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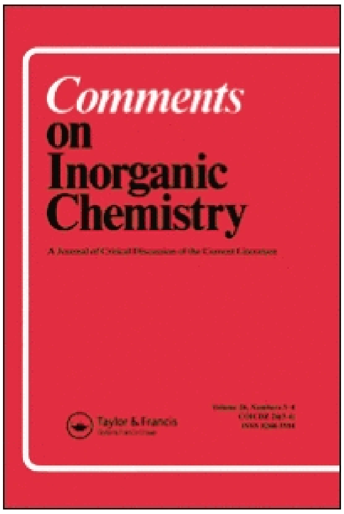

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Catalytic Pauson Khand and Related Cycloaddition Reactions

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Catalytic Pauson Khand and Related Cycloaddition Reactions

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The Pauson Khand reaction is a powerful synthetic tool that yields cyclopentenones by the 2 + 2 + 1 cycloaddition of an alkyne, an alkene, and carbon monoxide. The reaction is widely practiced stoichiometrically and requires an equivalent of dicobalt octacarbonyl to effect the cycloaddition. Recent advances in the development of catalysts have extended the application of the reaction. Catalysts include complexes of cobalt, rhodium, iridium, ruthenium, and titanium. With ruthenium catalysts it has been discovered that unsaturated substrates containing heteroatoms, such as imines and aldehydes, can be used in 2 + 2 + 1 cycloadditions. Catalysts and proposed mechanisms for the Pauson Khand reaction are reviewed here.

Keywords: catalysis, Pauson Khand reaction, cycloaddition reactions, cobalt, ruthenium, rhodium, iridium

INTRODUCTION

The Pauson Khand reaction refers specifically to the 2 + 2 + 1 cycloaddition reaction of an alkyne, an alkene, and CO over cobalt carbonyl. The reaction was first reported in 1973[1] and has seen a remarkable growth in popularity as it has been recognized as a powerful synthetic method for five-membered ring formation. A quick search on the term "Pauson Khand" in the ISI Web of Science database generates 98 citations in the period 1990–1995 and 319 citations in the period 1996 to September 2001.

The intermolecular and intramolecular versions of the 2 + 2 + 1 cycloaddition reaction are shown in Equations 1 and 2, respectively. Much of the interest in the area is due to the formation of bicyclic products from the intramolecular reaction.

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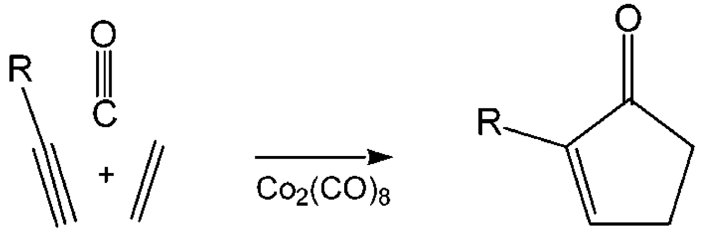

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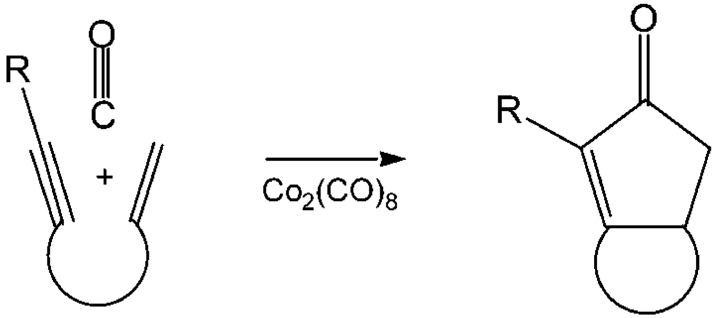

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The reaction is generally done stoichiometrically with one equivalent of dicobaltoctacarbonyl required for the transformation. Often the alkyne complex, (alkyne)$Co_2(CO)_6$, is premade and then reacted with alkene and CO. Although Pauson and Khand realized a catalytic cycloaddition for the reaction of acetylene and norbornene,[1] it is only in the last 10 years that the catalytic reaction has received serious attention in the literature.[2–8]

In principal, four isomeric cyclopentenones can form in the Pauson Khand reaction of a terminal alkyne with a terminal alkene. These are shown in Figure 1. Isomers **A** and **B**, in which the substituted end of the alkyne is found adjacent to the carbonyl group, are formed in the intermolecular reaction. Isomer **C** is not observed. In the case of internal alkynes there is slight

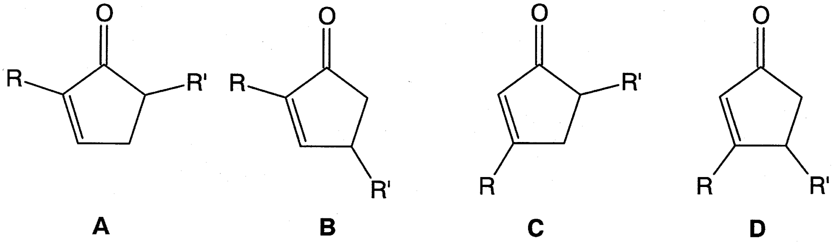


FIGURE 1 Four isomeric cyclopentenones are possible from the cycloaddition of a terminal alkyne with a terminal alkene and CO.

preference for the more bulky substituent to be located next to the carbonyl group. Isomer **D** is formed in the intramolecular reaction where R and R′ are linked. The intramolecular reaction leads to the formation of bicyclic compounds.

In addition to cobalt carbonyl it has been found that a wide variety of transition metal complexes are capable of either mediating or catalyzing 2+2+1 cycloadditions reaction of alkyne, alkene, and CO.[9–15] Furthermore, it has been found that aldehydes, ketones, imines, and other unsaturated groups can often replace either the alkyne or the alkene in the cycloaddition reaction.[16–18] It is evident from the literature that the scope of the Pauson Khand reaction has been greatly expanded from its origins with cobalt carbonyl and unsaturated hydrocarbons. The purpose of this review is to summarize the literature of catalytic cyclic 2+2+1 cycloaddition reactions regardless of the catalyst. In the context of this review these are referred to as Pauson Khand cycloaddition reactions.

Both cobalt carbonyl and other transition metal complexes that catalyze the Pauson Khand reaction can be further modified by the addition of ligands. The ligand donor atom may be incorporated into the substrate, e.g., into an enyne for the intramolecular reaction or into either the alkene or the alkyne for the intermolecular reaction. When the ligand is added to the substrate it may direct the regiochemistry of the cycloaddition reaction. The addition of chiral auxiliaries to the substrates has been very successful for the accomplishment of enantioselective cycloaddition reactions. Some examples of chiral auxiliaries are included in this review in the context of stoichiometric reactions. Alternatively, an independent ligand such as a phosphine or an amine may be added to the reaction. The role of the ligand in this case is to stabilize the catalyst or to modify the catalyst selectivity. With respect to selectivity, good success has been achieved recently for the catalytic enantioselective cycloaddition reaction through the use of chiral phosphines.

COBALT

Mechanism

The generally accepted mechanism for the cobalt carbonyl mediated reaction is that originally proposed by Magnus for the stoichiometric intramolecular cycloaddition reaction.[19] The catalytic Pauson Khand reaction as a synthetic method was realized by Rautenstrauch et al. in 1990.[2] They proposed a version of the Magnus mechanism that regenerates dicobalt octacarbonyl. The Rautenstrauch mechanism is shown in Figure 2 for the intermolecular Pauson Khand reaction. The stoichiometric transformation terminates with the formation of cyclopentenone. For the reaction to be catalytic either dicobaltoctacarbonyl or compound **1** must be regenerated after the reductive elimination of cyclopentenone. It has been observed that

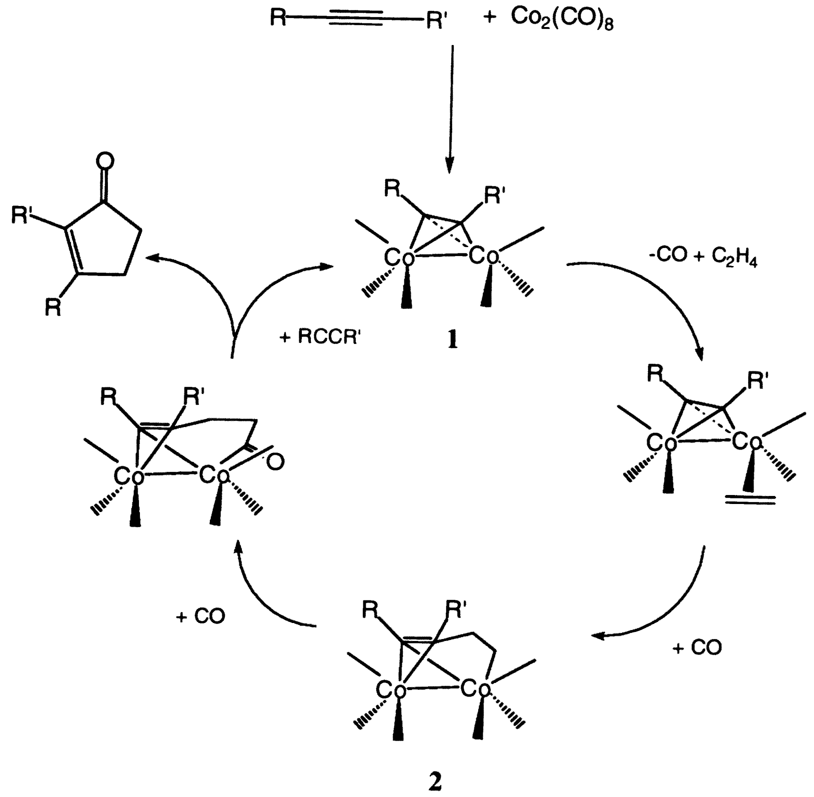


FIGURE 2 Proposed catalytic cycle for the intermolecular Pauson Khand reaction.[2,19]

both $Co_2(CO)_8$ and (alkyne)$Co_2(CO)_6$, compound **1**, can act as catalyst precursors for the cycloaddition reaction.

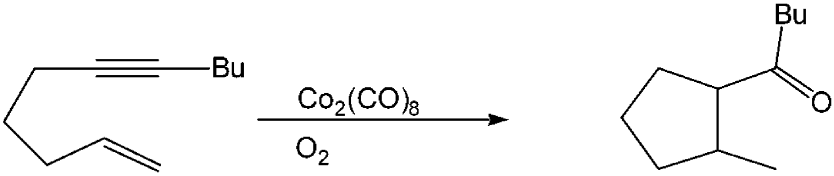
In the intermolecular reaction the alkene is proposed to insert into the least hindered alkyne-cobalt site. Carbon monoxide insertion then occurs at the cobalt-alkyl carbon bond. Thus, upon reductive elimination the carbonyl group is adjacent to the most hindered carbon of the alkyne. The intermolecular cycloaddition reaction is thought to require both cobalt atoms. The basis for this is that compound **1**, can be synthesized and used for the stoichiometric reaction.

As noted above, Pauson et al.[1] and Rautenstrauch et al.[2] showed that the 2+2+1 cycloaddition reaction can be done catalytically. More recently, Livinghouse reports that the catalytic Pauson Khand reaction can be performed reliably with photolytic activation of cobalt carbonyl at 50°C to 55°C[20] or with thermal activation in the temperature range 60°C to 70°C[6] in dimethoxyethane as the solvent. In both examples it is suggested that the cobalt carbonyl must be very pure and it is recommended that the $Co_2(CO)_8$ be freshly crystallized or sublimed. As a counterpoint, Krafft et al. report that cobalt carbonyl purity is not critical for catalytic activity.[21] They find that commercially prepared $Co_2(CO)_8$ can be used as received for the catalytic Pauson Khand reaction; the cobalt carbonyl is activated for the Pauson Khand reaction by the addition of cyclohexylamine.[21] The use of hard Lewis bases to activate cobalt carbonyl is a common protocol for the Pauson Khand reaction and is discussed in more detail later.

Carbon monoxide dissociation from compound **1** is required to open a site to allow alkene coordination. Not surprisingly, reagents that promote CO dissociation also promote the Pauson Khand reaction.[8,22] Amine oxides, which oxidize coordinated CO to CO_2 in metal carbonyls, are effective in promoting the Pauson Khand reaction.[23] Thus, many reaction protocols for the Pauson Khand reaction call for Brucine-N-oxide,[24,25] trimethylamine oxide,[26] or N-methylmorpholine-N-oxide.[27,28] Krafft et al. have demonstrated that the intramolecular Pauson Khand reaction can use the enyne equivalent of compound **1** as the catalyst precursor.[3]

Other cobalt compounds, including the clusters, $Co_4(CO)_{12}$ and MeC-$Co_3(CO)_9$, can act as the catalyst precursor.[29–32] In the case of $Co_4(C0)_{12}$ it is thought that complex **1** is formed in situ.[4] Interestingly, the methylidine capped cluster, $MeCCo_3(CO)_9$, is more active than $Co_2(CO)_8$ for the cycloaddition reaction.[32]

Additional mechanistic insight to the Pauson Khand reaction is seen when a reaction intermediate is intercepted by oxygen.[33] This interrupted Pauson Khand reaction is interpreted as evidence for the intermediate labeled **2** in Figure 2. In the presence of oxygen there is a competition between carbonyl insertion and oxidation to a ketone. The interrupted reaction was done with an enyne as shown in Equation 3.[33]



(3)

The site of CO dissociation is the subject of two recent theoretical studies.[34,35] Both argue for a trans effect. However, one study favors labilization trans to an electron-donating group while the other supports labilization trans to an electron-withdrawing group (i.e., labilization cis to the electron-donating group). For example, amine-substituted alkynes are electron rich at the substituted carbon. The bridging alkyne carbons are

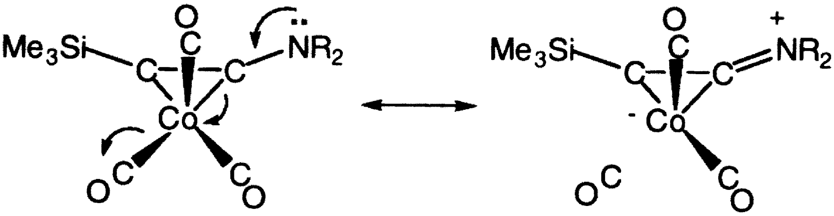


FIGURE 3 Scheme proposed for the labilization of a CO trans to an electron donating alkyne.[35]

trans to the pseudo equatorial carbonyls in (alkyne)$Co_2(CO)_6$, see Figure 3. It is argued by Pericas et al. that the CO trans to the amine-substituted alkyne carbon, in (trimethylsilylyneamine)$Co_2(CO)_6$, is activated for dissociation.[35] This is illustrated in Figure 3; the electron-pushing scheme is that of Pericas et al. The view is down the Co-Co bond and only the groups bonded to the visible cobalt are shown. This scheme is contrary to the generally accepted role of an electron-donating group in a position trans to carbon monoxide in metal carbonyl complexes. The metal-CO bond is strengthened by an increase in pi bonding from the metal to an antibonding orbital on CO when trans to an electron donating group. By this reasoning the trans position is less likely to dissociate and the cis position should be relatively more labile. A cis labilization, relative to the electron-donating group, is argued by Gimbert et al. for unsymmetrical (alkyne)$Co_2(CO)_6$ complexes[34] as illustrated in Figure 4.

In a separate theoretical study Gimbert et al. show that, irrespective of the site of CO dissociation and initial alkene coordination, the alkene moves to the axial site prior to addition to the bridging alkyne.[36] The cobalt atoms are five coordinate (if the alkyne is treated as occupying a single equatorial position) in (alkyne)$Co_2(CO)_6$, and thus capable of facile pseudorotation.

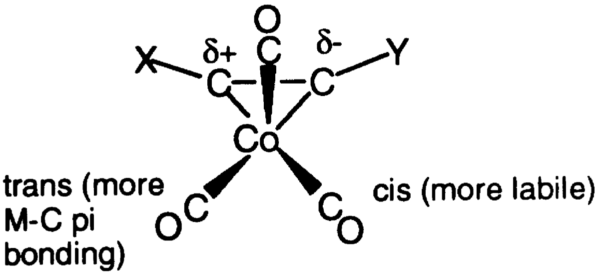


FIGURE 4 Scheme proposed for the labilization of a CO cis to an electron donating alkyne.[34]

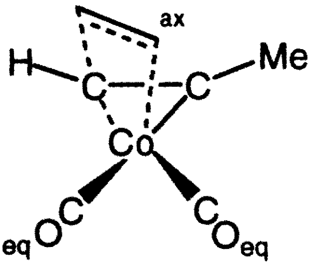


FIGURE 5 Transition state proposed for the insertion of an alkene into the bridging alkyne in the Pauson Khand reaction.[36]

This gives the coordinated alkene access to both axial and equatorial positions. The transition state calculated to be optimal for the insertion of the alkene is the axial position as shown in Figure 5. Independently, Yamanaka and Nakamura have evaluated potential reaction intermediates in the Pauson Khand reaction by density functional theory.[37] In this study the best transition state for alkene insertion also places the alkene in the axial position. Further, the authors suggest that it is the alkene insertion step that determines the reaction regio- and stereochemistry with substituted alkenes.

Cobalt Reagents for Stoichiometric and Catalytic Cycloaddition Reactions

As noted above, the compounds $Co_2(CO)_8$, $Co_4(CO)_{12}$, $MeCCo_3(CO)_9$, and (alkyne)$Co_2(CO)_6$ are all precursors for the Pauson Khand cycloaddition reaction. In addition, the cobalt complexes $CoCl_2$, $(\eta^5\text{-}C_5H_5)Co(CO)_2$, $(\eta^5\text{-}C_5Me_5)Co(acac)/MePPh_2$, $Co(PPh_3)_3Cl$, and $Co(acac)_2$ all act as catalyst precursors for the Pauson Khand reaction for some substrates.[4,22,38,39] These reactions are done at 110°C under 30 atm of carbon monoxide so it is possible that dicobaltoctacarbonyl is formed in situ. Of the compounds above, the best results were obtained with $Co(acac)_2$ plus $NaBH_4$, which leads to dicobaltoctacarbonyl formation. This is consistent with Krafft's suggestion that most cobalt precursors for the Pauson Khand reaction go through dicobaltoctacarbonyl.[4]

Interestingly, a comparison of $(\eta^5\text{-}C_5H_5)Co(CO)_2$ and $(\eta^5\text{-}C_9H_7)Co(CO)_2$ as precursors for the Pauson Khand reaction demonstrates that the indenyl complex is more active.[5,22] For example, the Pauson Khand reaction of propargyl alcohol and norbornadiene proceeds to nearly 500 turnovers with $(\eta^5\text{-}C_9H_7)Co(CO)_2$ as the catalyst.[5] It is difficult to attribute the difference in reactivity of these two complexes to formation of dicobaltoctacarbonyl; indene is essential to the enhanced reactivity.[5] If the indenyl ligand remains

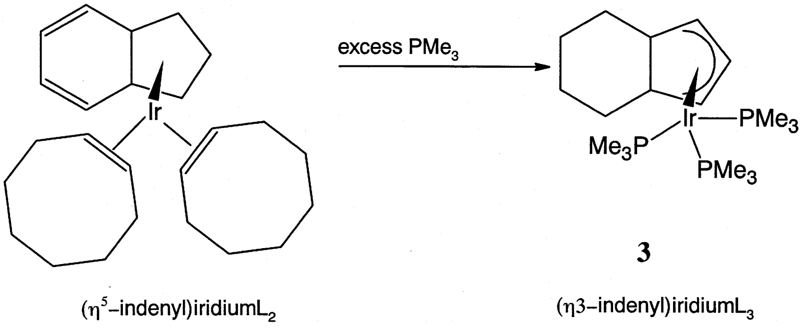
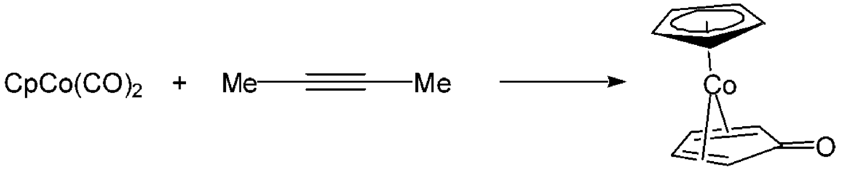


FIGURE 6 η^5 to η^3 conversion of an indenyl ligand bound to iridium.[41]

bound to the cobalt during the catalytic reaction then the difference in reactivity may be attributed to the well known indenyl effect in which the indenyl ligand slips from η^5 to η^3 coordination.[40,41] This is illustrated in Figure 6 for the trapping of an η^3 bound indenyl ligand on iridium, compound **3**.[41]

In the Pauson Khand reaction ring slippage in the indenyl cobalt complex could allow for sequential coordination of alkyne and alkene prior to insertion. There has been little consideration in the literature for mechanisms that involve just a single cobalt atom for the Pauson Khand reaction.

Reactions related to the Pauson Khand reaction can occur at a variety of mononuclear cobalt metal complexes. Notably (η^5-C_5H_5)$Co(CO)_2$ reacts with alkynes to yield coordinated cyclobutadienes and cyclopentadienones.[42,43] The reaction shown in Equation 4 to give compound **4**, as reported by Wender in 1959, is typical.[44] The sandwich motif for the bonding was established by Dahl.[45]



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(4)

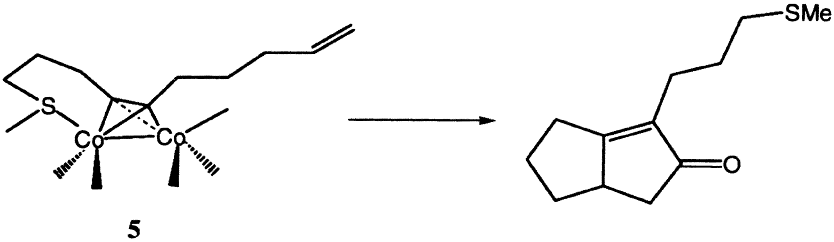
Recently, heterogeneous cobalt catalysts for the Pauson Khand reaction have been reported.[46,47] These are prepared by the thermal decomposition of cobalt carbonyl on mesoporous silica[47] or on charcoal;[46] metallic particles of 100–1000 nm in diameter are formed. High loadings of cobalt are required for good activity with maximum activity observed at 12 wt.% for the charcoal catalysts.[47] The catalysts could be recycled up to 10 times without loss of activity. Although the reaction is done at 130°C and 20 atm CO, very little leaching of cobalt was observed.[47]

Colloidal cobalt particles with a mean diameter of 8 nm can be prepared by refluxing dioctylether solutions of $Co_2(CO)_8$ in the presence of trioctylphosphine.[48] These are active catalysts for both the intra- and intermolecular Pauson Khand cycloaddition reactions at 130°C and 5 atm CO and are easily recycled.

Catalytic reactions of cobalt carbonyl in supercritical CO_2 have been reported for the hydroformylation of alkenes to aldehydes.[49] Unmodified cobalt carbonyl in supercritical CO_2 also catalyzes the Pauson Khand reaction.[50]

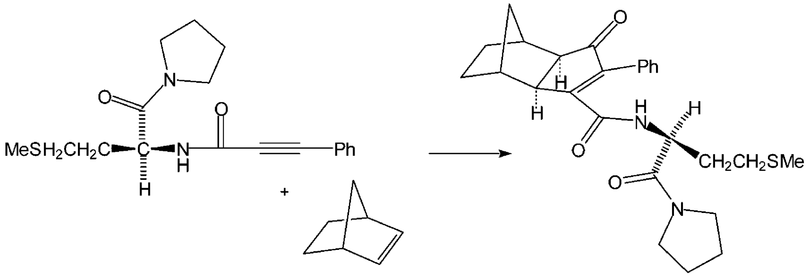
Cobalt-Mediated and Catalyzed Cycloadditions with Substrates Bearing Donor Atoms

When sulfur, nitrogen, or oxygen donor atoms are incorporated in enynes the rate of cyclization is improved.[51] Oxygen is the least effective of these donor atoms and the rate of cyclization increases as the donor atom is moved up to four carbons from the triple bond. The reaction shown in Equation 5 is typical.[51] The role of the donor atom is to coordinate to the metal and facilitate the reaction. Weakly coordinating solvents, such as THF, also accelerate the reaction.[51] The mechanism for these rate enhancements is not understood. It is not known, for example, whether the alkene displaces the weak donor or if a second equivalent of CO dissociates prior to alkene coordination.



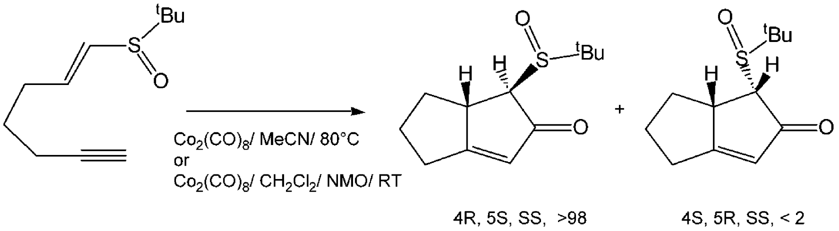
(5)

Hiroi and Watanabe have added S-donor atoms in chiral auxiliaries to alkynes for use in the intermolecular Pauson Khand reaction.[52] The chiral auxiliary approach is less effective in the intermolecular reaction than previously shown for the intramolecular reaction.[51] The best d.e., 90%, was obtained for the reaction shown in Equation 6. The reaction requires 1.2 equivalents of dicobaltoctacarbonyl and goes in only 13% yield. With the other substrates studied the d.e. was in the range of 5%–79%.



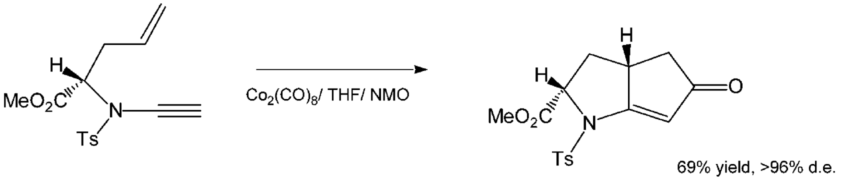
(6)

The t-butylsulfinyl group is easily incorporated into enynes. Recent work by Adrio and Carretero shows that chiral sulfur oxides are very effective for stereoselective Pauson Khand reactions; an example is given in Equation 7.[53] Presumably the oxygen of the sulfinyl group can act as a ligand to direct the cycloaddition reaction.



(7)

Witulski and Gossmann have prepared enynes that contain chiral allyl glycines as the auxiliary for the Pauson Khand reaction.[54] These afford the cycloaddition adducts in greater than 95% d.e., Equation 8.



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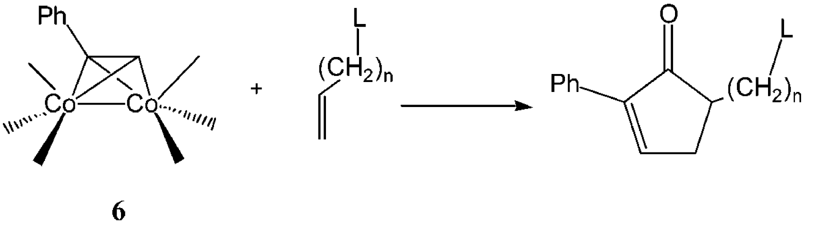
Tethering a heteroatom donor group to the alkene can also control the regioselectivity of the intramolecular Pauson Khand reaction.[55,56] An example is shown in Equation 9.



(9)

Ligand Modified Cobalt Carbonyl Reagents for Cycloaddition Reactions

Jeong reported in 1994 that phosphine and phosphite modified cobalt carbonyls are effective for the intramolecular Pauson Khand reaction.[57] The best results were obtained with a ten-fold excess of triphenylphosphite and 3 mol% cobalt carbonyl at 100°C and 3 atm CO in DME. More recently, Comely et al. showed that the isolated complexes, $Co_2(CO)_7(PR_3)$ and $Co_2(CO)_6(PR_3)_2$ where $PR_3 = PPh_3$, $P(OPh)_3$, PBu_3, and $P(C_6H_4OMe)_3$, serve as catalyst precursors for the Pauson Khand reaction.[58] Similarly, phosphine modified polymers may be used to generate polymer bound cobalt carbonyl catalysts.[59] These are thought to contain (polymer)-$(PPh_2)_2Co_2(CO)_6$.

A survey of phosphine oxides, sulfides, and selenides as modifiers for the Pauson Khand reaction shows that the sulfides enhance the reactivity of cobalt carbonyl by about 50%.[60] Although tributylphosphine oxide promotes the stoichiometric reaction,[61] Hayashi et al. see no effect of triphenylphosphine oxide on the catalytic reaction.

An important observation in the development of asymmetric Pauson Khand chemistry is that cobalt alkyne complexes of the type $Co_2(CO)_5L(HCCR)$ are chiral. When L = R-(+)-glyphos (a monodentate chiral phosphine) two diastereomers, compounds **7a** and **7b**, are formed; these are shown in Figure 7. Significantly, when a single diastereomer is treated with norbornene in the presence of excess amine oxide the Pauson Khand reaction is accomplished in 65%–90% yield and up to 99% e.e.[62,63]

When the complexes (alkyne)$Co_2(CO)_6$ and six equivalents of the chiral amine oxide, brucine N-oxide, are used to promote the Pauson Khand reaction, then up to 44% e.e. is observed when the reaction is done in THF at −70°C.[24] For asymmetric induction to occur either the amine, brucine, must coordinate to cobalt after the reaction of brucine oxide with coordinated CO to liberate an equivalent of CO_2, or the decarbonylation step occurs enantioselectively.[24,26]

Chiral chelating phosphines have been used successfully in the modification of cobalt carbonyl Pauson Khand catalysts.[64,65] For example, the intramolecular cyclization of the enyne in Equation 10 is accomplished in

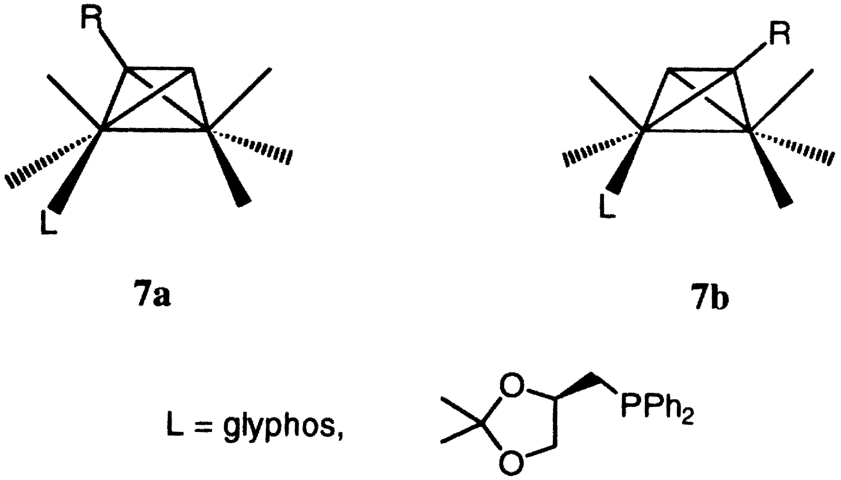
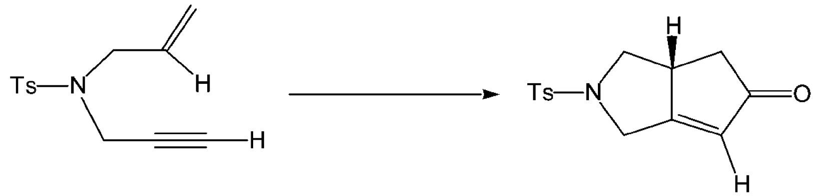


FIGURE 7 Schematic representation of the diatereomers formed from the reaction of a chiral phosphine with a cobalt carbonyl complex of a terminal alkyne.

60% yield with 93% e.e. with 20 mol% $Co_2(CO)_8$/S-BINAP.[64] These catalysts are prepared in situ; thus, the nature of the active catalyst is unknown. It is proposed that the catalyst is (μ-alkyne)-$Co_2(CO)_4$(μ-S-BINAP);[64] however, this may oversimplify the composition. Chelating phosphines often react with cobalt carbonyl via a well-known disproportionation reaction to yield, $[Co(CO_3)L\text{-}L]^+[Co(CO)_4]^-$.[66–68] Nevertheless, the catalysts prepared in situ give excellent results for the intramolecular Pauson Khand cyclization.



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In a separate study Laschat et al. show that the complex (3,3-dimethylbutyne)-$Co_2(CO)_4$[μ-(R)-BINAP], **8**, can be prepared and isolated.[69] The crystal structure establishes the bridging nature of the phosphine ligand. A schematic representation of the structure is shown in Figure 8.

Significantly, this complex was found to be *inactive* for the Pauson Khand reaction. This is in contrast to the in situ prepared catalyst noted above with

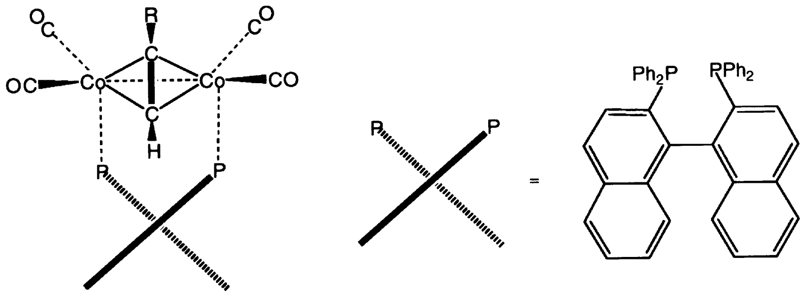

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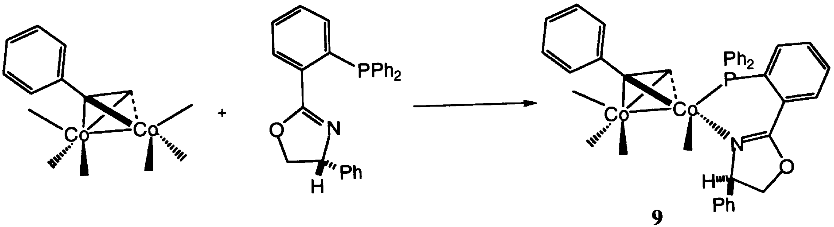
FIGURE 8 Representation of the BINAP complex 8.[69]

the same ligand.[64,65] Taken on the surface these results appear to be in conflict. Perhaps more likely is that the in situ prepared catalyst is not the supposed bridging phosphine complex but rather some other, as yet unidentified, cobalt phosphine complex. The closely related cobalt complex (μ-alkyne)$Co_2(CO)_4$(PNP), where PNP = N,N-bisdiphenylphosphino-(+)-α-methylbenzylamine, gives a 16% e.e. in the stoichiometric Pauson Khand reaction.[70]

Moyano et al. describe the reaction of (μ-alkyne)$Co_2(CO)_6$ with chelating phosphino-oxazoline ligands.[71] The synthesis is shown in Equation 11. Both

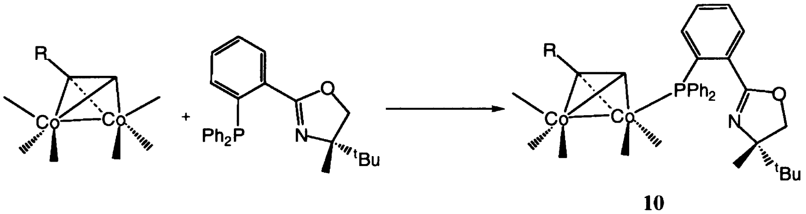


6 **9**

(11)

diastereomers are formed however, the diastereomer shown is favored by a ratio of 85:15.[71] The diastereomers are readily separated by chromatography. When the major diastereomer is used in the intermolecular Pauson Khand reaction with norbornadiene the corresponding cyclopentenone is obtained nearly quantitatively and in 51% e.e.

By adjusting the size of the phosphino-oxazoline ligand it was found that it could be forced to bond in a monodentate fashion to the alkyne complex of cobalt carbonyl, see Equation 12.[72] Again two diastereomeric cobalt complexes are formed and these are found to slowly epimerize. Nonetheless, the diastereomers can be separated by chromatography. Additionally, the ratio of the two diastereomers formed in the reaction depends on the substituent on the bridging alkyne with the best diastereomeric excess obtained with $R = CH_2OH$. As in the case of the glyphos complexes, the diastereomerically pure cobalt complexes of the monodentate phosphino-oxazoline ligands are far superior to the chelating structures in effecting the enantioselective Pauson Khand cycloaddition reaction.



10

(12)

When the complex, **10** in Equation 12 is activated by N-methyl-morpholine-N-oxide, remarkable enantioselectives are obtained for the intermolecular Pauson Khand reaction with norbornadiene. For example, when $R = Ph$, the cycloaddition product is prepared in 85% yield with 94% e.e. and when $R = CH_2OH$ the yield is 92% with 95% e.e. The use of an amine oxide to activate the complexes for cycloaddition leads to the oxidation of the phosphine during the reaction; the phosphine oxide can be recovered in up to 94% yield and after hydrolysis the chiral auxiliary, (S)-tert-leucinol, is recovered in 85% yield.

These results are interpreted by the authors in the context of the Magnus/Rautenstrauch mechanism (Figure 2) for the reaction.[72] They confirm the suggestion of Pauson et al. that diastereomerically pure intermediates lead to good enantioselectivity in the cycloaddition reaction provided that cycloaddition is faster than epimerization.[73] The authors suggest the following scenario for cycloaddition with the monodentate phosphino-oxazoline cobalt complexes:[72] (1) The two diastereomers, pro R and pro S, add alkene to the cobalt atom that is not substituted by phosphine. (2) The alkene orients in such a way to minimize the interaction of the methylene bridge with the C_2Co_2 cluster, (3) The alkene coordinates to an equatorial site "trans" to the substituted carbon of the alkyne. These features are illustrated in Figure 9. The complexes are drawn from the viewpoint of the C-C edge of the C_2Co_2 cluster. X-ray crystallography establishes that the phosphine occupies the axial position. The insertion step is shown to occur from the equatorial position. As noted above, DFT studies indicate insertion from the axial position. Importantly the stereochemistry of addition is the same from both the axial and equatorial sites.

The fact that this reaction goes with such high enantioselectivity is remarkable for several reasons. First, it demonstrates that a monodentate

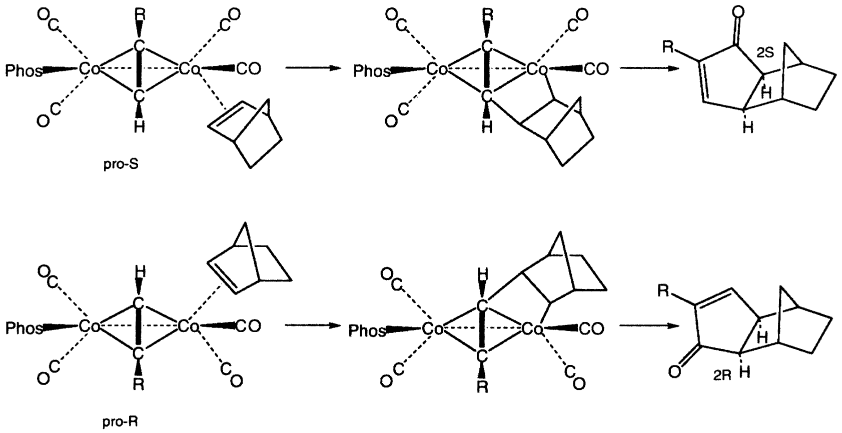
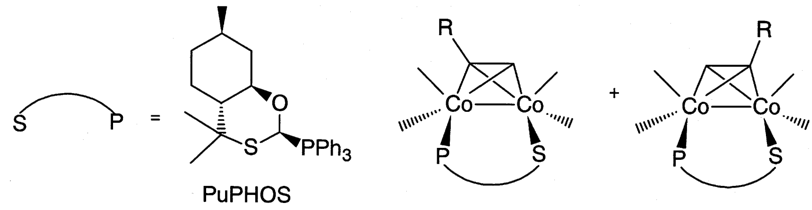


FIGURE 9 Representation of the insertion of norbornene into the bridging alkyne in pro-S and pro-R diastereomers. The insertion is shown to occur from the equatorial site.

chiral phosphine is superior to chelating chiral ligands in providing good enantioselection in the cycloaddition reaction. More typically chelating phosphines are preferred in asymmetric catalysis. Second, the chiral phosphine and the prochiral alkene substrate are not bound to the same metal atom in the proposed reaction mechanism. This is highly unusual in metal mediated asymmetric reactions. Finally, the chirality of the phosphine appears to be inconsequential in determining the stereochemical outcome of the reaction. Rather the key feature for asymmetric induction is the chirality of the C_2Co_2 cluster and the role of the phosphine is to allow easy separation of diastereomers.

The phosphine PuPHOS, shown in Figure 10, was designed as a chiral ligand with a hemilabile sulfur donor atom for the Pauson Khand reaction.[74]



11a **11b**

FIGURE 10 Schematic representation of the PuPHOS ligand and the diastereomeric cobalt complexes of (μ-alkyne)$Co_2(CO)_4$PuPHOS.

The reaction of PuPHOS with terminal alkyne complexes of cobalt carbonyl leads to the formation of diastereomers, **11a** and **11b**, as expected. These are initially formed in equal quantities; however, upon equilibration one diastereomer is generally favored (Figure 10) when $R = \text{-CMe}_2\text{OH}$ the diastereomeric ratio is 4.5:1. As seen in other cases when the diastereomers are separated, they give excellent enantioselectivity in the Pauson Khand reaction. With PuPHOS the best results are reported for the cycloaddition of phenylacetylene with norbornadiene and CO in 99% yield with 99% e.e. The authors suggest that the role of the sulfide group is as a hemilabile ligand that saves a coordination site for the incoming alkene.

These observations have important implications for the design of chiral cobalt catalysts for the asymmetric Pauson Khand reaction. Specifically, if a phosphine-substituted cobalt carbonyl complex is to be part of the catalytic cycle, then the diastereomers that form upon reaction with alkyne must lead to cycloaddition reactions at very different rates. The difference in selectivity can be due either to good diastereoselection upon addition of alkyne or very different reactivity of the diastereomers toward alkene insertion, CO insertion, and reductive elimination.

Hard Lewis bases, notably alcohols, amines, water, and ethers, are well-known promoters of the Pauson Khand reaction.[3,75–77] Sugihara et al. have recently reviewed the effect of hard Lewis bases on the stoichiometric and catalytic Pauson Khand reactions.[78] Significantly, all the hard Lewis bases that promote the Pauson Khand reaction also induce disproportionation of dicobaltoctacarbonyl.[79–81]

Several reaction pathways are available to $Co_2(CO)_8$ when reacting with nucleophiles; some of these are shown in Equations 13–15. The preferred pathway depends on the nucleophile and the reaction solvent. In many caes there is good evidence for radical reactions[82,83] that can lead to both neutral and ionic products.

$$\mathrm{Co_2(CO)_8} \xrightarrow{\mathrm{L}} \mathrm{Co_2(CO)_7L} \xrightarrow{\mathrm{L}} \mathrm{Co_2(CO)_6L_2} \tag{13}$$

$$\mathrm{Co_2(CO)_8} \xrightarrow{\mathrm{2\,L}} [\mathrm{Co(CO)_3L_2}]^+[\mathrm{Co(CO)_4}]^- \xrightarrow[\mathrm{-\,CO}]{} \mathrm{Co_2(CO)_6L_2} \tag{14}$$

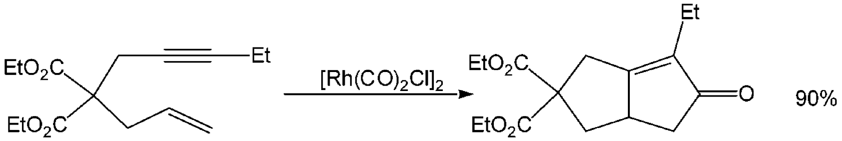
$$3/2\ \mathrm{Co_2(CO)_8} \xrightarrow{\mathrm{6\,L}} [\mathrm{CoL_6}]^{2+} + 2[\mathrm{Co(CO)_4}]^- \tag{15}$$

The literature of the Pauson Khand reaction suggests that reaction 1 above is preferred as a route to active catalysts.[78] Given the conditions of the

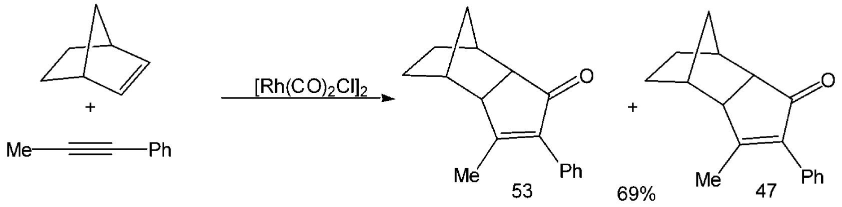
Pauson Khand reaction, however, it is possible that disproportionation reactions also lead to active catalysts. While it appears that the tetracarbonylcobaltate anion is inactive for the Pauson Khand reaction, there is no definitive evidence regarding the activity, or lack of activity, of cobalt carbonyl cations such as $[L_2Co(CO)_3]^+$. However, given the propensity for disproportionation and the catalytic activity of in situ preparations of $Co_2(CO)_8$ and BINAP the possibility that this system goes via $[(BINAP)Co(CO)_3]^+$ cannot yet be eliminated.

RHODIUM AND IRIDIUM

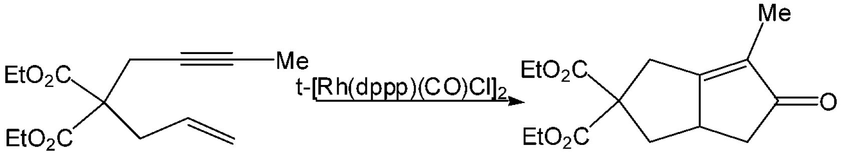
Mononuclear rhodium complexes such as $HRh(CO)(PPh_3)_3$ and $Rh(PPh_2)_3Cl$ also catalyze the Pauson Khand reaction.[84] These are used almost exclusively for the intramolecular Pauson Khand reaction, although with activated alkenes the intermolecular reaction works as well. The best catalytic results are obtained with chloro bridged rhodium dimers, including $[Rh(CO)_2Cl)]_2$, **12**, as the catalyst precursor.[14,84,85] The reactions shown in Equations 16–18 are typical.



(16)



(17)



(18)

The rhodium carbonyl chloride dimer has an Rh-Rh separation of 3.138 Å and the dihedral angle between the square planes is 53.25°[86] as illustrated in

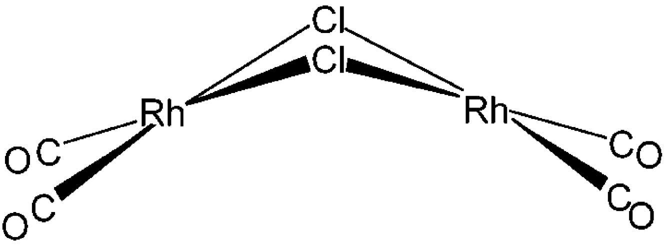


FIGURE 11 Representation of the structure of **12**. The Rh-Rh separation is 3.138 Å and the dihedral angle between the square planes is 53.25°.

Figure 11. Stoichiometric reactions of alkyne and rhodium carbonyl chloride dimer typically occur at a single rhodium atom. Alkyne addition products often contain two equivalents of alkyne and, depending upon the substituents on the alkyne, cyclopentadienones and p-benzoquinones are formed. Furthermore, the metallocycle intermediates have been observed. These include metallocyclopentadiene and metallocyclopentenedione as illustrated in Figure 12.[87]

Iridium phosphine complexes generated from $[Ir(COD)Cl]_2$, **13**, chelating phosphine and CO, are very effective for the intramolecular Pauson Khand reaction.[88] In the case of a chiral phosphine the resulting catalysts give very good enantioselectivity. While the intermolecular cycloaddition reaction is more difficult with the iridium catalysts, good enantioselectivity is observed for the reaction of 1-phenylpropyne with norbornene.[88] In one example 10 mol% catalyst was used for the intermolecular reaction and only 3 turnovers were obtained. The results are presented in Equation 19.[88]

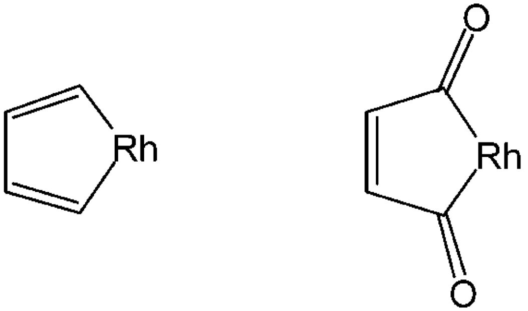
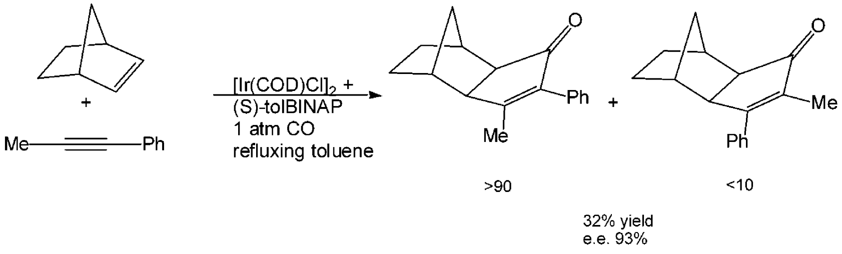


FIGURE 12 Metallocycle pentenes formed from the reaction of acetylene and CO with rhodium carbonyls.



(19)

The successful use of a variety of mononuclear metal complexes for the Pauson Khand reaction requires a mechanism that sequentially coordinates the substrates to a single metal atom. Shibata and Takagi suggested a mechanism for the intramolecular cycloaddition over iridium phosphine complexes. The principle difference between this mechanism and that suggested for dimeric cobalt complexes above, see Figure 2, is that the alkyne is coordinated to a single metal atom. The Shibata mechanism, modified for an intermolecular reaction, is given in Figure 13.

There is precedence for the formation of η^2 alkyne complexes to a single metal atom in both rhodium and iridium complexes, as for example in: $[(\eta^5\text{-}C_5Me_5)Ir(\eta^3\text{-}C_3H_3)(\eta^2\text{-}C_2R_2)]^+$,[89] $(\eta^5\text{-}C_5H_5)Ir\ P(^iPr_3)(\eta^2\text{-}C_2R_2)$,[90] $(\eta^5\text{-}C_5H_5)Rh(CO)(\eta^2\text{-}C_2R_2)$,[91,92] and $(\eta^5\text{-}C_9H_7)Ir\ (CO)(\eta^2\text{-}C_2R_2)$.[93] However, the remaining steps in the Shibata mechanism are speculative.

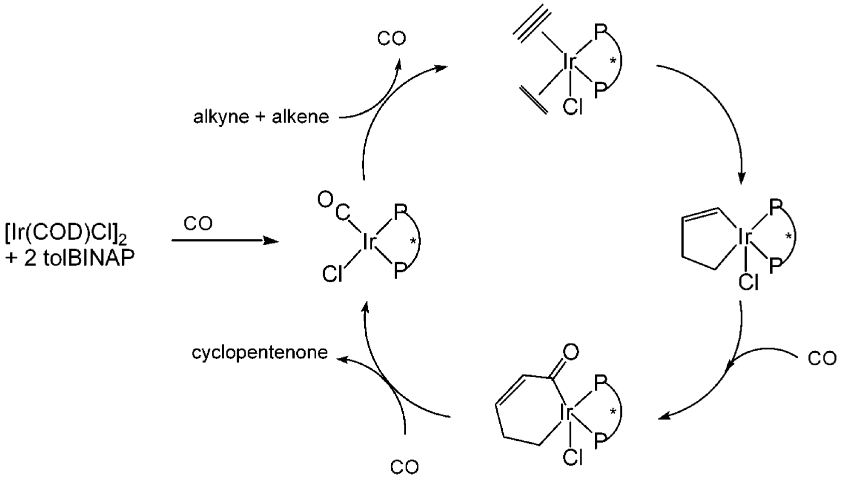
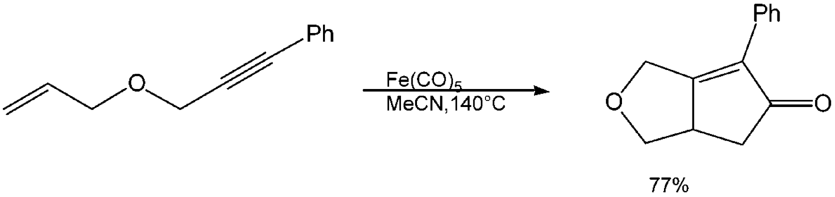


FIGURE 13 The mechanism proposed for cycloaddition of alkyne, alkene, and CO over iridium catalysts follows the Magnus-Rautenstrauch mechanism for the Pauson Khand reaction mediated or catalyzed by cobalt.

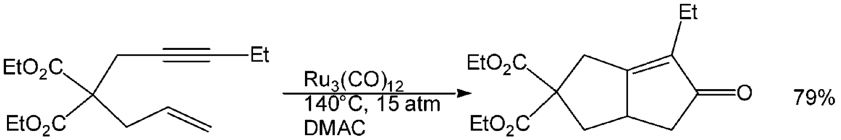
IRON AND RUTHENIUM

The iron carbonyl promoted Pauson Khand reaction was reported by Pearson and Dubbert in 1994.[11] The reaction with iron carbonyl is not catalytic and iron carbonyl is generally used in excess for the transformation. The reaction can be made more efficient if, in place of $Fe(CO)_5$, a premade complex such as $Fe(CO)_4$(solvent) is used as the reagent. Regardless of the form of the iron carbonyl high temperatures, e.g., 140°C, are required for the reaction (Equation 20).



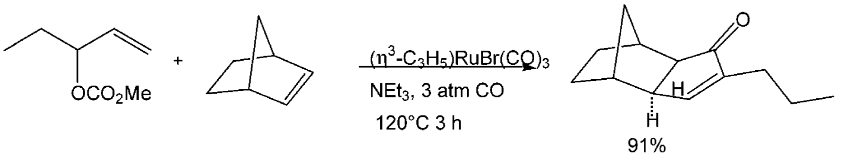
(20)

Ruthenium carbonyl catalyzes a number of carbon-carbon bond forming reactions including the Pauson Khand reaction.[9,10,94,95] The ruthenium catalyzed Pauson Khand reaction, independently reported for the first time in 1997 by Kondo et al.[94] and Morimoto et al.,[95] requires high temperatures of 140°C–180°C and 10–15 atm CO pressure. The reaction in Equation 21 is typical.



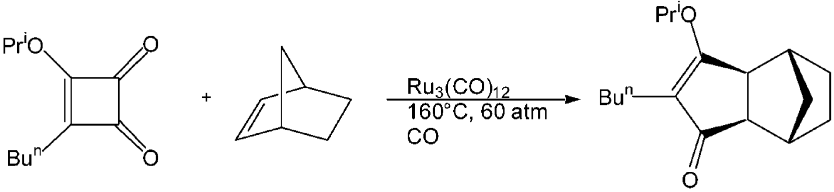
(21)

Allylic carbonates can be used as alkyne surrogates in the ruthenium carbonyl catalyzed cycloaddition reactions.[96] In this case triethylamine modified ruthenium(II) catalysts give the best results. The reaction is shown in Equation 22. Ruthenium allyls are suggested as reaction intermediates.



(22)

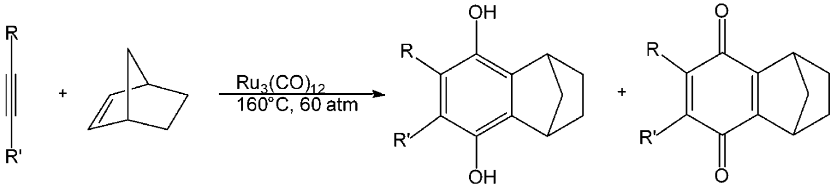
Cyclobutenediones can play a similar surrogate role in ruthenium catalyzed cycloaddition reactions.[97] An example is shown in Equation 23.



(23)

The cyclobutenedione does not simply liberate alkyne to react in the cycloaddition, rather it appears that C-C bond activation and decarbonylation to yield a metallocyclobutenone, Figure 14, is reversible. When the reaction is done under carbon-13–enriched CO, the labeled CO is incorporated into the product. The results are suggestive of an alternative mechanism for the Pauson Khand reaction, namely that CO insertion into the alkynemetal bond is possible.

At high pressures of CO, ruthenium carbonyl serves as a catalyst for the formation of hydroquinones.[98] An example is shown in Equation 24.



(24)

With ruthenium carbonyl as the catalyst it is possible to extend the 2+2+1 cycloaddition concept to include substrates such as imines and

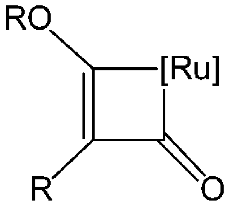
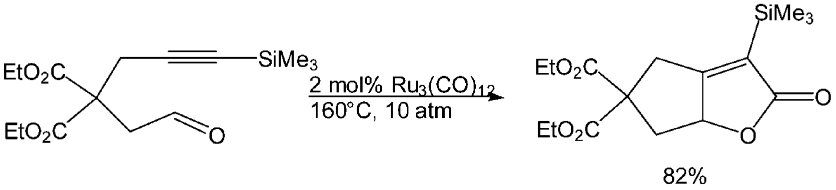


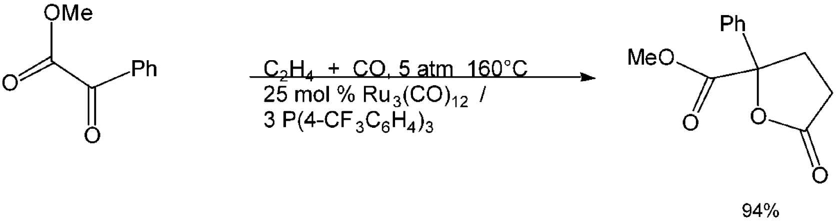
FIGURE 14 Metallocyclobutenone formed upon reaction of a cyclobutendione with ruthenium.

ketones in place of either an alkyne or an alkene. This approach was pioneered by the group of Murai. The first example was the intramolecular 2+2+1 cycloaddition of yne-aldehydes with CO to give unsaturated γ-butyrolatones, Equation 25.[16] In this reaction the aldehyde replaces the alkene in the Pauson Khand type reaction.



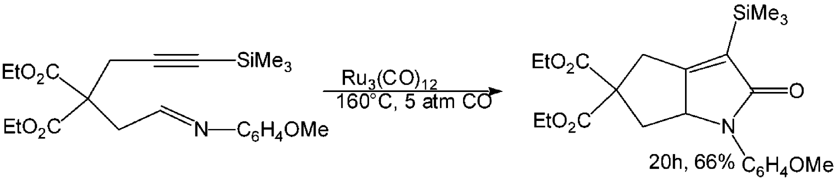
(25)

If an aldehyde or ketone is used in place of the alkyne functionality, then saturated lactones are formed. In this case it was found that electron-withdrawing phosphines improve the reaction yield (Equation 26).[17]

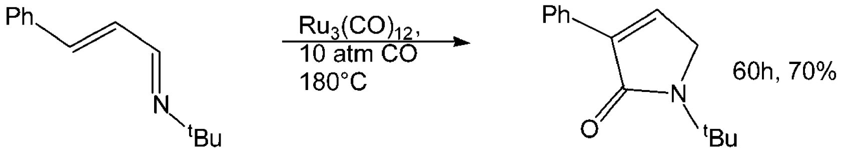


(26)

Similarly, if yne-imines are used as substrates for the ruthenium catalyzed reaction then unsaturated lactams are formed.[18] Unsaturated lactams are also the product of the ruthenium catalyzed carbonylation of α,β-unsaturated imines.[99] The carbonylation of cycloproylimines leads to the formation of unsaturated six membered ring lactams.[100] Examples of these reactions are shown in Equations 27–29; the catalyst concentrations are typical 2–5 mol%.



(27)



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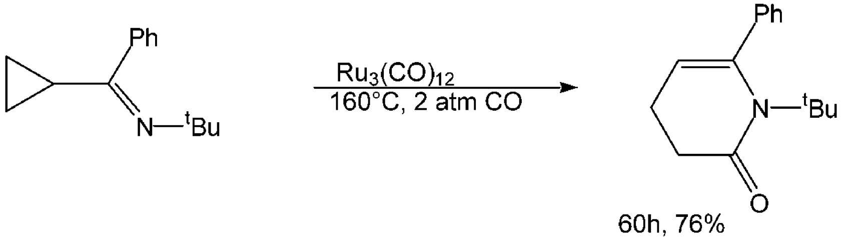
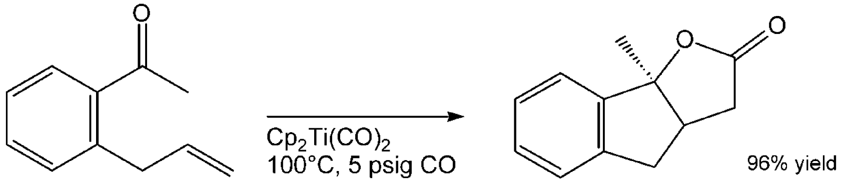


(29)

TITANIUM

A titanocene-mediated heteroatom version of the Pauson Khand reaction was first reported by Buchwald in 1996.[101] The titanocene reagent, $Cp_2Ti(PMe_3)_2$ reverts to $Cp_2Ti(CO)_2$ during the reaction. Further development of the cycloaddition reaction showed that o-allyl aryl ketones compete with CO for a coordination site at the metal and thus can be used as substrates for the titanocene catalyzed cycloaddition reaction.[101,102] The reaction in Equation 30 is typical.



(30)

Titanocene reagents also catalyze the intramolecular 2+2+1 cycloaddition reaction of enynes with CO.[103,104] The reaction is done at 90°C; CO dissociation from titanocene dicarbonyl is required to generate an open coordination site for alkyne coordination. The proposed mechanism is shown in Figure 15.[104]

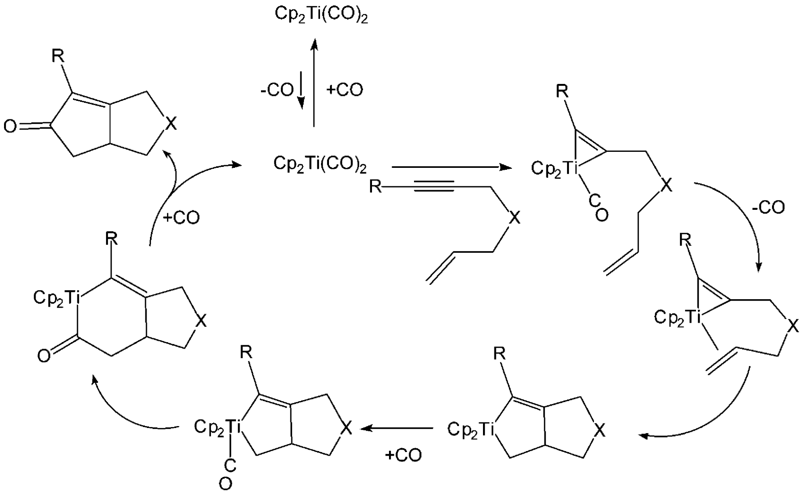


FIGURE 15 The mechanism proposed for the cycloaddition of enynes over titanium catalysts is very similar to the mechanism proposed by Shibata for mononuclear iridium catalysts.

SUMMARY

Several significant advances have been made recently in the catalytic Pauson Khand reaction. Cobalt carbonyl can be reliably activated for the intramolecular catalytic reaction with hard Lewis bases and/or amine oxides. The reaction can be accomplished under relatively mild conditions with as little as 1 mol% catalyst depending on the substrate. The asymmetric Pauson Khand reaction with cobalt carbonyl + BINAP as the catalyst goes in upto 93% e.e. with some enyne substrates. However 20 mol% catalyst is required and only three turnovers are observed. Clearly there is much to be done to improve catalyst activity and stability. Furthermore, the intermolecular reaction has not yet been satisfactorily catalyzed enantioselectively with cobalt reagents. The stoichiometric enantioselective reaction works well when diastereomerically pure C_2Co_2 clusters are isolated. The best result for the catalyzed intermolecular asymmetric reaction was accomplished with an iridium complex of tolBINAP; again 93% e.e. was observed at only three turnovers of the catalyst. Ruthenium carbonyl complexes show some promise for catalytic reactions. The activity is low and high temperatures are required, but the catalysts appear to be stable at the temperatures required for the reaction.

The proposed mechanisms for the Pauson Khand reaction are consistent in the order of addition substrates, alkyne followed by alkene, then CO. Of course there are a number of examples where CO adds directly to coordinated alkyne in the absence of alkene. Few details on the proposed reaction intermediates have been elucidated. Cobalt catalysts appear to go via dimeric complexes while titanium, rhodium, and iridium catalysts appear to effect the cyclization at a single metal center. The ruthenium carbonyl precursor to the Pauson Khand reaction is $Ru_3(CO)_{12}$; however, it is not certain whether the cluster remains intact during the reaction. At the high temperatures and CO pressure required for the ruthenium catalyzed reaction, it is likely that the cluster fragments to give monomeric ruthenium complexes. Clearly there is a need for continued mechanistic studies of the Pauson Khand reaction.

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