhCl(cod)]₂/dppp as the catalyst system. In the presence of an excess of aldehyde the corresponding products were isolated in the range of 52–97%.



Scheme 2 Proposed catalytic mechanism for PK transfer carbonylations

Later, Shibata et al. reported PK-type transfer carbonylation reactions in the absence of solvent and employing a large excess of aldehyde [69]. Also in this case, the reactions went smoothly yielding cyclopentenones in the range of 56–96%. Interestingly, it was also demonstrated that this methodology provides access to chiral products. By applying the chiral catalyst system $[\text{RhCl}(\text{cod})]_2/\text{tolBINAP}$, ee values of 45–90% were observed. Another convincing approach to carrying out PK-type transfer carbonylation reactions was again reported by Kakiuchi et al. [70]. Herein, formaldehyde was employed as decarbonylating agent in the presence of a micelle-containing aqueous system. It was proposed that the decarbonylation and carbonylation reactions take place in different phases. More precisely, the water-



conditions:

- a: 5 mol% $\text{Rh}(\text{dppp})_2\text{Cl}$, 20 eq. cinnamaldehyde, 2h, 120 °C, [69]
 b: 5 mol% $[\text{RhCl}(\text{cod})]_2$, 11 mol%. dppp, 2 eq. $\text{C}_6\text{F}_5\text{CHO}$, xylene, 4h, 130 °C [68]
 c: 5 mol% $[\text{RhCl}(\text{cod})]_2$, 10 mol% dppp, 10 mol% TPPTS, 2 eq. SDS, 10 eq. HCHO , 2h, refluxing water [70]

Equation 12

soluble formaldehyde is decarbonylated in the aqueous phase, enabled by the $[\text{RhCl}(\text{cod})]_2/\text{TPPTS}$ system, while carbonylation takes place in a micelle formed by the surfactant SDS. Also, in this case the yields obtained were good to quantitative (67–96%). Recently, the same group reported on the first asymmetric version of this procedure [71]. By applying the catalyst system $[\text{RhCl}(\text{cod})]_2/(S)\text{-tolBINAP}$, the reactions resulted in ee values of 74–95% and yields up to 83%. Selected examples of PK-type transfer carbonylation reactions are shown in Eq. 12.

6

Conclusions and Outlook

Recent developments have impressively enlarged the scope of Pauson–Khand reactions. Besides the elaboration of strategies for the enantioselective synthesis of cyclopentenones, it is often possible to perform PKR efficiently with a catalytic amount of a late transition metal complex. In general, different transition metal sources, e.g., Co, Rh, Ir, and Ti, can be applied in these reactions. Actual achievements demonstrate the possibility of replacing “external” carbon monoxide by transfer carbonylations. This procedure will surely encourage synthetic chemists to use the potential of the PKR more often in organic synthesis. However, apart from academic research, industrial applications of this methodology are still awaited.

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