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Recent Advances in the Pauson–Khand Reaction and Related [2+2+1] Cycloadditions

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1. An Introduction to the Pauson–Khand (P–K) Reaction

The Pauson–Khand (P–K) reaction, formally a [2+2+1] cycloaddition involving an alkene, an alkyne and carbon monoxide moieties to form a cyclopentenone, was first discovered in the early seventies.[1] At that time, this cycloaddition process was effected thermally using a stoichiometric amount of dicobaltoctacarbonyl. While this reaction represented a dramatic increase in molecular complexity in proceeding from starting material to product, the reaction was somewhat limited in its application to the synthesis of complex molecules. For instance, unless strained olefins were used, the efficiency of the cycloadditions was typically low. Moreover, the use of unsymmetrical alkenes led to mixtures of cyclopentenone regioisomers. This reaction was also sensitive to steric and electronic effects introduced into either the alkene or alkyne precursors. Finally, the conditions required to effect this

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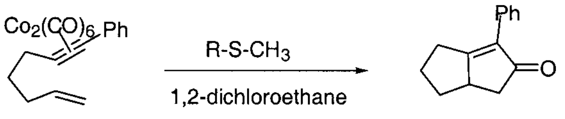
process (high temperatures and long reaction times) many times led to decomposition of starting materials and/or products. In 1981, Schore expanded the synthetic utility of this reaction considerably by attaching the alkene to the alkyne via a carbon tether and demonstrating the first intramolecular P–K cycloaddition.[2] In this variant, the reaction was now regioselective with respect to the olefin and strained olefins were no longer required. In the mid- to late eighties evidence accumulated suggesting that this reaction could be accelerated. Smit and Caple were the first to demonstrate this concept by adsorption of the cyclization precursor onto silica gel or alumina allowing the reactions to be carried out at lower temperatures with shorter reaction times.[3] In addition, Krafft attached a directing/accelerating ligand to an unstrained olefin and obtained both high levels of regiocontrol and high yields in the intermolecular P–K reaction.[4] In the early nineties, Schreiber[5] and Jeong[6] independently reported the promotion of the P–K reaction at room temperature using *N*-methylmorpholine *N*-oxide and trimethylamine *N*-oxide, respectively. Since these initial reports there have been a variety of additives discovered that accelerate the P–K reaction, resulting in a significant increase in reaction efficiency. Dicobaltoctacarbonyl sports the yellow-jersey when it comes to metals used to effect this formal [2+2+1] cycloaddition; however, much like the chemistry associated with π-allyl metal complexes, a variety of other metals have proven to be very effective. The use of additives to accelerate and increase the efficiency and the variety of metal carbonyls used to effect the [2+2+1] process have enhanced the synthetic utility of this reaction tremendously. The P–K reaction can now be effected catalytically, asymmetrically and on a solid support. In addition, a variety of precursors that were previously unstable or unreactive to the traditional reaction conditions have now been shown to cyclize to give a diverse array of functionalized cyclopentenones. Thus, there has been a re-emergence of the application of this reaction to the synthesis of natural products. This review is meant to provide a guide to the abundant P–K literature of the past decade.

2. Promoters of the Pauson–Khand Cycloaddition

2.1. Stoichiometric dicobaltoctacarbonyl

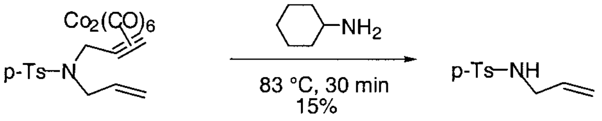
For more than a decade following the initial report of the P–K cycloaddition, the standard reaction conditions used to effect this process involved the formation of the dicobalthexacarbonyl–alkyne complex followed by heating in the presence of an alkene.[1] Attempts were made to accelerate the P–K reaction with the first real success achieved by Smit and Caple in 1986.[3] Subsequent to this report, it was discovered that amine oxides also facilitate the P–K reaction.[5,6] It is widely accepted that these amine oxides act as oxidants to create a vacant site on the cobalt by oxidative removal of a carbon monoxide ligand. This vacancy subsequently leads to oxidative addition of the olefin, which is thought to be the rate limiting step. More recently, it has been shown that a variety of additives can facilitate the P–K reaction leading to shorter reaction times at lower temperatures, thus extending the scope of this reaction. Increasing the scope of the P–K reaction has been reviewed,[7] so this section of the review will highlight the most recent developments in the area of new promoters to facilitate the P–K reaction.

Sugihara and Yamaguchi report various sulfides can be used to promote the stoichiometric P–K reaction (Eq. (1)).[8] Sugihara attributes this finding to Krafft's demonstration that a suitably positioned sulfur moiety tethered to the P–K precursor increases the reaction efficiency.[4] Interestingly, the sulfur additives promoted both the inter- and the intramolecular P–K reaction. A systematic study was performed using a variety of conditions and sulfides. It was found that 3.5 equiv. of an alkyl or aryl methyl sulfide (R=Ph, *i*-Pr, *n*-Bu, *t*-Bu) affords excellent yields of the cycloadduct. Electron donating groups attached to an aromatic ring were more beneficial than electron withdrawing groups. Finally, less sterically hindered sulfides functioned as better promoters.

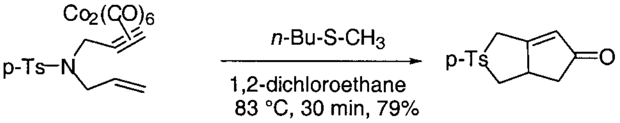


(1)

The mildness of the sulfide promoters was shown by doing a direct comparison with amine promoters. When cyclohexylamine was used as a promoter of the reaction (Eq. (2)), only the hydrolysis product was obtained. In contrast, the use of *n*-butyl methylsulfide gave the bicyclic enone in good yield (79%) (Eq. (3)).

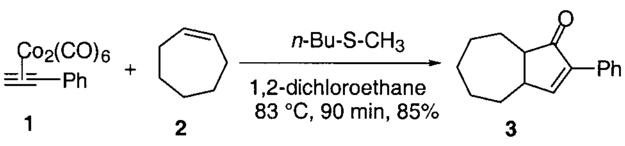


(2)



(3)

Also very useful is the application of the sulfide promoter technology to the intermolecular P–K reaction, which typically requires the use of strained and reactive olefins for maximum efficiency. Reaction of the dicobalthexacarbonyl complex of phenyl acetylene (**1**) with cycloheptene (**2**) using 4 equiv. of *n*-butyl methyl sulfide as a promoter provided the cycloadduct **3** in 85% yield in 90 min (Eq. (4)). Comparison is made to other conditions used to effect this intermolecular reaction, for instance *N*-methylmorpholine *N*-oxide (Eq. (5)) results in decomplexation of the alkyne and thermal conditions require 3 days and result in only a 23% yield of product (Eq. (6)).

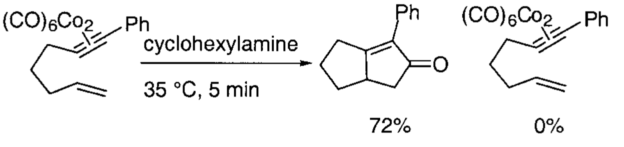


(4)

$$\mathbf{1} + \mathbf{2} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, 10 min}]{\text{NMO (6 equiv)}} \text{decomplexation} \quad (5)$$

$$\mathbf{1} + \mathbf{2} \xrightarrow[\text{3d, 23\%}]{\text{toluene, reflux}} \mathbf{3} \quad (6)$$

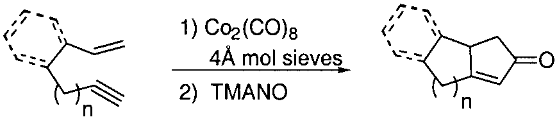
Sugihara and Yamaguchi have demonstrated a rate enhancement of the stoichiometric P–K reaction by the use of primary amines as the solvent (Eq. (7)).[9] A variety of solvents were tried, hexane, toluene, 1,2-dichloroethane, 1,2-dioxane, ethanol and triethylamine, all resulting in nearly quantitative recovery of starting material. However, the use of primary amines containing secondary alkyl groups effectively promoted the reaction. Cyclohexylamine was found to function as an excellent promoter, so reactions were carried out using 1,2-dichloroethane as solvent and cyclohexylamine as an additive. A systematic study varying the amounts of cyclohexylamine additive showed that the addition of 3.5 equiv. gave the highest conversions (99% yield, 5 min) for the P–K reaction shown in Eq. (7).



(7)

Ammonia as a promoter was investigated using a biphasic system of an aqueous solution of ammonium hydroxide.[9] Optimum conditions were found where conversions of the cyclization precursors to the products were nearly quantitative in less than an hour. To explore the scope of these two sets of conditions, nine substituted substrates of varying complexity (1,2-disubstituted olefins, enynes possessing four-carbon tethers, terminal alkynes) were cyclized using: (a) 3.5 equiv. of cyclohexylamine in dichloroethane at 83°C; and (b) a 1:3 mixture (v/v) of 1,4-dioxane and 2 M aqueous solution of ammonium hydroxide at 100°C. Both methods provided excellent yields of the cycloadducts (60–100% in most cases) in short periods of time (10–135 min).

Pérez-Castells has shown that the addition of molecular sieves to the *N*-oxide promoted cycloaddition results in improved yields of cycloadduct (Eq. (8)).[10] Powdered sieves were added in amounts eight times the mass of the starting material. In the presence of trimethylamine *N*-oxide (TMANO), yields of 45–90% were obtained in five intramolecular and one intermolecular examples.



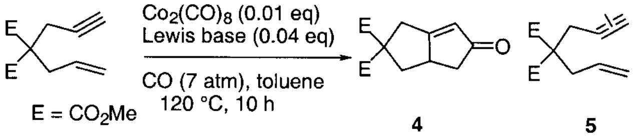
(8)

2.2. Catalytic dicobaltoctacarbonyl

Conditions to effect the P–K reaction catalytically have been worked out by Sugihara using dicobaltoctacarbonyl (0.01 equiv.) and hard Lewis bases.[11] These reactions were done under 7 atm of carbon monoxide at 120°C in toluene (Eq. (9)). A systematic study was done using a variety of Lewis bases and a few of these are highlighted in an abbreviated version of the table published by Sugihara (Table 1). If no Lewis base was used, very low conversions were obtained (entry 1, Table 1). Interestingly, while cyclohexylamine worked as the best promoter in the stoichiometric P–K cycloaddition,[9] it had very little effect on the progress of the catalytic P–K reaction (entry 2, Table 1). Diisopropylethylamine proved to be the best amine promoter (entry 3, Table 1). Alcohols were also used to promote the cycloaddition with benzyl alcohol functioning as the best of the alcohol promoters (entry 4, Table 1). Ethers were found to function as useful promoters with 1,2-dimethoxyethane giving the highest overall conversions (entry 5, Table 1). Based upon these studies, the optimum conditions [dicobaltoctacarbonyl (0.01 equiv.), dimethoxyethane (0.04 equiv.), CO (7 atm), toluene at 120°C] were applied to 12 different cyclization substrates and the yields in all cases were excellent, ranging from 72–100%. In particular, cyclization of 2,2-disubstituted olefins, enynes possessing 4-carbon tethers, enynes with tethers containing nitrogen or oxygen, terminal alkynes and intermolecular cyclizations were all effected quite efficiently.

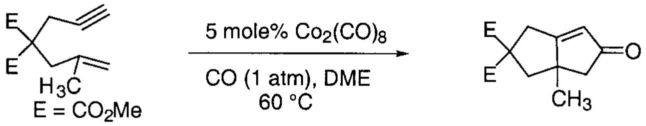
Table 1.

Entry	Lewis base	Yield (**4**/**5**) (%)
1	None	12/82
2	Cyclohexylamine	5/93
3	Diisopropylethylamine	81/7
4	Benzyl alcohol	73/21
5	Dimethoxyethane	91/0



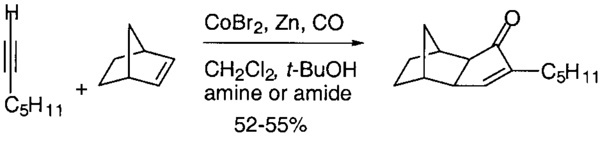
(9)

During experiments using high intensity visible light, Livinghouse recognized a thermal dependence of the P–K reaction that led to studies of a thermally catalyzed enyne cyclization.[12] It was observed that when the P–K reaction was run in 0.1 M DME using 5 mol% catalyst, the temperature was critical to the success of the catalytic turnover (Eq. (10)). Excellent yields (77–86%) of cycloadducts were obtained when the temperature was maintained at 60°C, but much lower yields were obtained at temperatures of 50 and 80°C. Eight cyclization substrates were examined including 1,2- and 2,2-disubstituted olefins, heteroatom containing tethers, terminal alkynes, allylic acetates and silyl ethers.



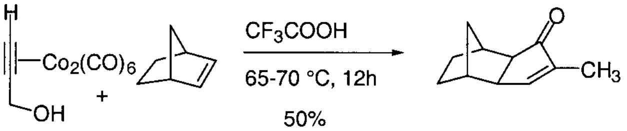
(10)

Periasamy has developed a method for the in situ generation of the dicobalthexacarbonyl–alkyne complex.[13] Tetramethylethylenediamine, α-methylbenzylamine and dimethylformamide were shown to promote the reaction when the complexes were prepared using this in situ method (Eq. (11)).



(11)

The Periasamy group has also shown that, in the presence of trifluoracetic acid, cobalt complexed propargyl alcohols give methyl substituted cyclopentenones rendering the propargyl alcohol a propyne equivalent under these reaction conditions (Eq. (12)).[14] A deoxygenated cobalt alkyne intermediate is proposed to arise via an in situ hydridocobalt reduction of a stabilized carbocation intermediate.



(12)

Attempts have been made to use chiral promoters to induce asymmetry in the P–K reaction. This is reviewed in the section on the asymmetric P–K reaction (Section 5, part 3).

3. Effecting the [2+2+1] Reaction with Metals Other Than Dicobaltoctacarbonyl

Cobalt remains the metal of choice in effecting the formal [2+2+1] cycloaddition process involved in the P–K reaction. However, other transition metals have been shown to be quite effective in inducing this transformation. Negishi reported a zirconium promoted intramolecular variation of the P–K reaction involving a zirconabicyclic intermediate.[15] Carbonylation occurs under an atmosphere of CO to afford the cyclopentenone in good yields. Nickel(0) has been shown to effect the intramolecular cyclization of enynes with isocyanides to form the 1-imino-2-cyclopentenes.[16] This product is subsequently hydrolyzed to afford the formal P–K cycloadduct, the cyclopentenone. Later, a carbonylative $Ni(CO)_4$ mediated intermolecular cycloaddition between acetylenes and allylic halides was reported by Moretó that affords the cyclopentenone directly.[17] Iron carbonyls were found to promote the intramolecular cyclocarbonylation of enynes to afford bicyclic enones in good yield.[18] This followed an earlier report by Aumann in which $Fe(CO)_5$ promoted the intermolecular [2+2+1] cycloaddition between an alkyne and an allene to produce a 4-alkylidene cyclopentenone.[19] Molybdenum carbonyl species also effect the intra- and intermolecular [2+2+1] cycloaddition process. Hanaoka has shown that bis(cyclopentadienyl) tetracarbonyldimolybdenum–alkyne complexes react analogously to their dicobalthexacarbonyl–alkyne counterpart to afford cyclopentenones.[20] Jeong reported that molybdenum hexacarbonyl also effects the cycloaddition in the presence of DMSO.[21] These latter conditions have been used effectively in our laboratories to promote the intramolecular allenic variant of the P–K cycloaddition.[22] Buchwald has shown that the titanocene reagent formed from treatment of Cp_2TiCl_2 with ethyl Grignard effects a reductive cyclization of enynes affording a titanocycle.[23] Analogous to Negishi's zirconium work, conversion to the cyclopentenone is effected under an atmosphere of CO. Hoye has demonstrated that tungsten carbonyl species promote the intramolecular P–K cycloaddition.[24] A THF solution of $W(CO)_6$ is photolyzed to form $W(CO)_5 \cdot THF$ which effects the cyclization of enynes in good yield.

The use of alternative metals has been most effective in the development of a catalytic version of the [2+2+1] cycloaddition. Catalytic versions of the P–K reaction are discussed later but the different metals used to effect the cycloaddition will be mentioned here. Buchwald has extended his titanocene methodology to a catalytic version for the synthesis of both 1-imino-2-cyclopentenes[25] and cyclopentanones.[26] Buchwald has also reported a nickel(0) catalyzed synthesis of 1-imino-2-cyclopentenes.[27]

Catalytic versions of the cycloaddition have also been reported using later transition metals. Murai[28] and Mitsudo[29] simultaneously reported that $Ru_3(CO)_{12}$ catalyzes the intramolecular cycloaddition of enynes in good yield. Likewise, the laboratories of Narasaka[30] and Jeong[31] both reported on the catalysis of the intramolecular cycloaddition of enynes using rhodium carbonyl metal species.

While cobalt appears to be the metal of choice for the P–K reaction, the discovery of other metals capable of effecting the cycloaddition has undoubtedly increased the overall scope of the reaction.

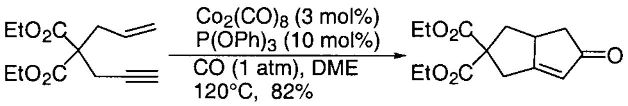
4. Catalytic Pauson–Khand and Related [2+2+1] Reactions

There has been significant interest in developing catalytic variants of the P–K cycloaddition. Recently there have been notable advances toward this end using sub-stoichiometric amounts of a variety of early and late transition metals such as cobalt, titanium, ruthenium and rhodium.

4.1. Cobalt catalyzed cycloadditions

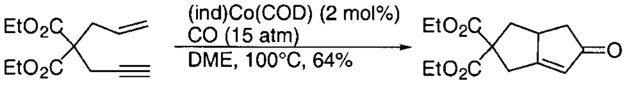
Since its discovery in the early 1970s, attempts to develop a catalytic version of the P–K cycloaddition utilizing cobalt as the metal have been numerous. Indeed, Pauson reports early success in the intermolecular version.[1a] However, this initial example involved only the strained reactive alkenes norbornene and norbornadiene, and required relatively high amounts of the cobalt catalyst (10 mol%). The first truly catalytic cobalt mediated intermolecular cycloaddition involving a non-strained alkene was demonstrated by Rautenstrauch.[32] In the single reported example, 1-heptyne was reacted with ethylene in the presence of 0.22 mol% of $Co_2(CO)_8$ and high pressure CO (100 bar) to afford 2-pentyl-2-cyclopentenone in 47% yield.

Modifications to the reaction conditions and/or the cobalt metal catalyst have proven to be effective in increasing the yields of the cycloaddition. Jeong reports that one of the main obstacles to overcome in the development of a catalytic process is the formation of metal clusters or other inactive cobalt carbonyl species.[33] To this end, they felt that modification of the ligands might stabilize the active cobalt intermediates. Use of triphenylphosphite (10 mol%) as a coligand with dicobaltoctacarbonyl (3 mol%) gave 51–94% yields in seven examples of intramolecular cycloadditions (Eq. (13)).



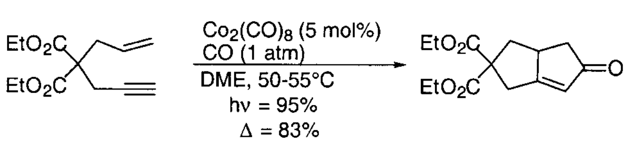
(13)

In a second communication, Jeong reports the use of a 1,5-cyclooctadiene(indenyl)cobalt(I) complex for the catalysis of both inter- and intramolecular cycloadditions.[34] High yields (53–97%) were obtained in the intermolecular cycloadditions of norbornene and norbornadiene with a variety of alkynes and 64 and 94% yields were reported in two intramolecular examples (Eq. (14)). In these examples 1–2 mol% of catalyst with high pressure CO (15 atm) at 100°C were the standard conditions.



(14)

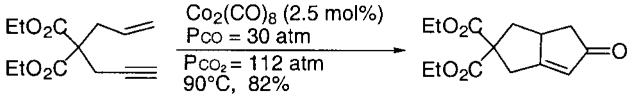
The use of high intensity light to promote the catalytic P–K cycloaddition was reported by Livinghouse.[35] Using 5 mol% of $Co_2(CO)_8$ as catalyst with a 10^6 candle-power spotlight for photoinitiation, yields of 67–95% were realized in nine examples of the intramolecular P–K cycloaddition. In a later report, Livinghouse determined that the cobalt catalyzed intramolecular P–K reaction can also be promoted thermally.[12] Typical conditions involve stirring the enyne of interest in the presence of 5 mol% $Co_2(CO)_8$ at 60°C under an atmosphere of CO for 12–15 h. Reaction yields are high, ranging from 77–86%. In a direct comparison between the thermal and photochemical promoted reactions, Livinghouse found the photochemically promoted catalytic P–K to be slightly more efficient than the thermal variation (Eq. (15)). Under otherwise identical reaction conditions, the photochemically catalyzed reaction was found to contain only 8% of the starting enyne after 14 h at 55°C, while the thermally catalyzed reaction contained 15% starting enyne after the same time. Livinghouse stresses the importance of using high purity $Co_2(CO)_8$ in both the thermal and photochemical variations and reports a method in which very high purity catalyst can be generated in situ via a reduction of the hexacarbonyldicobalt–alkyne complexes.[36] Krafft has reported a modification to the Livinghouse procedure for the in situ generation of catalyst which eliminates the reduction step by incorporating dicobalthexacarbonyl complexes of enynes to serve as the high purity catalyst source.[37]



photochemical - 8% starting enyne remaining after 14 h
thermal - 15% starting enyne remaining after 14 h

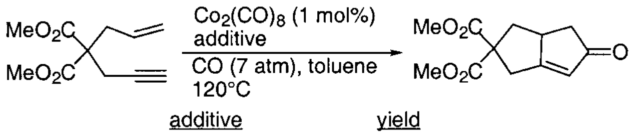
(15)

Jeong has demonstrated that super critical fluids can promote the P–K cycloaddition process.[38] Reactions were performed in super critical CO_2 (PCO2 110–120 atm at 37°C) with 2–5 mol% of $Co_2(CO)_8$ and CO (15–30 atm) at 90°C (Eq. (16)). Yields of cycloadduct were 51–91%. This process demonstrates the feasibility of conducting such transition metal mediated transformations in super critical fluid media.



(16)

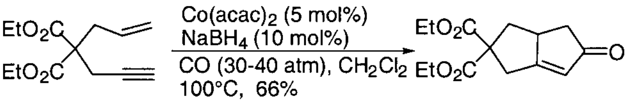
Sugihara has reported that both the inter- and intramolecular catalytic P–K cycloaddition of enynes are promoted using 'hard' Lewis bases.[11] Sugihara utilizes the fact that 'hard' Lewis bases are known to labilize the ligands of low-valent organotransition metal complexes as a method to promote the catalytic cycloaddition. The cycloaddition was found to proceed readily in the presence of 1 mol% $Co_2(CO)_8$ with 4 mol% of various Lewis bases under a CO atmosphere (7 atm) at 120°C (Eq. (17)). 1,2-Dimethoxyethane was found to be the most efficient promoter providing cycloadducts in 75–100% yields. Water was found to be less efficient at promoting the reaction at these concentrations but comparable yields (72–98%) were obtained when the concentration of water was increased. Twelve examples including both inter- and intramolecular cases are reported.



additive	yield
DME (4 mol%)	94%
H_2O (4 mL)	97%

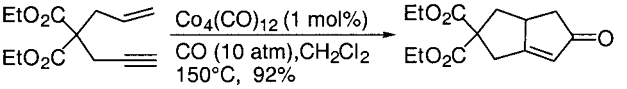
(17)

Other sources of cobalt have proven effective in promoting the catalytic P–K reaction. Chung reports two different variants utilizing alternative cobalt catalysts. In the first, a combination of $Co(acac)_2$ and $NaBH_4$ in catalytic amounts was found to effectively promote either the inter- or intramolecular cycloaddition (Eq. (18)).[39] Typical conditions required 5–10 mol% of $Co(acac)_2$ and 10–20 mol% $NaBH_4$ in the presence of 30–40 atm of CO at 80–100°C to afford yields of 33–100%.



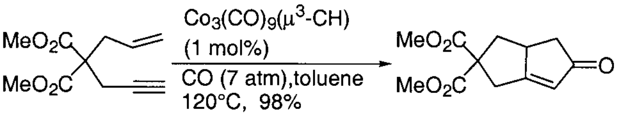
(18)

In a second communication, Chung utilizes the cobalt cluster compound $Co_4(CO)_{12}$ as the cobalt source.[40] Under high pressures of CO an equilibrium between $Co_4(CO)_{12}$ and $Co_2(CO)_8$ is established, with $Co_2(CO)_8$ believed to be the active catalyst. Reaction conditions involved 0.5–1 mol% of the cobalt cluster under 10 atm of CO at 150°C (Eq. (19)). Yields were good, ranging from 58–100% in the intermolecular examples and 81–92% in the intramolecular examples. Chung found that $Co_2(CO)_8$ also effectively catalyzes the cycloaddition process under the same conditions, affording yields of 73–96% in seven intermolecular examples.



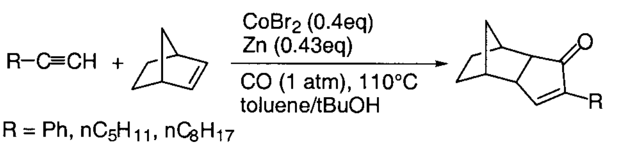
(19)

Sugihara reports that alkylidynetricobalt nonacarbonyl clusters were found to mediate the P–K cycloaddition under catalytic conditions.[41] Methylidynetricobalt nonacarbonyl (1–2 mol%) under an atmosphere of CO (7 atm) at 120°C catalyzed both inter- and intramolecular cycloadditions (Eq. 20). Yields were excellent with cycloadditions proceeding in 78–98%. The air stability and ease of preparation of the methylidynetricobalt cluster is noted as a highlight of this procedure.



(20)

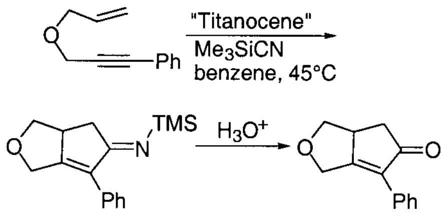
Periasamy has shown that the alkyne–$Co_2(CO)_6$ complex can be generated in situ using sub-stoichiometric amounts of $CoBr_2$ (40 mol%) and Zn (43 mol%) in the presence of CO (1 atm).[42] Intermolecular cycloaddition of norbornene with three alkynes afforded 83–88% yields of cycloadducts (Eq. (21)). Reactions with a non-strained alkene (cyclopentene) proved less efficient, proceeding in yields of 30–35%.



(21)

4.2. Titanium catalyzed cycloadditions

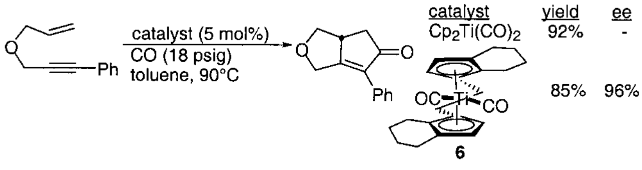
The use of other metals to promote the catalytic P–K cycloaddition has attracted much attention recently. Buchwald has devoted significant effort to the development of a titanium catalyzed P–K reaction. In a series of reports, Buchwald highlights a catalytic P–K reaction equivalent that utilizes a titanocene as the catalytic species to promote cycloaddition between an enyne and an isocyanide.[25] The resulting bicyclic iminocyclopentene is hydrolyzed directly to the cyclopentenone to provide the equivalent of the P–K cycloadduct (Eq. (22)). The titanocene catalyst of 10 mol% $Cp_2Ti(PMe_3)_2$ was reacted with a slight excess of (trialkylsilyl)cyanide. Direct utilization of conventional free isocyanides proved fruitless, thus the (trialkylsilyl)cyanide-(trialkylsilyl)isocyanide tautomeric equilibrium was utilized to limit the concentration of the free isocyanide. Under these conditions the intramolecular cycloaddition provided bicyclic enones in 42–80% yields after hydrolysis of the resultant imine. Buchwald later reports the use of Cp_2TiCl_2 as an air- and moisture-stable, inexpensive titanocene source that provides equivalent yields of cycloadduct in the catalytic process.[25c] Buchwald has also used nickel(0) to catalyze the isocyanide cycloaddition reaction.[27]



catalyst	mol%	yield
$Cp_2Ti(PMe_3)_2$	10	80%
Cp_2TiCl_2/nBuLi	10	82%
$Ni(COD)_2$/Ligand	5	60%

(22)

Buchwald was able to form cyclopentenones directly via a titanocene catalyzed cyclocarbonylation in the first early transition metal catalyzed P–K type cycloaddition.[26a] In his previous work, Buchwald determined that the hydrolysis of the iminocyclopentenes moderated the overall yield of the cycloaddition process. To circumnavigate this bottleneck, direct conversion of enynes to cyclopentenones was effected using $Cp_2Ti(CO)_2$ (5–20 mol%) under a CO atmosphere (18 psig) (Eq. (23)). Cycloadducts were isolated in 58–95% yields in fifteen examples. In subsequent papers, Buchwald reports an enantioselective variant of the titanium catalyzed P–K using an enantiomerically pure chiral titanocene catalyst (Eq. (23)).[26b,c] Under analogous conditions, catalytic amounts of enantiomerically pure (*S*,*S*)-(EBTHI)$Ti(CO)_2$, **6** afforded cyclopentenones in 70–94% yields with enantiomeric excesses of 72–96%.

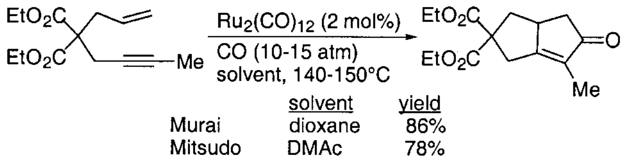


catalyst	yield	ee
$Cp_2Ti(CO)_2$	92%	-
6	85%	96%

(23)

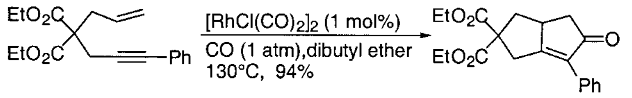
4.3. Ruthenium and rhodium catalyzed cycloadditions

Examples of P–K type cycloaddition processes catalyzed by late transitions metal complexes have recently begun to appear in the literature. The first of these involved the use of ruthenium to promote cycloaddition. Murai[28] and Mitsudo[29] reported almost simultaneously that $Ru_3(CO)_{12}$ effectively catalyzed the intramolecular cycloaddition of enynes to form cyclopentenones (Eq. (24)). Under similar conditions [2 mol% $Ru_3(CO)_{12}$ under a CO atmosphere (10–15 atm) at 140–160°C] that differed only in the solvent, cycloadducts were isolated in 41–95% yields.



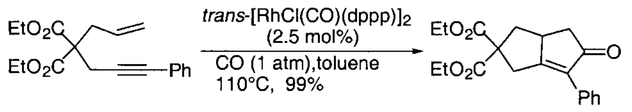
(24)

Rhodium has also been shown to catalyze the intramolecular P–K cycloaddition. Narasaka has established that rhodium dinuclear carbonyl complexes promote the cycloaddition process.[30] A series of seven enynes were treated with catalytic amounts of $[RhCl(CO)_2]_2$ (1–5 mol%) in dibutyl ether under a CO atmosphere (1 atm) at 130–160°C to afford 41–94% yields of bicyclic cyclopentenones (Eq. (25)).



(25)

In another report, Jeong has determined that other rhodium(I) complexes can effect the intramolecular cycloaddition of enynes.[31] Complexes such as $RhCl(PPh_3)_3$ or *trans*-$RhCl(CO)(PPh_3)_2$ required the addition of silver(I) salts (10 mol%) to catalyze the reaction, however, 2.5 mol% of *trans*-$[RhCl(CO)(dppp)]_2$ efficiently promoted cyclization in the absence of silver(I) (Eq. (26)). Yields of 55–99% were observed in seven cases.

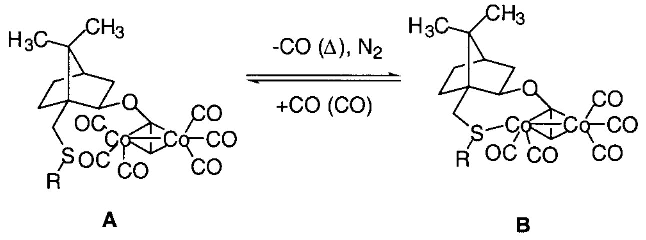


(26)

5. Asymmetric Pauson–Khand and Related [2+2+1] Cycloadditions

There have been extensive efforts made in the past decade directed toward an asymmetric P–K reaction. Much of the work done in the area of asymmetric synthesis has been reviewed by Marco-Contelles in 1998.[43] The Marco-Contelles review covers developments in the late-eighties to the mid-nineties. The content of this review is therefore not exhaustive but is meant to provide an up-to-date account of the asymmetric P–K reaction since 1996.

The most successful approaches to the preparation of chiral cyclopentenones have involved the use of: (1) a chiral auxiliary which is removed once the cyclization is affected; (2) the use of chiral metal complexes; (3) chiral promoters; and (4) the direct incorporation of the chirality in the cyclization precursor.



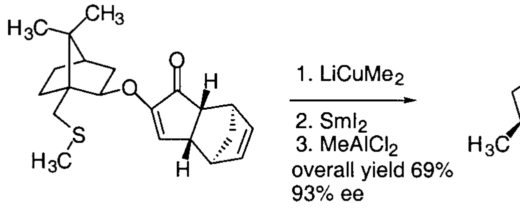
Scheme 1.

5.1. Chiral auxiliary approach

An interesting approach to the asymmetric synthesis of cyclopentenones has been reported by Pericàs and Riera.[44] The Krafft[4,45] technology is used whereby a suitably positioned sulfur moiety coordinates to the cobalt–alkyne complex and in some cases the resulting sulfur ligated complex can be isolated.[45d] It was shown that the equilibrium between the complexes **A** and **B** can be controlled (Scheme 1). Heating the ligated complex **A** to 50°C under a nitrogen purge results in the formation of complex **B** with slight contamination with complex **A**.

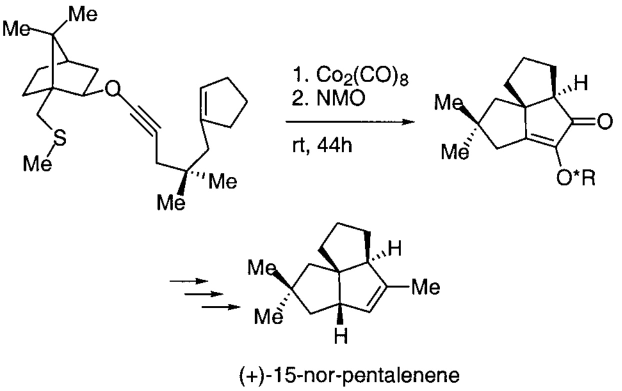
Alternatively, cooling the mixture to room temperature under a carbon monoxide atmosphere causes the equilibrium of the mixture to revert back to complex **A**. Subsequently, it was found that the addition of 6 equiv. of *N*-methylmorpholine *N*-oxide (NMO) under nitrogen in methylene chloride pushed the equilibrium entirely to complex **B**. The chiral information of the auxiliary is transmitted to the cobalt which in turn is transmitted to the product. A variety of experiments were tried, systematically varying the reaction conditions, R groups and strained alkenes. Low de's (40%) and yields (65%) were obtained if conditions were used that ensured maximum concentration of complex **A**. Reaction conditions ensuring maximum concentration of **B** gave higher de's (92%). Unfortunately, the highly reactive complex **B** could not be used with less reactive olefins. For example, reaction of complex **B** with cyclopentene afforded a 14% yield of the cycloadduct as a 1:1 mixture of diastereomers.

Pericàs and Riera demonstrated the synthetic usefulness of this method by showing that it can be used in the preparation of chiral cyclopentenones (Eq. (27)). Lithium dimethylcuprate was added to the enone followed by a reductive cleavage of the chiral auxiliary using samarium diiodide. Finally, a Lewis-acid catalyzed retro-Diels–Alder reaction was done to afford the (*S*)-4-methyl-2-cyclopentenone in 93% ee.



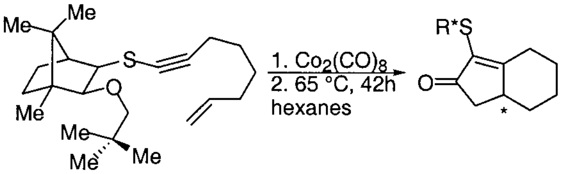
(27)

Similarly high diastereoselectivities were observed in the intramolecular P–K reaction, but only in cases where the chelated pentacarbonyl cobalt complex could be observed by TLC. For example, Pericàs and Moyano applied this chiral auxiliary technology to the synthesis of (+)-15-nor-pentalenene.[46] The chiral camphor-derived alkoxyacetylene possessing the sulfur tether cyclized to give the tricyclic enone in high diastereoselectivities (9:1) in good yield (Eq. (28)). The tricycle was then converted to (+)-15-nor-pentalenene in several steps.



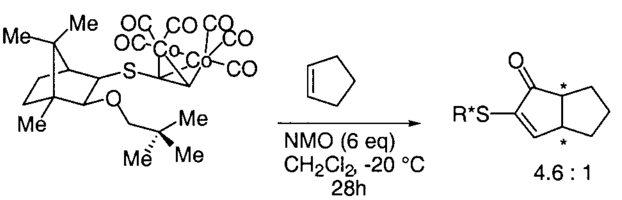
(28)

Alternatively, Pericàs and Riera found in the absence of the chelating sulfur moiety, the chiral thioalkoxyacetylene gave very low diastereomeric excesses (1.4:1) in moderate yields (60%) for the intramolecular P–K reaction (Eq. (29)).[47]



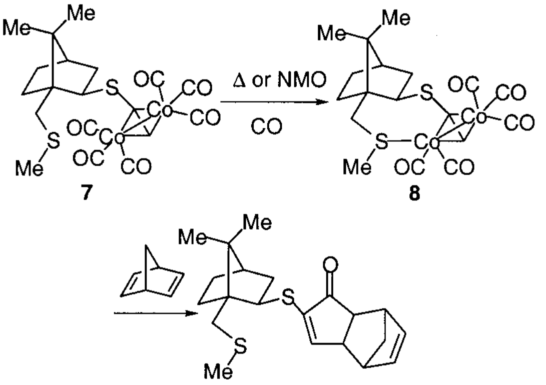
(29)

Similarly, the intermolecular P–K reaction afforded high yields of the cyclization products when unstrained or reactive olefins were used. However, as in the intramolecular case, very low diastereoselectivities were obtained in the absence of a chelating sulfur moiety. A variety of systems were investigated and the best diastereoselectivity obtained was 4.6:1 (Eq. (30)).



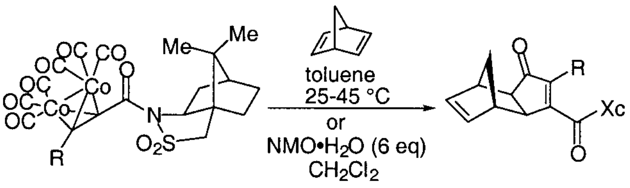
(30)

Pericàs and Riera prepared a chiral thioalkoxyacetylene complex in which a sulfur moiety was a part of the chiral auxiliary.[48] It was maintained that the thioalkoxyacetylene complexes were more thermally and hydrolytically stable than the alkoxyacetylene complexes. The chelated complex **8** could be readily formed either under thermal conditions and a stream of nitrogen, or alternatively by using oxidative conditions (NMO). Each of the complexes (**7** or **8**) were reacted with strained olefins (Eq. (31)). Complex **7** and norbornadiene gave only a 31% yield of the norbornene cycloadduct over 552 h and the diastereomeric ratio was low (2:1). Interestingly, when the reaction was done using oxidative conditions (NMO) to form complex **8**, nearly a 1:1 mixture of diastereomeric cycloadducts was observed. This is in contrast to the observation made earlier whereby the same reaction using chiral alkoxyacetylenes afforded very high diastereomeric ratios. Subsequently, Pericàs and Riera determined that the highest diastereomeric ratios were observed by generating the sulfur chelated pentacarbonyl complex using heat, then cooling the solution to −10°C prior to the addition of the olefin. Under these conditions, the cycloadduct was obtained in a 65% yield after 72 h and the diastereomeric ratio observed was very high (95:5) when strained olefins were used. Unstrained olefins were not investigated.



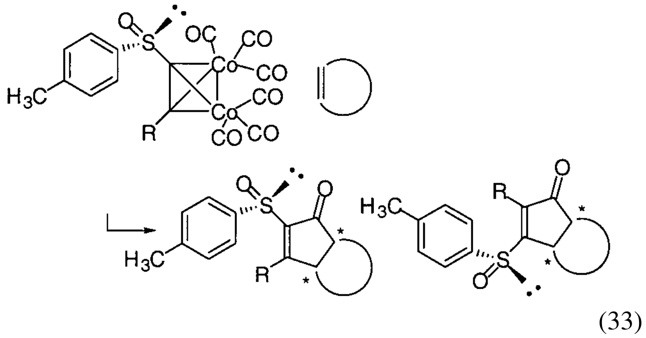
(31)

Moyano and Pericàs have found exceptionally high levels of regio- and stereocontrol can be achieved using Oppolzer's bornane sultam as a *steric* control element and norbornadiene in the intermolecular P–K reaction (Eq. (32)).[49] When R=Ph, the level of stereoinduction was 523:1 using thermal conditions. This diastereomeric ratio was higher (800:1) when the P–K reaction was promoted under oxidative conditions (NMO·H_2O). Similarly high diastereomeric ratios were observed when R=TMS (800:1). The reported yields for each of these reactions were very high ranging from 78–93%.



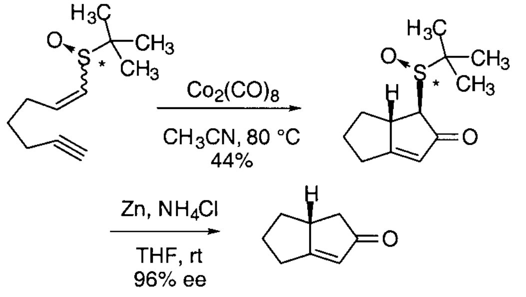
(32)

Chiral alkynyl sulfoxides have been prepared for use in a diastereoselective P–K reaction (Eq. (33)).[50] Unlike the previous chiral auxiliary approaches (using alkoxy and thioalkoxyalkynes), the stereogenic center is bound directly to the acetylenic carbon. This close proximity was predicted to give good transfer of chirality to the corresponding cycloadduct. Unfortunately, where R=TMS or H, cycloaddition either did not occur or gave very low conversions. Where R=*n*-Bu or Ph, cycloaddition occurred but mixtures of regioisomers were obtained. Finally, when the transfer of chirality from the sulfoxide to the cyclopentenone was measured, there was significant loss of enantiomeric excess. It was subsequently determined that the dicobalthexacarbonyl alkynyl sulfoxide complex is configurationally unstable and efforts are underway to determine the reason for this instability.



(33)

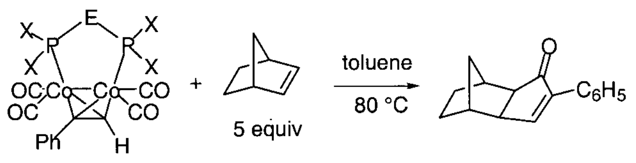
Recently, Carretero has shown that the attachment of the chiral sulfoxide moiety to the olefin instead of the alkyne, does provide enones in high enantiomeric excesses (Eq. (34)).[51] Interestingly, treatment of a mixture of *cis* and *trans* vinyl sulfoxides afforded only one isomer upon cyclization. The sulfoxide could be removed in high yields (92–96%) to provide the optically active bicyclic enones.



(34)

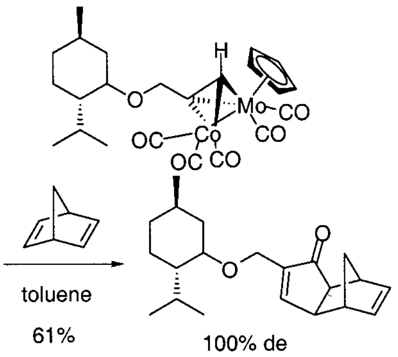
5.2. Chiral complex approach

Greene reports the synthesis of a variety of binuclear cobalt complexes with diphosphinamine ligands (Eq. (35)).[52] These complexes are reacted with norbornene and the results are summarized below. Phosphorous ligands bearing an amine tether (E=NCH$_3$) and electron withdrawing groups (X=F, (CF$_3$)$_2$CHO, pyrrolyl) gave the most efficient conversions to cycloadducts (90–98% yields) but relatively long reaction times are required (3–5 days). As a preliminary study directed toward the goal of asymmetric synthesis using these chelated bidentate complexes, (−)-α-methylbenzylamine was used in place of the methylamine tether. The norbornene cycloadduct was obtained in low but promising 16% enantiomeric excess.



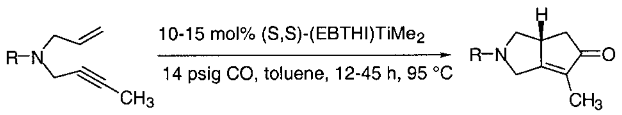
(35)

Christie has demonstrated an asymmetric variant of the P–K reaction by preparing a chiral mixed metal complex (Eq. (36)).[53] These complexes are reportedly handled in air for extended periods of time and they are more thermally stable than the previously reported phosphine substituted complexes. The diastereoselectivity is believed to result from the reaction occurring selectively with one chiral metal site over the other.



(36)

Buchwald has demonstrated an intramolecular asymmetric P–K type cyclization of enynes possessing a nitrogen atom in the tether using carbon monoxide and a catalytic amount of (*S*,*S*)-(EBTHI)TiMe$_2$ (Eq. (37)).[54] The substituent on the nitrogen atom had an influence on the enantioselectivity and the yield of this reaction.



(37)

5.3. Chiral promoter approach

For many P–K cycloaddition substrates, the rate of the reaction increases significantly when amine *N*-oxides are added to the reaction media. It is thought that the rate enhancement is due to the freeing-up of a ligand site on the cobalt via oxidative removal of carbon monoxide. The first example of an asymmetric P–K reaction effected by a chiral amine *N*-oxide was reported in 1995 by Kerr.[55] Brucine *N*-oxide was used as the promoter to give a cycloadduct in low enantiomeric excess.

It was reasoned by Laschat that a chiral amine *N*-oxide should be able to differentiate between the two enantiotopic ligands A and A′ (the least sterically hindered COs) (Fig. 1).[56] (−)-Sparteine *N*-16-oxide, (+)-sparteine *N*-1-oxide and (−)-17-oxosparteine *N*-oxide all gave low enantiomeric excesses when used as promoters in the P–K

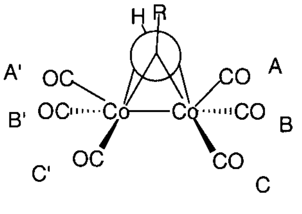
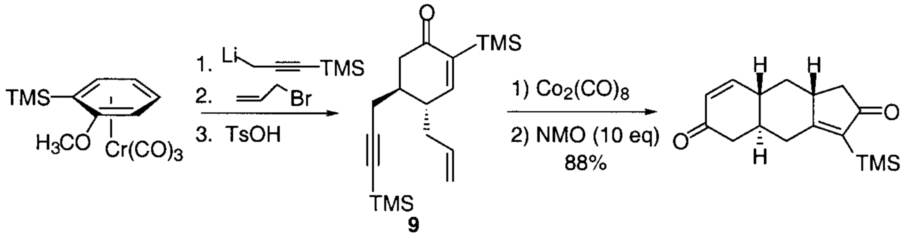


Figure 1.



Scheme 2.

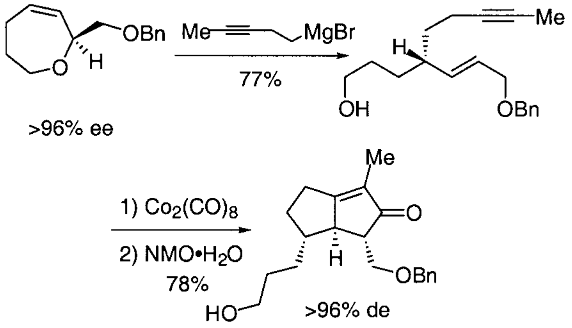
reaction. The best enantioselectivity observed (33%) was in the case of *tert*-butyl acetylene in a low yield (37%).

5.4. Chiral precursor approach

Many researchers have taken advantage of the stereoselective nature of the formal [2+2+1] cycloaddition and by incorporating chirality into the starting material have subsequently effected a transfer of chirality into the P–K cycloadduct. A few of the more recent examples are presented below. A new method involving the generation of two stereogenic centers from a benzene ring was used in combination with a diastereospecific P–K reaction (Scheme 2).[57] Complexation of compound **9**, generated from the anisole chromium tricarbonyl complex, with dicobaltoctacarbonyl followed by P–K cyclization promoted with NMO resulted in the formation of the tricyclic compound as a single diastereomer with complete transfer of chirality.

Mukai and Hanaoka have shown that optically active bicyclo[3.3.0]octenone derivatives possessing two distinguishable hydroxyl groups can be prepared using an intramolecular P–K reaction (Scheme 3).[58a,b] The chiral P–K precursor in the example below could be obtained from either dimethyl L-tartrate or L-ascorbic acid. A variety of R groups and conditions were examined which led to P–K cycloadducts in yields ranging from 0–96%. Even more interesting, the product ratio of **10** to **11** for each of these variations ranged from 1:1 to 100:0. A few trends were observed in this study: (1) Under purely thermal P–K conditions, groups at the terminus of the alkyne other than hydrogen produced compound **10** diastereoselectively and bulky groups such as a TMS-moiety resulted in the exclusive formation of compound **10**; (2) When the P–K reaction was promoted with TMANO, a TMS-moiety on the terminus of the alkyne sufficiently inhibited the reaction to the point where in some cases no product was obtained; (3) Bulky groups on the hydroxyl moieties showed varying degrees of selectivity, however a *tert*-butyl dimethylsilyl moiety proved to give high diastereoselectivities in all cases. A mechanistic hypothesis was offered to explain these results. In a more recent article, Mukai and Hanaoka have extended this methodology to the formation of optically active bicyclo[4.3.0]nonenones in high yields and diastereoselectivities.[58c]

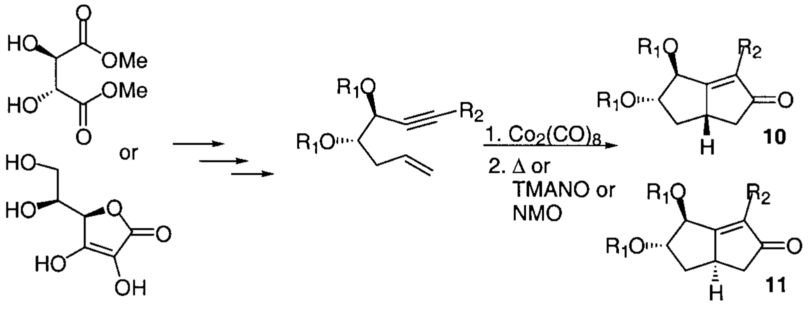
Hoveyda combined a stereoselective allylic alkylation of a cyclic ether and a P–K cycloaddition of the resulting enyne to produce a bicyclic enone in high yield (Eq. (38)).[59] Excellent diastereoselectivities are observed as a result of the allylic substituent with the product obtained in optically pure form.



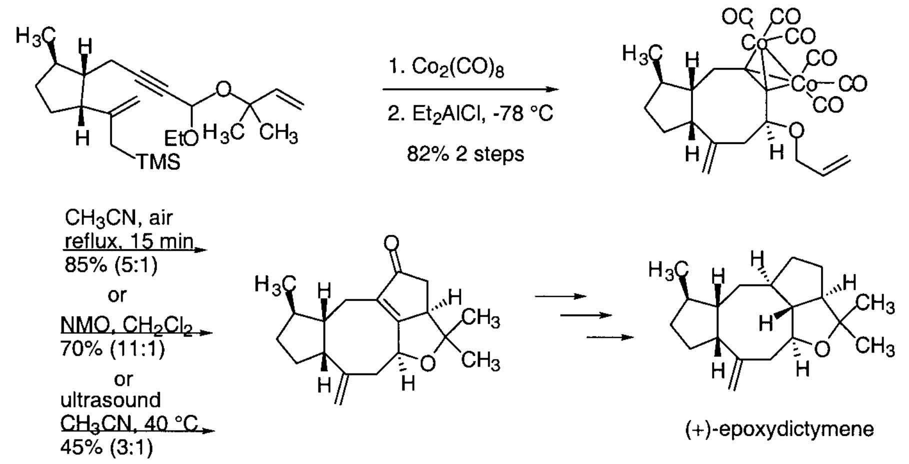
(38)

Schreiber used a tandem Lewis acid-promoted Nicholas reaction and a P–K reaction to construct (+)-epoxydictymene (Scheme 4).[60] Treatment of the alkyne with dicobaltoctacarbonyl followed by Lewis acid provided the bicyclic system in high yield and high diastereoselectivity. A brief study was done to determine the best Lewis acid for the Nicholas reaction and a variety of conditions proved effective in the P–K cyclization.

Marco-Contelles demonstrated the P–K cycloaddition of a chiral enyne derived from 3,4-di-*O*-acetyl-L-arabinal

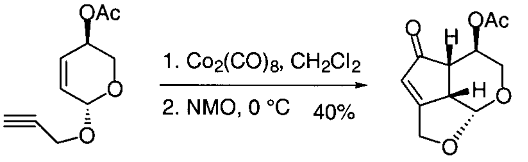


Scheme 3.



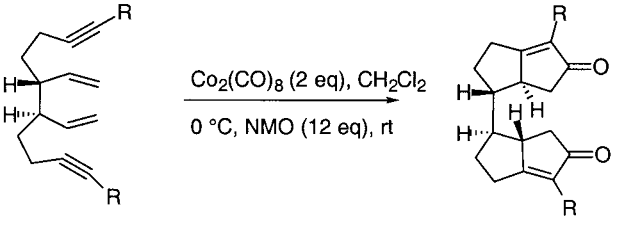
Scheme 4.

(Eq. (39)).[61] This cycloaddition occurred to give the enantiomerically pure highly oxygenated tricycle which possesses the stereochemistry suitable for the conversion to the natural iridoid aglycones.



(39)

Grossman subjected the *bis*-enyne to the P–K cyclization conditions to afford the *bis*-bicyclic compound regio- and stereoselectively (Eq. (40)).[62] These diastereomerically pure enones were used in the preparation of *ansa* metallocene complexes.



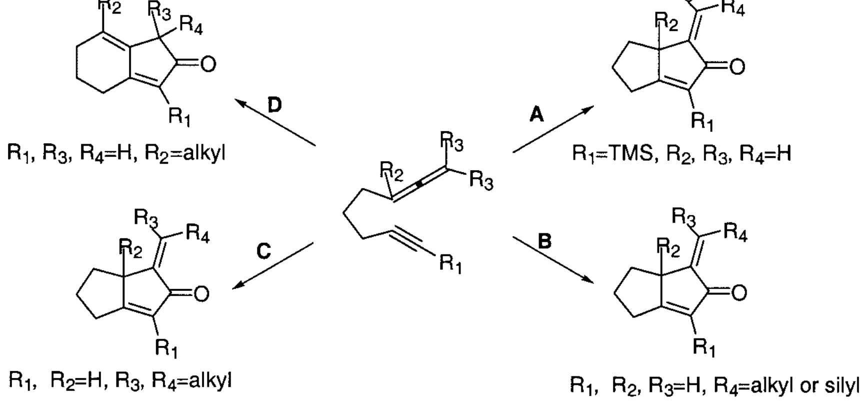
(40)

6. [2+2+1] Cycloaddition Precursor Alternatives

6.1. The allenic Pauson–Khand type reaction

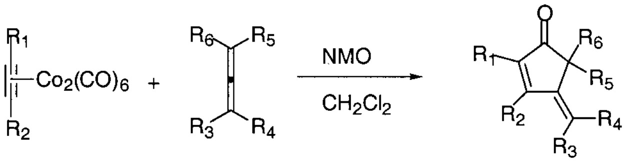
It has been demonstrated that allenes can be used in place of olefins in the P–K reaction and this work has been recently reviewed.[63] The intramolecular P–K can give two different cycloadducts depending upon the substitution pattern of the allene (Scheme 5). For substitution patterns **A**, **B** and **C** the reaction occurs to give the α-methylene cyclopentenone. Alternatively, if R_2 is an alkyl group (substitution pattern **D**) the reaction occurs with the external π-system of the allene to afford the 4-alkylidene cyclopentenone. The standard conditions used to effect the intramolecular allenic P–K reaction are molybdenum hexacarbonyl, dimethylsulfoxide and toluene at 100°C.[22]

Cazes and coworkers have extensively investigated the intermolecular allenic P–K reaction using dicobaltoctacarbonyl and NMO (Eq. (41)).[64] In nearly all cases the reaction occurs selectively with the less substituted π-bond of the allene. In addition, if one of the substituents on the allene is an electron withdrawing group such as an ester or a sulfone moiety, the reaction still occurs primarily with the less substituted double bond, but mixtures of



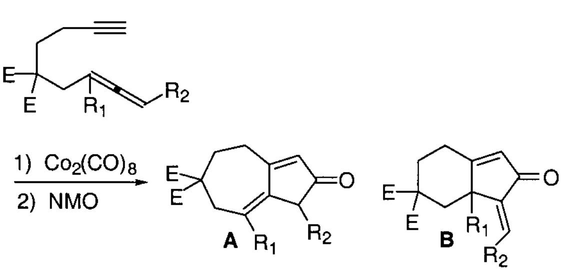
Scheme 5.

α-methylene- and 4-alkylidene cyclopentenones are obtained. A mechanistic rational is offered to explain these results. Other groups have also shown that allenes can be used in these types of cycloadditions using catalytic cobalt and metals other than cobalt and molybdenum.[19,26a,65]



(41)

Cazes has shown that medium rings can be formed in the intramolecular variant of the cobalt/NMO promoted allenic P–K reaction (Eq. (42)).[64a] These are the first reported examples of a seven membered ring formed via an intramolecular P–K reaction.



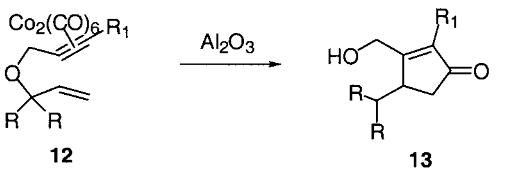
(42)

R_1	R_2	A:B ratio	combined yield
CH_3	H	1:0	10%
H	CH_3	45:55	50%

6.2. Traceless tethers

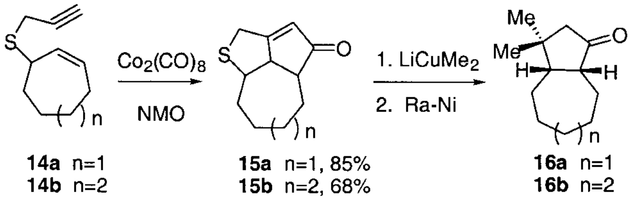
Despite the advances made in the area of the P–K cycloaddition, the intermolecular cycloaddition is still largely restricted to the use of strained olefins. Thus, using this method to access monocyclic products is limited. This strained olefin restriction does not hold true for the intramolecular version of this cycloaddition and so a potential solution would be to take advantage of the ease of the intramolecular cycloaddition using a traceless tether to access monocyclic compounds. Once the cycloaddition is effected, removal or ring opening of the tether affords a monocyclic product. The most common heteroatom-tethers used to date contain sulfur, nitrogen or oxygen. These efforts are summarized briefly below.

Smit demonstrated that the cobalt–complex of an allyl propargyl ether **12** undergoes cyclization to afford the hydrogenolyzed product **13** under 'dry' alumina conditions (Eq. (43)).[66] The hydrogenolysis is presumably effected by a hydridocobalt species formed during the adsorption process. This represents the first of only a few examples where an intramolecular P–K cycloaddition has been effected, followed by a ring opening of the tether to afford a product that would typically be obtained from the intermolecular P–K cycloaddition.



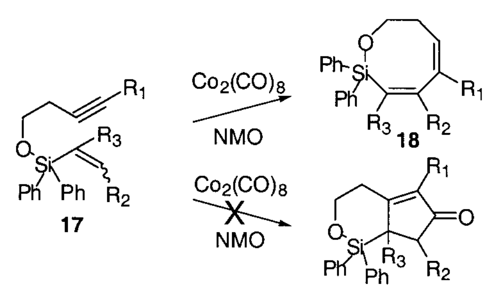
(43)

Although there have been many P–K cycloadditions effected containing an oxygen atom in the tether, less common is the use of a sulfur atom. Pericas and Moyano have demonstrated that treatment of compound **14a,b** to the P–K reaction conditions [$Co_2(CO)_8$, NMO] afforded the tricyclic enones **15a,b** in 85 and 68% yield, respectively (Eq. (44)).[67] Cycloadducts **15a,b** were then subjected to a conjugate addition (lithium dimethylcuprate) followed by a Raney–nickel desulfurization to afford **16a,b** in good yield. Thus, removal of the sulfur containing tether constitutes a diastereoselective approach to *cis*-perhydroazulenes and *cis*-perhydrocyclopentacyclooctenones.



(44)

An alternative approach involves the use of a silicon atom as a traceless tether. Silicon tethers have already been used quite successfully in a variety of cycloaddition reactions. A report by Saigo, shows the results of their attempt to effect a silicon-tethered P–K cyclization (Scheme 6).[68] Treatment of the tethered silyl ether enyne **17a–e** to dicobaltoctacarbonyl and *N*-methylmorpholine *N*-oxide gave none of the [2+2+1] cycloadduct but instead afforded the corresponding eight-membered rings **18a–e** in low yields (Table 2).

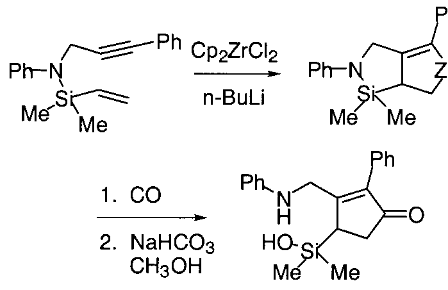


Scheme 6.

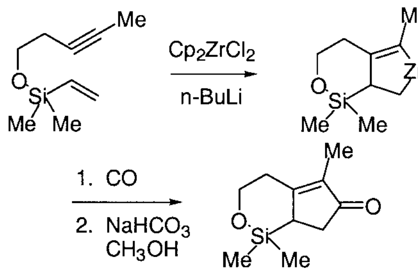
Table 2.

Entry	R_1	R_2	R_3	Yield (%)
a	H	H	H	46
b	Me	H	H	30
c	TMS	H	H	0
d	H	Me	H	24
e	H	H	Me	24

Finally, Whitby has shown that 1,6- and 1,7- enynes incorporating a silicon–oxygen or a silicon–nitrogen link can be cyclized using the Negishi cyclization protocol (Eqs. (45) and (46)).[69] The enyne cyclized to afford the zirconocycle, which was then subjected to carbonylation and hydrolytic conditions to afford the cyclopentenone.



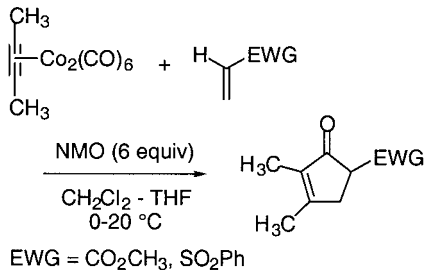
(45)



(46)

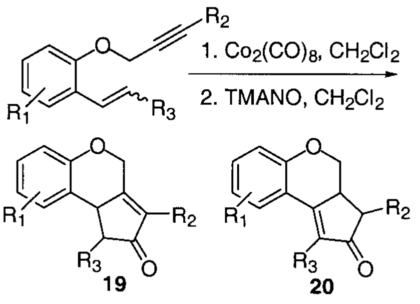
6.3. Miscellaneous

Recently, Cazes has shown that, contrary to popular thought, the intermolecular P–K reaction can be performed using electron deficient olefins.[70] Treatment of cobalt complexed alkynes with electron deficient olefins possessing ester and sulfonyl moieties affords cyclopentenones in good to moderate yields (Eq. (47)). The success of this reaction was dependent upon the conditions employed.



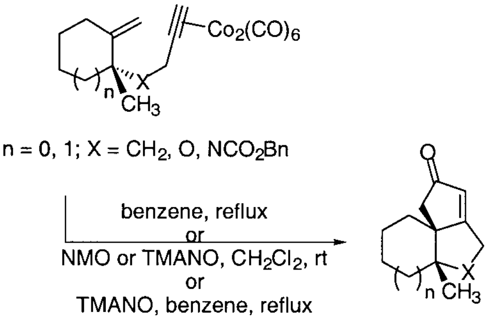
(47)

Pérez-Castells has used aromatic enynes as substrates for the intramolecular P–K reaction in order to obtain polycyclic systems possessing aromatic rings (Eq. (48)).[71] Interestingly, a double bond isomerization occurred in almost all cyclizations to afford compound **20** instead of the expected cyclopentenone **19**. At this time, it is not known when the isomerization occurs.



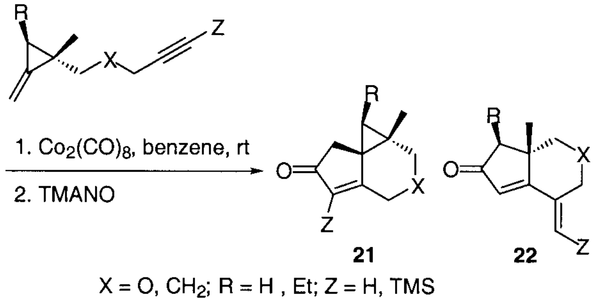
(48)

Hoshino has effected the P–K reaction using exocyclic olefins to synthesize angular tricyclic compounds (Eq. (49)).[72] A variety of 6,6,5- and 5,5,5-tricyclic systems were obtained containing contiguous quaternary centers in good to moderate yields using a variety of conditions.



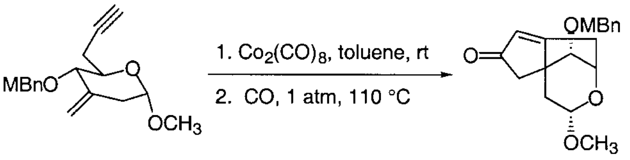
(49)

Motherwell has shown that methylenecyclopropanes can function as the olefin component in the intramolecular P–K reaction (Eq. (50)).[73] If the R group of the cyclization precursor is a hydrogen atom then cycloaddition occurs as expected to give compound **21**. Interestingly, if R is an alkyl moiety then rearrangement occurs to afford the unexpected compound **22**. A mechanism whereby formation of this unusual rearrangement product occurs is proposed.

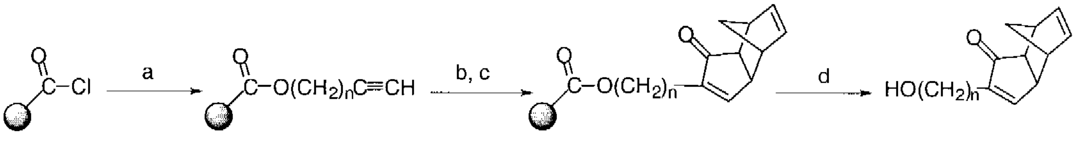


(50)

Borodkin has demonstrated the intramolecular cyclization of an exocyclic methylene moiety and a tethered alkyne to afford a bridged bicyclic octenone (Eq. (51)).[74]

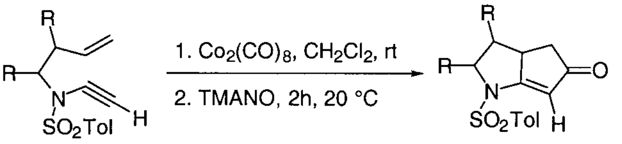


(51)



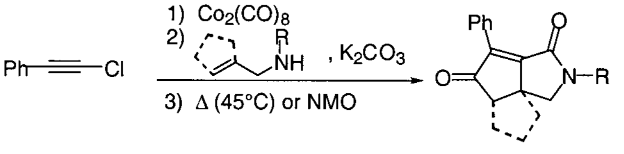
Scheme 7. (a) $HC{\equiv}C(CH_2)_nOH$, pyridine; (b) $Co_2(CO)_8$; (c) norbornadiene, 80°C; (d) nBu_4NCl, KOH.

Witulski has used an *N*-functionalized alkynylamide in a P–K type cycloaddition to afford nitrogen containing heterocycles in good yields (Eq. (52)).[75]



(52)

Finally, Pericàs has reported a tandem aminocarbonylation/P–K reaction of haloacetylenes (Eq. (53)).[76] The cobalt complex of the haloacetylene is proposed to rearrange to form a 1-chloroacetylene acylcobalt complex which can be trapped by allylamines and submitted to the P–K reaction. The process can be achieved as a one-pot procedure without decrease in efficiency. Three intermolecular and three intramolecular examples are reported.



(53)

7. Pauson–Khand Reactions Performed on a Solid Support

The development of broad-based screening assays has led to the need for the rapid synthesis of large numbers of small organic molecules. One way in which the pharmaceutical industry is addressing this issue is by the generation of molecular libraries. Synthesis of these compounds on a solid polymeric support is the primary method in which these libraries are created. The adaptation of well-known solution phase synthetic reactions to the solid phase is a major focus of chemists in this area. The P–K cycloaddition has been shown to be amenable to reaction on a polymeric support.

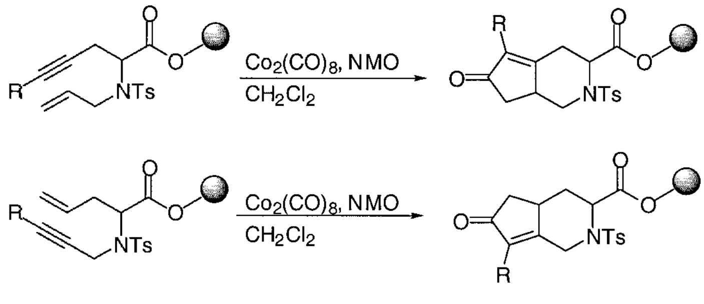
7.1. Intermolecular cycloadditions

Schore demonstrated early on that the intermolecular P–K cycloaddition could be effected with one of the reactants linked to a polymeric bead.[77] Low molecular weight functionalized alkynes, such as ω-alkynols and their derivatives are notoriously bad substrates in the P–K cycloaddition. Side reactions, including alkyne trimerization and alkene oligomerization, are believed to be the primary cause of the observed low yields. Schore felt that attachment of the alkyne to a solid support would suppress reactions involving multiple alkyne moieties. Reaction of the alkynol with a modified Merrifield resin afforded the resin linked substrate (Scheme 7). The cobalt complex of the alkyne formed by reaction with $Co_2(CO)_8$ reacted readily with reactive alkenes to afford the P–K cycloadduct.

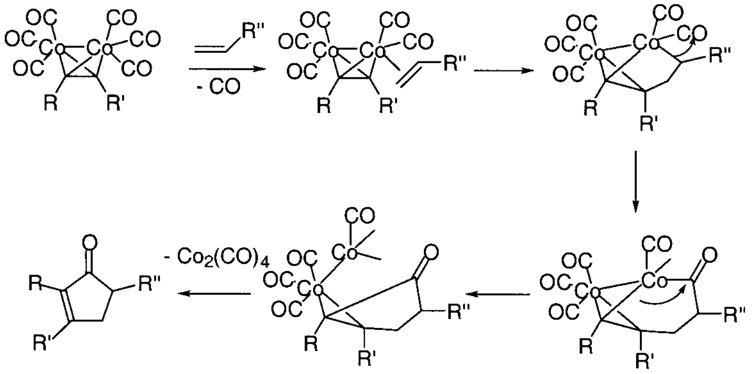
Hydrolysis of the ester linkage freed the cycloadduct from the polymer. The reactions of five different resin bound alkynes are reported with up to three reactive alkenes. Yields ranged from 0–99% with most yields being significantly higher than the analogous solution-phase reaction.

7.2. Intramolecular cycloadditions

The only other examples of a P–K cycloaddition performed on a solid support are the intramolecular versions reported by Bolton.[78] In these examples, azabicyclo[4.3.0]nonen-8-one systems are rapidly synthesized on a polymeric bead. Bolton attaches an allyl or propargyl α-amino acid to the polymeric support via an ester linkage (Scheme 8). The enyne is formed and the cycloaddition is effected via the cobalt complex using *N*-methylmorpholine *N*-oxide as a promoter. Cleavage from the resin followed by esterification of the resulting acid afforded P–K cycloadducts in good yield (38–88%) from the enyne. Bolton has also shown that the enyne can be diversified while attached to the resin leading the way to the development of combinatorial libraries by this method.



Scheme 8.

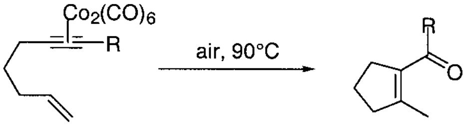


Scheme 9.

8. Mechanistic Studies

Beyond the fact that a hexacarbonyldicobalt–alkyne complex is involved, little is actually known about the mechanism of the P–K cycloaddition. The currently accepted mechanistic pathway was originally proposed by Magnus (Scheme 9).[79] Initial support for the proposed mechanism cited steric control of the regiochemical outcome in the intermolecular cycloaddition.[80] Electronics have also been shown to have an effect on the regiochemical product mixture.[81] Krafft lent support to the mechanism by showing that regiocontrol in the intermolecular cycloaddition can be achieved via a coordinating ligand attached to the alkene moiety.[4,45]

While no group has observed any of the proposed intermediates of the Magnus mechanism, Krafft has successfully interrupted the intramolecular cycloaddition process by exposing the reaction mixture to an oxygen containing atmosphere (Eq. (54)).[82]



(54)

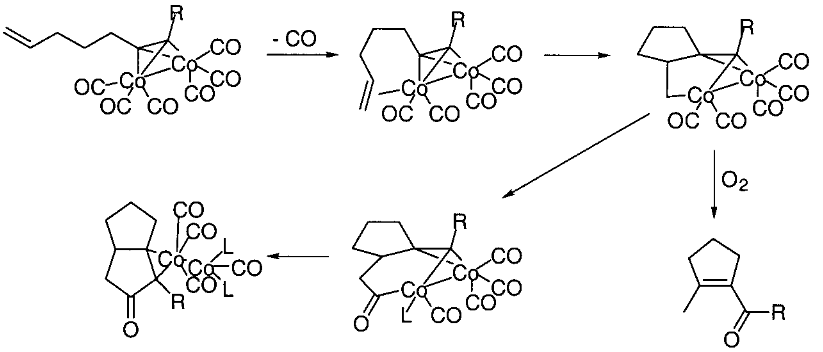
Krafft suggests that both the enone product from the interrupted P–K and the expected cyclopentenone product can arise from a common intermediate in the proposed mechanism (Scheme 10).

Moyano and Pericàs use a molecular mechanics approach involving both experimental and computational studies to explain the diastereoselectivities in their asymmetric P–K reaction.[44,83] The authors rationalize the observed selectivities based on the Magnus mechanism. With the development of the Livinghouse photochemical P–K,[35] Gordon has used infrared spectroscopy to establish that loss of one CO ligand is the initial step after irradiation with shortwave UV photolysis.[84] This result implies that the loss of CO is the initial step in the photochemical P–K and that it might follow a mechanism similar to that proposed for the non-photochemical variant. Krafft and Schore have used molecular mechanics to study the intramolecular P–K reaction of substituted acyclic and cyclic dienynes.[85] Through comparison of the calculated energy differences of the putative metallacycle intermediates, Krafft and Schore have developed a model that can qualitatively predict the relative stereochemical outcome of the cycloaddition, thus lending support to a metallacyclic intermediate in the reaction mechanism.

Further study is required to firmly establish the mechanistic aspects of the P–K reaction. This is especially true with the development of reaction variations including the use of alternative metals and catalytic processes.

9. Recent Applications to Natural Product Synthesis

Many natural products incorporate a cyclopentane ring as one of their structural features. As one of the primary

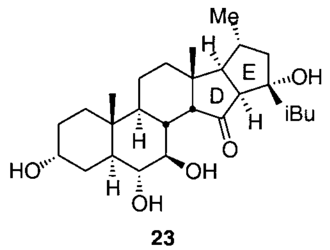


Scheme 10.

methods for the synthesis of cyclopentanes, the P–K cycloaddition has seen extensive use in a variety of approaches to natural product synthesis. Some of the more recent applications to natural product synthesis are discussed below.

Many of these endeavors have been noted in previous reviews of the P–K reaction.[7] Approaches to such complex natural products as furanether B,[86] hirsutene,[87] PGA_2,[88] fenestranes,[89] kainic acid,[90] loganine,[91] brefeldin A[92] and epoxydictymene[60] are addressed in these reviews.

Krafft has utilized the P–K reaction to establish the D/E rings of the pentacyclic steroid derivative xestobergsterol (**23**).[93] Several approaches to the cyclopentene unit of taylorione (**24**) have also incorporated this methodology.[94] Kowalczyk installed the *cis*-anti-*cis* ring fusion stereochemistry of the spatane diterpenoids **25** in an efficient manner using a cobalt mediated cycloaddition.[95]



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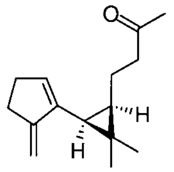

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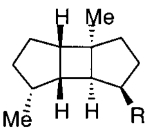
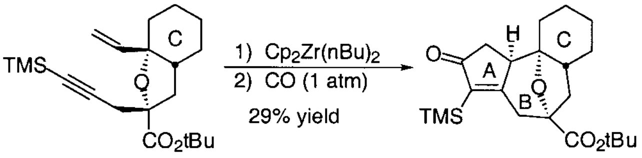


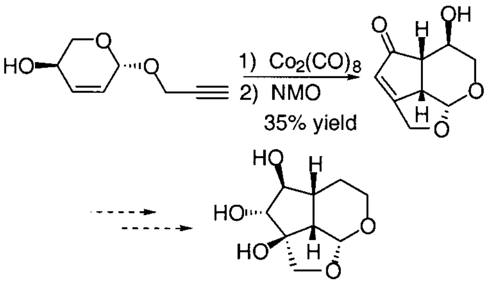
25

Wender used a zirconium mediated intramolecular carbonylative cyclization to rapidly develop the A/B/C ring system on the tigliane and daphnane skeletons (Eq. (55)).[96] This is the first example of a bridged system installed by a P–K like cycloaddition; however, the yield for the reaction was low (29%).



(55)

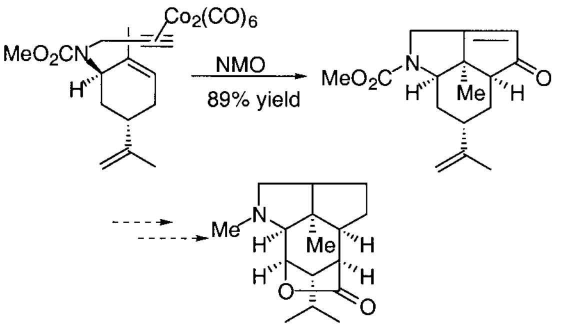
Negishi also used a zirconium carbonylative procedure to synthesize the cyclopentane of (+)-iridomyrmecin.[97] More recently, in an approach to the iridoid skeleton of rehmaglutin A (**26**), Marco-Contelles established the stereochemistry of all three rings of the target although in only 35% yield (Eq. (56)).[61]



26

(56)

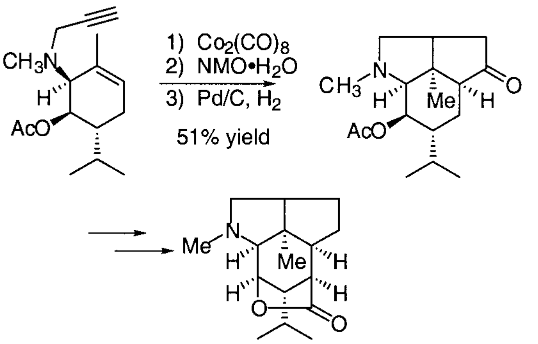
The intramolecular variant of the P–K cycloaddition has been particularly effective in the rapid synthesis of complex fused tricycles. In his approach to dendrobine (**27**), Takano established the carbocyclic skeleton of the target molecule in one process (Eq. (57)).[98] The reaction proceeded in excellent yield (89%) and set the correct stereochemistry at the ring fusions.



27

(57)

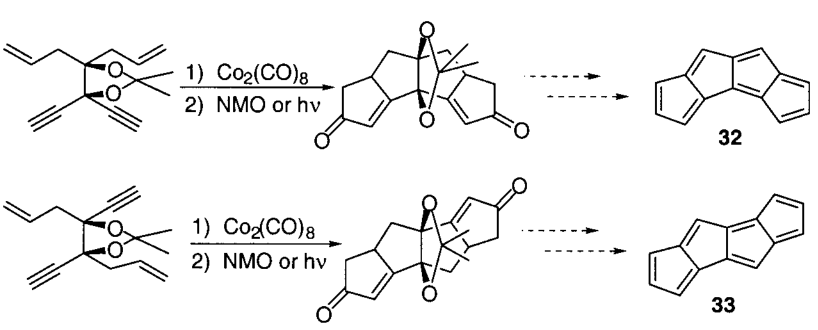
Using a similar approach, Cassayre and Zard successfully completed an asymmetric synthesis of (−)-dendrobine (**27**), setting the stereochemical features of the tricycle with a P–K cycloaddition (Eq. (58)).[99]



27

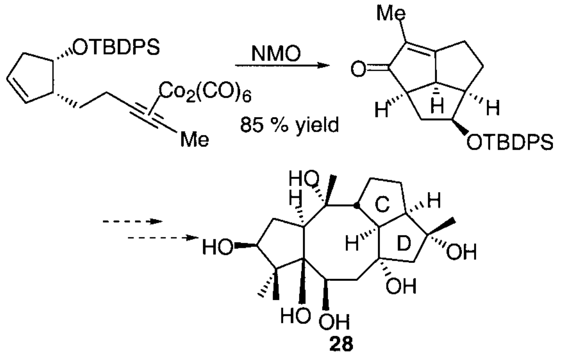
(58)

Paquette's approach to kalmanol (**28**) incorporates an NMO promoted P–K cycloaddition to form a tricyclic framework incorporating the appropriate stereochemistry for the C/D



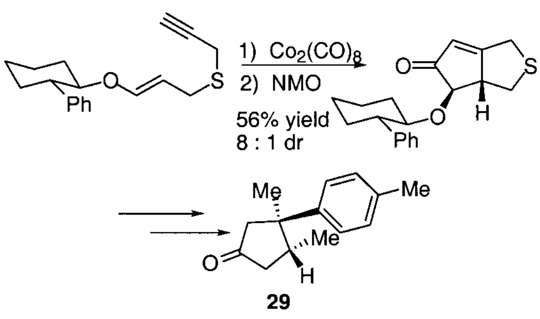
Scheme 11.

ring fusion (Eq. (59)).[100]



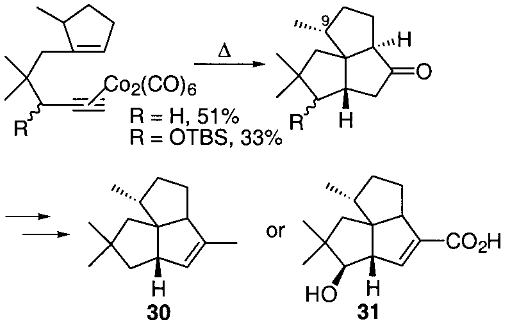
(59)

Synthesis of monocyclic cyclopentenones via the P–K reaction can suffer from lack of regioselectivity. In their approach to the monocyclic β-cuparenone (**29**), Moyano and Pericàs circumvent this drawback by use of a removable sulfur tether to transform the reaction to the more predictable intramolecular variant (Eq. (60)).[101] By utilization of a chiral auxiliary, they were able to effect the transformation asymmetrically in 56% yield. Removal of the chiral auxiliary and reductive cleavage of the sulfide afforded the desired monocycle.



(60)

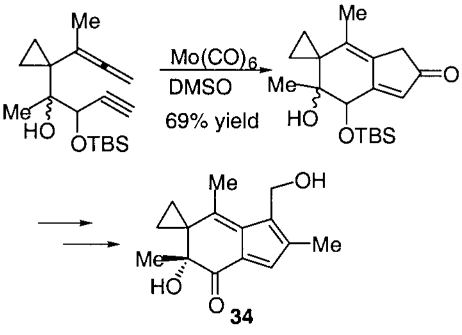
As an approach toward natural products containing an angular triquinane skeleton, the intramolecular P–K cycloaddition appears ideally suited. One such target framework is that of pentalenene (**30**) and pentalenic acid (**31**). Schore has established that the intramolecular cycloaddition forms the desired triquinane possessing the necessary *exo*-methyl stereochemistry at C9 as the major cycloadduct (Eq. (61)).[102] Moyano and Pericàs reported an asymmetric synthesis of 15-nor-pentalenene via an analogous approach incorporating a chiral directing group into the precyclization substrate.[46]



(61)

Cook has reported the use of a tandem intramolecular P–K reaction in an approach to the dicyclopentapentalene polyquinane ring system (Scheme 11).[103] By control of the relative regiochemistry of the bis-enyne, the parent ring system of either dicyclopenta[a,f]pentalene (**32**) or dicyclopenta[a,e]pentalene (**33**) can be created in one synthetic transformation. The bis-cycloaddition has been effected with either NMO or photochemical promotion in good to excellent yields.

We have recently demonstrated the utility of the allenic variant of the P–K reaction for the synthesis of 4-alkylidene cyclopentenone containing targets. Hydroxymethylacylfulvene (**34**), an analog of the illudane class of compounds, was synthesized via a molybdenum mediated cycloaddition process (Eq. (62)).[104] The cycloaddition occurs regiospecifically with the external π-system of the allene forming the desired 6,5 ring system in good yield (69%).



(62)

10. Conclusions

The P–K reaction allows for a rapid increase in molecular complexity from relatively simple starting materials.

Manuscripts adding to the scope of the P–K reaction and related [2+2+1] cycloadditions are being published at a rapid rate attesting to its interest in the chemical community. With the development of new catalytic and asymmetric methodologies, the P–K reaction will continue to occupy a prominent place within the pantheon of synthetic reactions. This review is meant to provide an up-to-date practical guide to the recent literature of the P–K cycloaddition.

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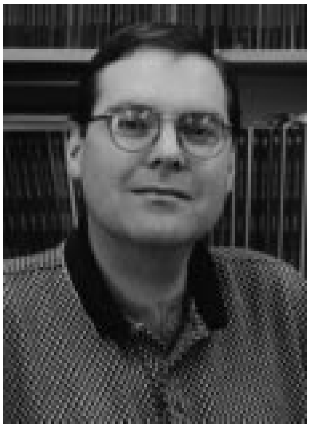

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