New Developments in the Pauson – Khand Reaction**

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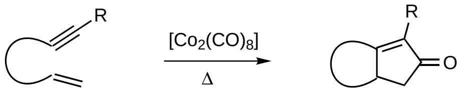
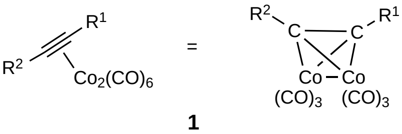
Metal mediated and catalyzed reactions have made significant contributions to organic synthesis over the past two decades.[1] One of the earliest and most useful of these is the Pauson – Khand carbon – carbon coupling reaction first reported in 1971.[2] In this reaction, a cyclopentenone is formed from an alkyne and an alkene in the presence of [$Co_2(CO)_8$] with insertion of carbon monoxide in a formal [2+2+1] cycloaddition. The exceptional potential of this reaction has been demonstrated in many (mostly intramolecular) syntheses (Scheme 1).[3]



Scheme 1. The general pattern of the Pauson – Khand reaction.

Although a catalytic approach was discussed in the initial publication,[2b] stoichiometric amounts of the metal were usually required to achieve acceptable yields. In most cases, the readily prepared and air-stable alkyne – $Co_2(CO)_6$ complexes (**1**) were heated (60 – 120 °C) with the alkene (occasionally under CO atmosphere), but long reaction times (often several days) were needed and the yields were frequently unsatisfactory.



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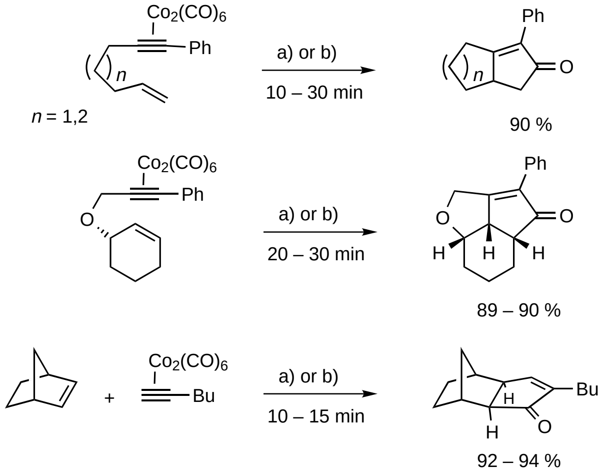
Improved Reaction Conditions

Once the high synthetic value of the Pauson – Khand reaction was recognized, considerable efforts were made by several groups in the early 1990s to optimize the reaction conditions. An important improvement came with the use of tertiary amine N-oxides that generate free coordination sites at cobalt by oxidative removal of CO ligands. These reactions proceed rapidly at room temperature, often in high yields.[4] A very promising procedure for the stoichiometric Pauson – Khand reaction was described recently by Sugihara et al,[5] who discovered that the use of primary amines as solvent leads to a dramatic increase in reaction rates. Excellent yields are obtained within few minutes with only 3.5 equivalents of cyclohexylamine when the reactions are run in dichloromethane at 83 °C under argon. Alternatively, the reactions can be performed in a 1:3 mixture of 1,4-dioxane and 2 M aqueous ammonia at 100 °C (Scheme 2).

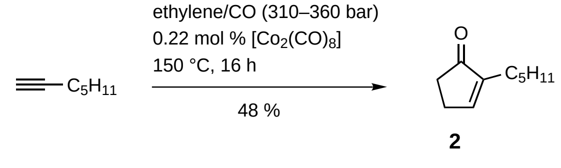


Scheme 2. Stoichiometric Pauson – Khand reactions according to Sugihara. a) 3.5 equiv of cyclohexylamine, 1,2-dichloroethane, 83 °C; b) 1,4-dioxane/2 N NH_3(aq) (1/3), 100 °C.

Catalytic Variants

Only catalytic Pauson – Khand reactions fulfil the criterion of atom economy,[6] and the use of stoichiometrical amounts of the transition metal is not acceptable commercially. It is not surprising, therefore, that several research groups have focused more recently on the development of catalytic variants.

Based on the work of Pauson and Billington,[2,7] Rautenstrauch et al. showed in their 1990 synthesis of the dihydrojasmonate precursor **2** (Scheme 3) that catalytic Pauson – Khand reactions are possible if high CO pressure and high temperature are used.[8] Korean laboratories have since found that more efficient transformations can be achieved with modified cobalt catalysts such as [$Co_2(CO)_8$/$P(OPh)_3$], [(indenyl)Co(cod)] or [$Co(acac)_2$/$NaBH_4$] under CO pressure or with [$Co_2(CO)_8$] in supercritical fluids.[9] A very practical procedure was published recently by Pagenkopf and Livinghouse, who obtained high yields with photo-activation of [$Co_2(CO)_8$] and low CO pressures (Scheme 4).[10]



Scheme 3. Catalytic Pauson – Khand reactions according to Rautenstrauch.

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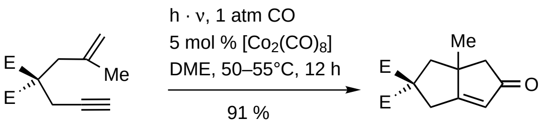
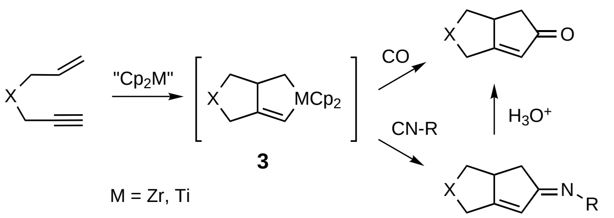


Scheme 4. Photochemically induced, catalytic Pauson–Khand reactions according to Livinghouse.

Although a whole series of carbonyl complexes of other transition metals (Fe, Mo, W, Ni) could only be used in stoichiometric Pauson–Khand reactions,[11] two Japanese laboratories have since independently reported efficient ruthenium-catalyzed (intramolecular) reactions. The desired cyclopentenones are formed in good to excellent yields in dimethylacetamide[12] or dioxane[13] in the presence of 2 mol% of $[Ru_3(CO)_{12}]$ at 140–160 °C and 10–15 atm CO pressure.

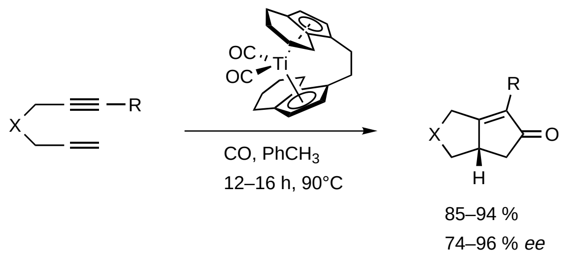
Pauson–Khand Type Reactions with Metallocenes

Negishi et al. have demonstrated that alkynes react with "zirconocene" generated in situ to give metallacyclopentene species of type **3**, which when treated with carbon monoxide afford typical Pauson–Khand products (Scheme 5).[14] Tamao et al. have also shown that enynes react with isocyanides to form iminocyclopentenones in the presence of stoichiometric amounts of $[Ni(cod)_2/n Bu_3P]$.[15] More recently, Buchwald and co-workers have developed a titanocene-based method in which the intermediate titanacyclopentenes are initially captured by isocyanides and the resulting imines are subsequently hydrolyzed to the cyclopentenones.[16] They have also succeeded in performing the reactions catalytically with trialkylsilylcyanides as isocyanide source and catalytic amounts of $[Cp_2Ti(PMe_3)_2]$ or, alternatively, a catalyst which is generated in situ from $[Cp_2TiCl_2]$ by addition of two equivalents of *n*BuLi or EtMgBr.[17] A Ni-based catalyst system ($[Ni(cod)_2]$/BDPEDA) has also proved to be efficient.[18]



Scheme 5. Metallocene-mediated Pauson–Khand type reactions.

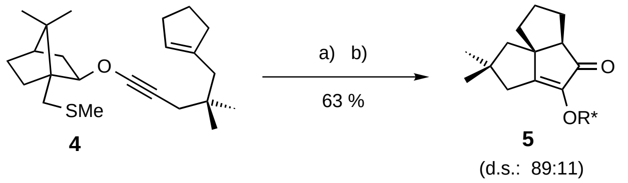
Recently Buchwald and co-workers devised an outstanding procedure for the direct, titanocene-catalyzed cyclocarbonylation of enynes.[19] This catalytic method has a number of advantages: it occurs at low CO pressure, tolerates a variety of functional groups including disubstituted alkenes, and gives the cyclopentenones in high yields (> 85 %). This industrially attractive process was later modified to proceed enantioselectively. With 5–20% of $[(S,S)\text{-(EBTHI)Ti(CO)}_2]$ as chiral catalyst[20] the desired cyclopentenones are obtained in high enantiomeric purity (Scheme 6).[21]



Scheme 6. Catalytic enantioselective bicyclizations according to Buchwald.

Asymmetric Pauson–Khand Reactions

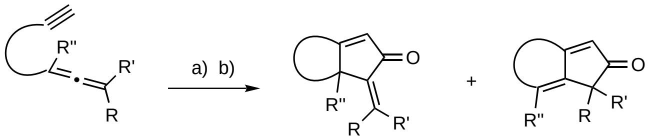
Considerable efforts have been made to develop asymmetrical variants of the classical Pauson–Khand reaction. Initial investigations have shown that compounds derived from cobalt complexes of type **1**, in which a carbonyl ligand is replaced by a chiral phosphane (glyphos), react with high enantioselectivity.[22] However, the procedure is too complex to be of preparative value. The concept of Kerr et al., who achieved significant enantioselectivities (max. 44 % *ee*) in intermolecular Pauson–Khand reactions by employing chiral amine-oxides as promoters, appears more elegant.[23] A different approach was used by Pericàs, Moyano, Riera, and Greene, who observed high levels of asymmetric induction in Pauson–Khand reactions when chirally modified substrates were used.[24] The potential of this method was demonstrated in total syntheses of hirsutene,[25] brefeldin A,[26] and *β*-cuparenone.[27] The same concept was applied successfully in a recently published synthesis of (+)-15-norpentalenene in which the key step is the conversion of enyne **4** into the tricyclic product **5** (Scheme 7).[28] As the preparation of chirally modified substrates always requires considerable effort, the attractiveness of the above-mentioned catalytic enantioselective method is obvious, and it would be interesting to test the Buchwald procedure with the achiral analogues of Pericàs' substrates.



Scheme 7. A diastereoselective Pauson–Khand reaction with a chirally modified substrate according to Pericàs. a) 1.1 equiv of $[Co_2(CO)_8]$; b) 9 equiv of *N*-methylmorpholin-*N*-oxide, 20 °C.

Pauson–Khand Reactions with Allenes

Several authors have demonstrated that a Pauson–Khand type formation of methylenecyclopentenones from enynes, allenes, and carbon monoxide occurs with stoichiometric amounts of $[Fe_2(CO)_9]$ or $[Mo(CO)_6]$, and catalytically with $[Cp_2Ti(CO)_2]$.[29,19] Cazes et al. recently reported that cobalt-mediated inter- and intramolecular conversions of allenes with enynes are also possible (Scheme 8).[30] In these reac-

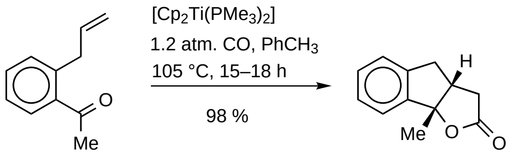


Scheme 8. Pauson–Khand reactions with allenes. a) $[Co_2(CO)_8]$; b) 6 equiv of *N*-methylmorpholin-*N*-oxide, THF/CH_2Cl_2, $-78 \rightarrow 20\,°C$, 3 h.

tions, however, the formation of β-methylenecyclopentenone is favored and di- or trisubstituted allenes must be employed in intramolecular reactions, because less substituted allenes tend to polymerize in the presence of $[Co_2(CO)_8]$.

"Hetero-Pauson–Khand Reactions": Synthesis of γ-Butyrolactones

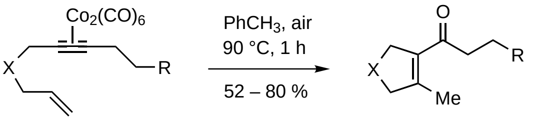
Buchwald and his group have also synthesized γ-butyrolactones successfully by a metallocene mediated cyclization of enones (and ynones) with carbon monoxide in a formal [2+2+1] addition, and have thus achieved the first hetero-Pauson–Khand reaction".[31] The reactions can be conducted in high yields with either stoichiometrical or catalytical amounts of $[Cp_2Ti(PMe_3)_2]$ as the example shown in Scheme 9.



Scheme 9. An example of a "hetero-Pauson–Khand reaction" according to Buchwald.

"Interrupted" Pauson–Khand Reactions

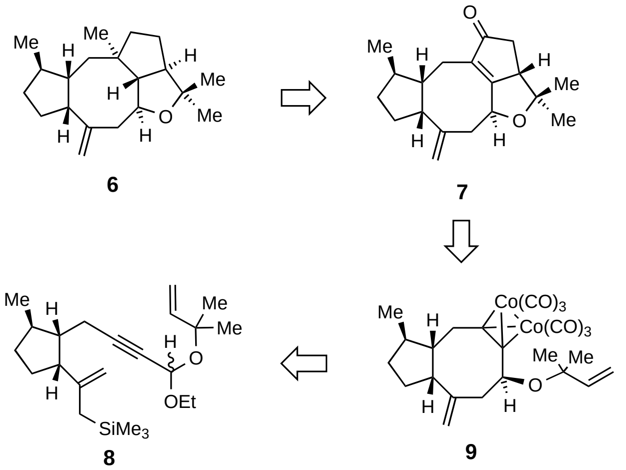
Krafft et al. have found that in the conversions of enyne-$Co_2(CO)_6$ complexes significant amounts of monocyclic by-products are obtained in addition to the desired cyclopentenones (via oxidation of the primary enyne cyclization product).[32] In fact, the conventional Pauson–Khand reaction can be almost totally suppressed if it is conducted in air. An example of an "interrupted Pauson–Khand reaction" is illustrated in Scheme 10.



Scheme 10. The "interrupted Pauson–Khand reaction" according to Krafft.

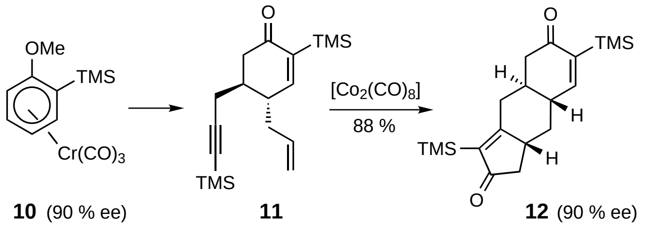
New Synthetic Applications of the Pauson–Khand Reaction

The high value of the Pauson–Khand reaction in the synthesis of natural products and other complex compounds was frequently demonstrated.[3] One of the most impressive examples is the recently published synthesis of the marine natural product (+)-epoxydictymene (**6**) by Schreiber and co-workers.[33] The synthetic strategy (Scheme 11) uses an intramolecular Nicholas reaction[34] (the Lewis acid mediated conversion of **8**) for the preparation of the actual Pauson–Khand substrate **9**, which is then converted into the epoxydictymene precursor **7**.



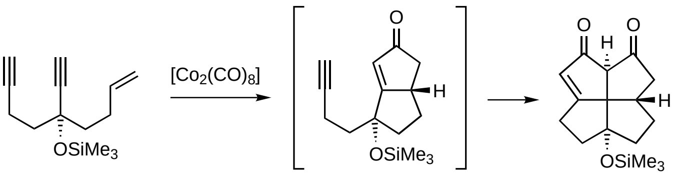
Scheme 11. Retrosynthetic strategy of the Schreiber synthesis of (+)-epoxydictymene.

A reaction sequence published recently by Kündig and co-workers also deserves notice:[35] In a one-pot reaction the planar chiral arene-$Cr(CO)_3$ complex **10** is first converted (with chirality transfer) into the enyne **11,** which then affords the tricyclic Pauson–Khand product **12** in high yield and completely diastereoselectively (Scheme 12).



Scheme 12. Combined arene-$Cr(CO)_3$ and Pauson–Khand chemistry according to Kündig.

Finally, sequential Pauson–Khand reactions (domino reactions) are possible.[36,37] A particularly fascinating application of this concept is the synthesis of a fenestrane by Keese and co-workers (Scheme 13).[36]



Scheme 13. Synthesis of a fenestrane by domino-Pauson–Khand reaction according to Keese.

Conclusions

The Pauson–Khand reaction (together with related metallocene-catalyzed transformations) has established a prominent place in the repertoire of synthetic organic chemists. Its use enables the construction of complex molecules in a convergent and atom economic way starting from structurally simple precursors. High levels of enantioselectivity can be achieved. It is therefore not surprising that an increasing number of research groups is focusing on the further development of this reaction. In the era of combinatorial chemistry the conversion of solid-supported substrates is just one possiblity.[38]

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