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A Decade of Advancements in Pauson–Khand-Type Reactions

Hang-Wai Lee[a] and Fuk-Yee Kwong*[a]

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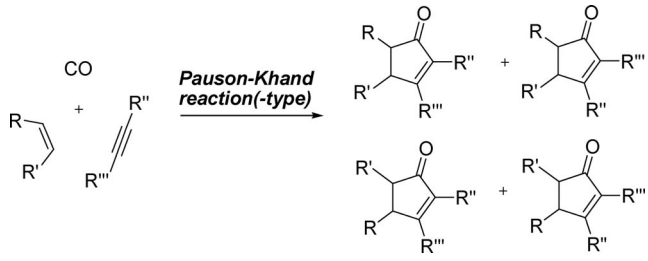
This Microreview illustrates the conceptual evolution of Pauson–Khand-type reactions and the recent advancements in catalyst design and applications. Intra- and intermolecular Pauson–Khand-type reactions, as well as their enantioselective versions, are reviewed. In addition to previous reviews, this article mainly covers literature references on the developments between the late 1990s and early 2009.

1. Introduction

Cycloaddition is one of the most attractive synthetic protocols for accessing a variety of scientifically interesting and pharmaceutically attractive ring-structured skeletons. Because these transformations are addition reactions, it is to be expected that the waste materials generated should be minimized, thus endowing them with favourable environmental characteristics. Indeed, their significance was highlighted by Trost, who commented that "*an ideal chemical reaction must be not only selective, but also a simple addition in which the other reactants are required only in catalytic amounts.*"[1] Transition-metal-mediated reactions and catalysis play a versatile role in addressing the atom economy issue. One of the earliest examples is the [2+2+1] carbonylative cyclization reaction, pioneered by Pauson and Khand in 1971.[2] This transition-metal-mediated reaction is a cycloaddition with three components – an alkyne, an alkene and a carbon monoxide moiety – for the generation of a variety of synthetically useful cyclopentenones (Scheme 1).[3]



Scheme 1.

In the initial study of the intermolecular-type reactions, only active alkenes of symmetrical natures, such as ethylene and norbornene, were used, because it was expected that regioisomers could be formed if unsymmetrical alkynes and alkenes were to be utilized and that this could present diffi-

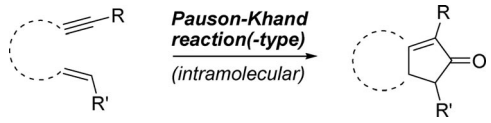
[a] Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis, and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University,
Kowloon, Hong Kong
E-mail: bcfyk@inet.polyu.edu.hk

Hang-Wai Lee completed his B.Sc. degree in Chemical Technology at The Hong Kong Polytechnic University in 2005. He immediately started his M.Phil. training under the supervision of Dr. Fuk-Yee Kwong. His research was focused on catalytic Pauson–Khand-type reactions with use of carbonyl compounds as CO surrogates for carbonylative cyclization. He is currently working as a research associate in Dr. Kwong's research group exploring rhodium-catalysed cross-coupling and related reactions.

Prof. Fuk-Yee (Michael) Kwong is currently an Assistant Professor in the Department of Applied Biology and Chemical Technology of The Hong Kong Polytechnic University. He received his B.Sc. degree in 1996 and completed his Ph.D at The Chinese University of Hong Kong in 2000 under the supervision of Prof. Kin Shing Chan. In 2001–2003 he went to Massachusetts Institute of Technology (MIT) as the Croucher Foundation postdoctoral fellow in Prof. Stephen L. Buchwald's research group. Kwong's research interests are in the area of cross-coupling methodologies and catalytic enantioselective reactions.

culties in separation and purification. However, research studies have shown that the regiochemistry with respect to the alkyne part is predictable and does not generally give mixtures of products.

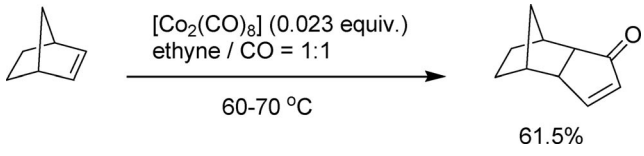
The intramolecular variant of this reaction could be expected not to suffer from the formation of mixtures of regioisomers and thus to give only one type of bicyclic cyclopentenones (Scheme 2). In this Microreview we briefly summarize the early developments in the catalytic Pauson–Khand reaction (PK reaction, PKR). More particularly, though, we focus on the evolution of the catalytic systems and their potential applications of this type of reaction from the late 1990s to early 2009: a decade of progress!



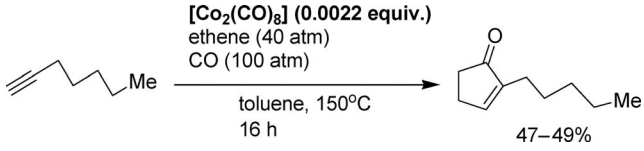
Scheme 2.

2. Cobalt-Mediated/Catalysed Pauson–Khand-Type Cyclization

The classical Pauson–Khand reaction involves the stoichiometric use of highly toxic and expensive transition metals, which are generally not economical and are usually environmentally unfriendly, so it is preferable to carry out the transformation in a catalytic manner. In 1973, Pauson and coworkers reported the first examples of catalytic cycloaddition of constrained reactive alkenes with octacarbonyldicobalt(0) complexes under a continuous supply of gaseous ethyne (Scheme 3).[2b] Following the work of Pauson and coworkers, Rautenstrauch and coworkers employed 0.0022 equiv. of $[Co_2(CO)_8]$ to catalyse cycloadditions of unconstrained alkenes (Scheme 4).[4] However, the reactions had to be conducted under very high partial pressures of carbon monoxide and ethene.

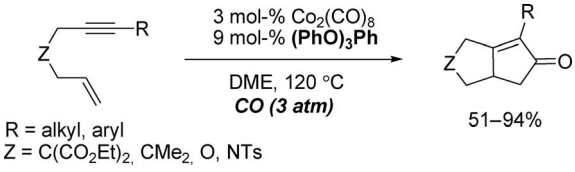


Scheme 3.

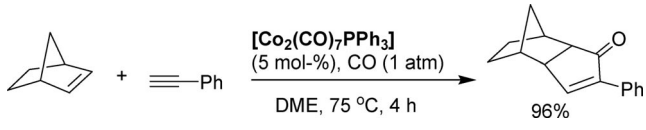


Scheme 4.

Although catalytic Pauson–Khand reactions had been successful in lowering the amounts of toxic transition metals used, drastic conditions such as high partial pressures of carbon monoxide still remained. In attempts to improve reaction efficiency, the introduction of various types of promoters – such as tertiary amine *N*-oxides, dimethyl sulfoxide, hard Lewis bases, sulfides, phosphanes and phosphites – into the systems has been investigated.[3n] In 1994, Jeong and coworkers reported successful catalytic carbonylative couplings of enynes (Scheme 5).[5] The key to the success of these transformations was the cobalt catalytic system, based on $Co_2(CO)_8$ and triphenyl phosphate. It is noteworthy that the reaction could be carried out at ambient CO pressure (i.e. ca. 1 atm). These achievements served as a platform for further development of the Co catalysts to achieve practical [2+2+1] cycloaddition reactions, as well as their enantioselective variants. Seminal work relating to the intermolecular version was reported by the same group.[6] An (indenyl)cobalt(I) complex was used for the cocyclization of alkynes, alkenes and carbon monoxide to give cyclopentenones. Interestingly, Jeong and coworker also demonstrated an efficient catalytic Pauson–Khand reaction in supercritical ethylene.[7] In this reaction, the supercritical ethylene served not only as a substrate, but also as a solvent. Under these reaction conditions, a low CO pressure (ca. 5 atm) was found to be sufficient for this reaction to take place. In addition to cobalt phosphite complexes, Gibson and coworkers demonstrated that $Co_2(CO)_7PPh_3$ was able to catalyse Pauson–Khand reactions (Scheme 6) and that its turnover numbers (TONs) were comparable with those of other mild systems. In addition to its attractive catalytic activity, it was shown that the complex was easily to handle and air-stable.[8]



Scheme 5.

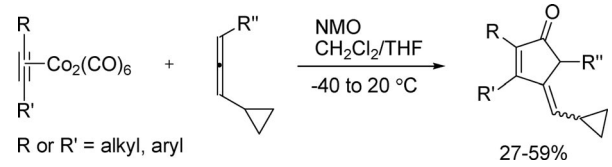


Scheme 6.

Recently, Arias and coworkers showed that $Co_2(CO)_6(PPh_3)_2$ was also effective for catalysing the Pauson–Khand reaction, with similar efficiency.[9]

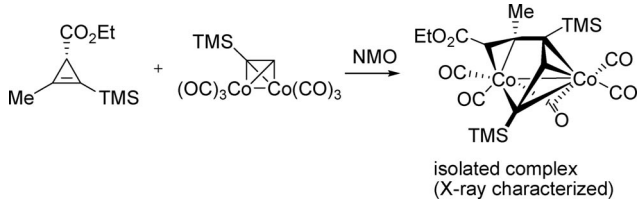
Intermolecular Pauson–Khand carbonylative cyclization showed applicability for reactions between acetylenes and cyclopropylallenes (Scheme 7).[10] These reactions proceeded without cyclopropyl ring opening and allowed the regioselective generation of 4-(cyclopropylmethylene)cyclopentenones.

In 2008, Fox and coworkers reported the first examples of isolated Co complexes derived from the putative alkene-insertion intermediates of Pauson–Khand reactions



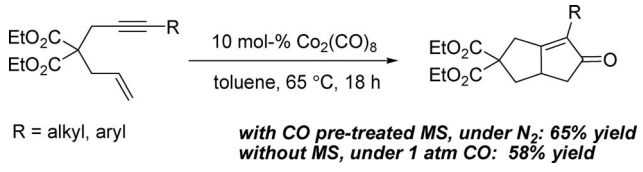
Scheme 7.

(Scheme 8).[11] The binuclear Co complexes were coordinated to five-carbon, μ-bonded "flyover" carbene ligands. It was proposed that the complexes were the result of cyclopropane fragmentation and subsequent alkene insertion. This study indicated that the high regioselectivity of the intermolecular cyclopropene Pauson–Khand reaction was not solely a consequence of selective alkene insertion. Indeed, these complexes indirectly suggested a Magnus–Schore-type mechanism for the Pauson–Khand reaction.



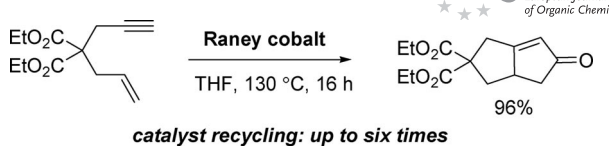
Scheme 8.

Gaseous carbon monoxide is routinely used for Pauson–Khand-type reactions. Recently, Pérez-Castells and coworkers reported an interesting approach eliminating the requirement to purge CO gas during the course of the reaction.[12] They demonstrated that molecular sieves could entrap CO gas, and so they prepared CO-pretreated molecular sieves. Under the reaction conditions, especially in *tert*-butyl alcohol, these sieves slowly released their CO. Particularly noteworthy was that the desired product yield exceeded that obtained under traditional reaction conditions (Scheme 9).



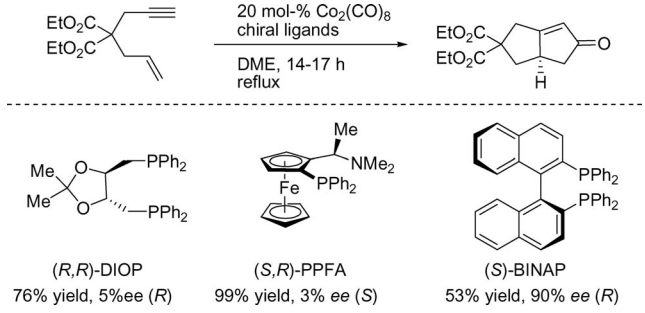
Scheme 9.

In 2007, Leitner and coworkers reported that commercially available Raney cobalt could be effective as a recyclable catalyst for carbonylative cyclization (Scheme 10).[13] The catalyst could be recycled and reused for six runs. Moreover, this catalytic system was found also to be applicable in the intermolecular Pauson–Khand reaction. The same research group has also recently established a catalytic system for Pauson–Khand transformations based on PEG-stabilised Co nanoparticles.[14]



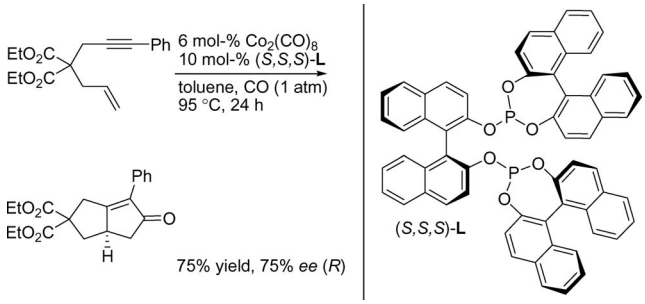
Scheme 10.

The asymmetric version of the Co-catalysed Pauson–Khand reaction was first achieved by Hiroi in 2000.[15,16] A range of commercially available ligands for this enantioselective transformation were examined (Scheme 11). The synthesis of optically active cyclopent-2-en-1-one derivatives was successfully accomplished with the aid of a catalytic amount of $Co_2(CO)_8$ and (*S*)-BINAP. Recently, Gibson and coworkers reported a detailed mechanistic study of the Co/BINAP system in the asymmetric Pauson–Khand reaction.[17,18] The proposed stereoinduction steps were also described. These findings served as a foundation for future design of chiral Co complexes.



Scheme 11.

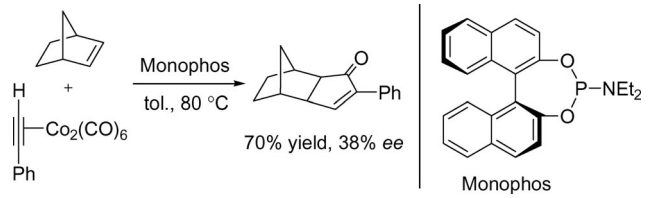
In 2002, Buchwald and Sturla described a chiral diphosphite ligand[19] based on a binaphthyl scaffold, which could be employed to induce asymmetry in the Pauson–Khand reaction (Scheme 12).[20] Good enantioselectivity was observed. In addition, they also showed that the enantioselectivity was dramatically decreased when a mismatched situation between the chiral backbone and terminal biaryl moieties applied in the supporting ligand.



Scheme 12.

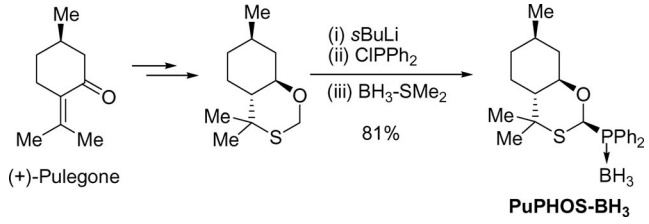
Unlike the catalytic intramolecular reaction, the enantioselective intermolecular Pauson–Khand-type reaction was mainly stoichiometric (non-catalytic amounts of Co complexes and chiral ligands were used). In addition to the previously described chiral bidentate diphosphite ligands, commercially available BINOL-derived monodentate

phosphoramidite ligands have proved to be efficient in intermolecular asymmetric Pauson–Khand reactions (Scheme 13).[21]



Scheme 13.

In fact, the reaction enhancements are not limited to bidentate diphosphane and diphosphite ligands. In 2000, Pericàs and Riera introduced a new class of chiral bidentate P,S-type ligand for asymmetric intermolecular Pauson–Khand reactions.[22] This new class of ligand (**PuPHOS**) was prepared directly from optically active (+)-pulegone (Scheme 14).

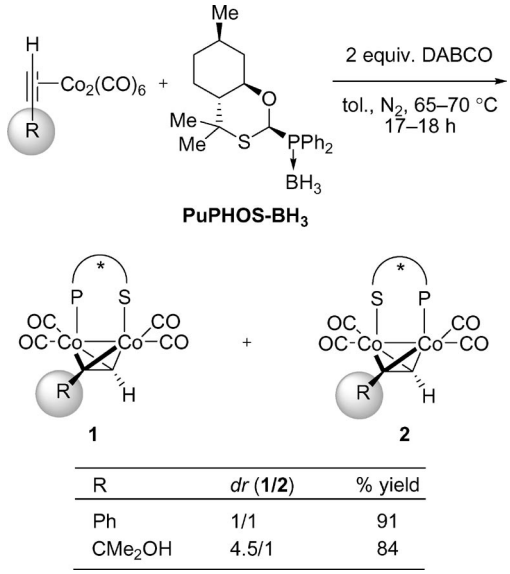


Scheme 14.

The complexation of the P,S-type ligand to alkyne-dicobalt hexacarbonyl precursors yielded diastereomeric mixtures of the Co complexes (Scheme 15). The diastereomeric outcomes depended on the substituent on the acetylene. The isolated complex **3** (Scheme 16) was exceedingly efficient in mediating the intermolecular asymmetric Pauson–Khand reaction, to give a 99% yield and 99% *ee*.

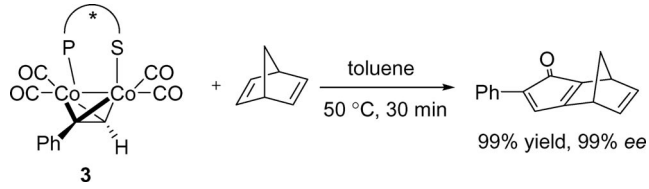
Riera and Verdaguer found interesting effects on ligand–substrate coordination in the Co complex, through the C–H···O hydrogen bond.[23] The unique methine moiety attached to three heteroatoms (O,P,S) in **PuPHOS** served as a strong H-bond donor (Scheme 17).

This nonclassical H-bond of the methine with an amidocarbonyl acceptor provided an essentially completely diastereoselective ligand-exchange process (Scheme 18). This complex was fully examined by X-ray analysis. Indeed the

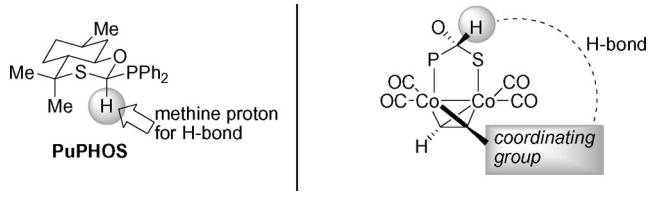


R	*dr* (**1**/**2**)	% yield
Ph	1/1	91
CMe_2OH	4.5/1	84

Scheme 15.

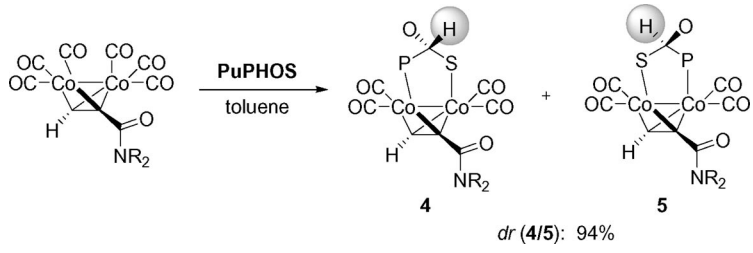


Scheme 16.

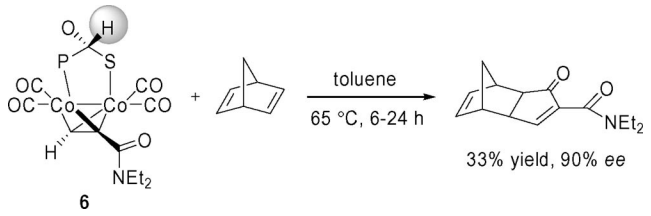


Scheme 17.

H-bond obtained selectively in the ligand-exchange process was exploited in the asymmetric intermolecular Pauson–Khand reaction to afford the cyclized product in up to 94% *ee* (Scheme 19).



Scheme 18.



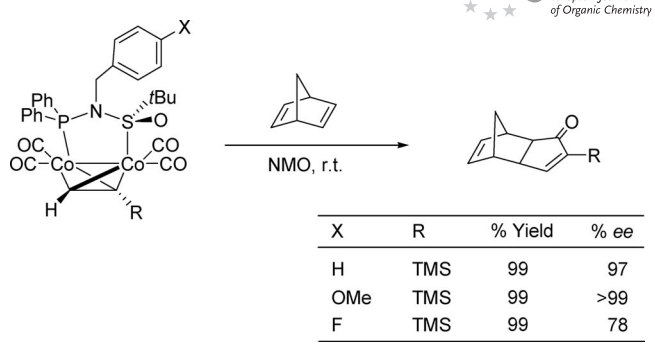
Scheme 19.

In 2007, the same research group reported another chiral system – the Co-**CamPHOS** complex (Scheme 20) – for use in the asymmetric Pauson–Khand reaction.[24] This methodology represented the first intermolecular asymmetric Co-catalysed Pauson–Khand reaction, although only moderate *ee* values (%) were obtained.

In addition to **PuPHOS** and **CamPHOS**, Riera and Verdaguer demonstrated a series of easily accessible chiral *N*-phosphanyl sulfinamide ligands for promoting the asymmetric Pauson–Khand reaction (Scheme 21).[25,26] Interestingly, an unprecedented electronic effect was observed: use of a P,S ligand with an electron-withdrawing substituent provided a lower % *ee* value in the desired product.

Following good obtained results, the same research group attempted to use diphenylacetylene as a benchmark symmetrical and internal alkyne in the enantioselective Pauson–Khand reaction (Scheme 22).[27] They demonstrated that the use of the *N*-oxides of **7** and **8** could effectively enhance both productivity and enantioselectivity. Moreover, the stereochemistry of the sulfinyl moiety in the ligand scaffold was found to be important in determining the absolute configurations of the cycloadducts: the *R*s ligand **7** provided levorotatory cyclopentenones whereas the *S*s ligand **8** afforded the dextrorotatory products. They proposed an explanation for the observed outcomes. In the presence of the *N*-oxide, the PNSO ligand chelates on the dicobalt complex, and because of the steric factors and the acidity, olefin insertions occurs on the cobalt centre where the sulfinyl group is bound (Scheme 23). With use of these bridge-type PNSO ligands, they reported the first asymmetric intermolecular Pauson–Khand reaction for internal symmetrical alkynes.

In view of the successful results achieved with the use of PNSO ligands in the asymmetric intermolecular Pauson–Khand reaction, Verdaguer and coworkers explored the feasibility of PCSO ligands in carbonylative cycloaddition. Various kinds of *p*-tolyl and *tert*-butyl PCSO ligands were synthesized and subjected to the Pauson–Khand reaction



X	R	% Yield	% *ee*
H	TMS	99	97
OMe	TMS	99	>99
F	TMS	99	78

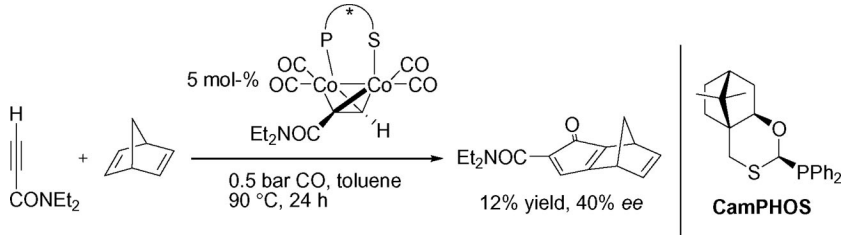
Scheme 21.

conditions (Scheme 24).[28] *p*-Tolyl PCSO ligands were found to be more selective than their PNSO analogues, whereas the *tert*-butyl PCSO ligands were difficult to prepare and less selective toward the intermolecular Pauson–Khand reaction than their PNSO analogues.

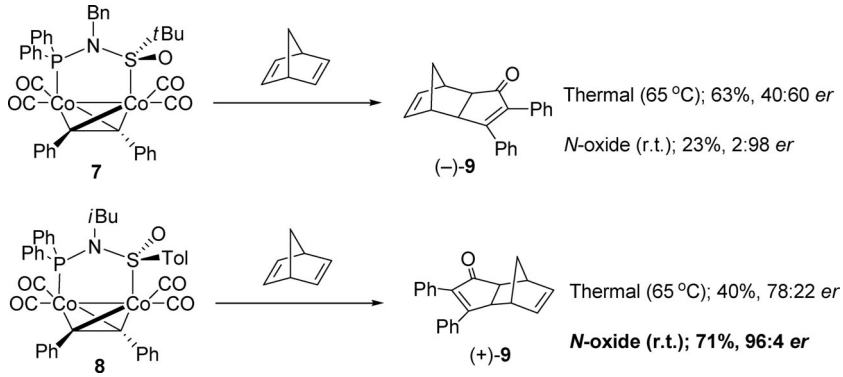
In this section we also cover the use of mixed catalysts (associated with cobalt complexes) for Pauson–Khand-type reactions. Recently, Chung and coworkers demonstrated that Co/Ru nanoparticles on charcoal were effective for the Pauson–Khand reaction.[29] They reported that neither Co nor Ru nanoparticles by themselves provided substrate conversion; possibly a synergistic effect of the Co/Ru nanoparticles was necessary for this transformation. Isolated yields of up to 98% were obtained with a range of enyne substrates (Scheme 25). Also notably, pyridylmethyl formate was used as the CO source for this carbonylative reaction.

In 2008, Chung's group showed that cobalt/rhodium heterobimetallic nanoparticles could be useful for achieving carbonylative [2+2+1] cycloadditions of allenes (Scheme 26).[30,31] Good yields of cycloadducts were obtained under these reaction conditions. In addition to alkynes as substrates, the applicability of allenes in this protocol potentially enriches the chemistry of Pauson–Khand-type and related transformations. As a nitrogen analogue of an allene, a carbodiimide could also function as an ene moiety in the PKR. Mukai reported a $Co_2(CO)_8$-catalysed hetero-Pauson–Khand reaction of an alkyne-carbodiimide in the presence of tetramethylthiourea (TMTU) as supporting ligand.[32]

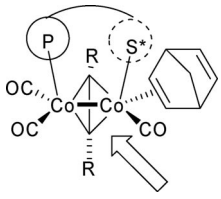
Colloidal cobalt nanoparticles were an efficient catalyst for the PKR even in aqueous media, as reported by Chung et al.,[33] who demonstrated that the nanoparticles could be reused several times without apparent loss of activity. Krafft and coworkers also achieved stoichiometric Co-me-



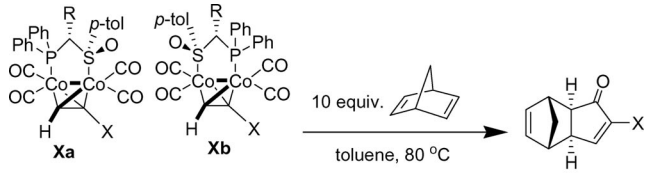
Scheme 20.



Scheme 22.

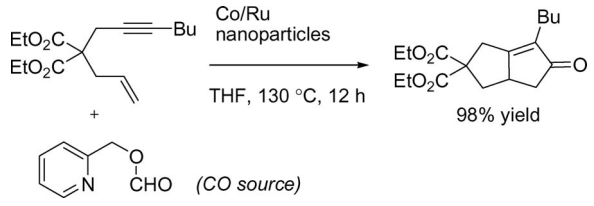


Scheme 23.

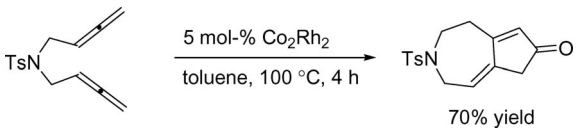


Entry	Complex	R	X	*t* (h)	Yield (%)	*ee* (%)
1	**10b**	Ph	Ph	1	90	97
2	**11b**	Bn	TMS	0.5	94	96
3	**12a**	Bn	Ph	0.5	98	87

Scheme 24.



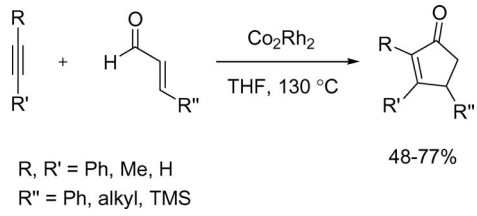
Scheme 25.



Scheme 26.

diated PK reactions in water, in the presence of surfactants.[34] They reported that the cationic surfactant cetyltrimethylammonium bromide was the most effective additive.

The most atom-economical PK reaction is that of an α,β-unsaturated aldehyde, which can be used both as CO source and as alkene moiety. Chung reported that Co/Rh heterobimetallic nanoparticles, derived from $Co_2Rh_2(CO)_{12}$, catalysed the reactions between α,β-unsaturated aldehydes and alkynes to generate cyclopentenones (Scheme 27).[35] Chung ascertained that the reactions are carbonylative couplings of an alkyne and alkene, and not hydroacylations together with cyclizations.



Scheme 27.

In order to provide a better picture of cobalt complexes for the Pauson–Khand reaction, we have summarized recently reported cobalt catalysts in Table 1. This table is intended to provide a brief overview of the catalyst activity, as well as applicability for intra- or intermolecular Pauson–Khand and related reactions (Table 1).

3. Rhodium-Catalysed Pauson–Khand-Type Cyclizations

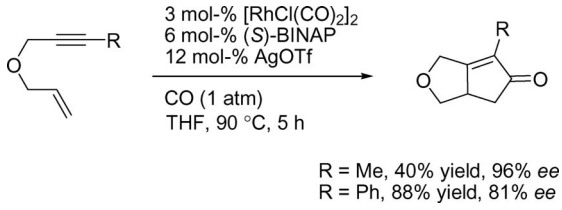
The first successful Rh-catalysed asymmetric intramolecular Pauson–Khand-type reaction was reported by Jeong et al. in 2000.[44] They disclosed that a catalytic system comprising $[RhCl(CO)_2]_2$ and (*S*)-BINAP was an effective catalyst for these enantioselective transformations (Scheme 28).

A variety of *C*-, *O*- and *N*-tethered 1,6-enynes gave good to excellent product and optical yields. The authors proposed a cationic pathway in the PKR mechanism. It was suggested that the 1,6-enyne might bind to the $[Rh(CO)(S)\text{-BINAP}]^+$ complex and be transformed into an octahedral Rh^{III} metallocyclopentene intermediate. Subsequent migratory insertion of CO and final reductive elimination would furnish the desired carbonylative cycloadduct. On the basis of literature reports describing the successful use

Table 1. A summary of cobalt catalysts' activities.

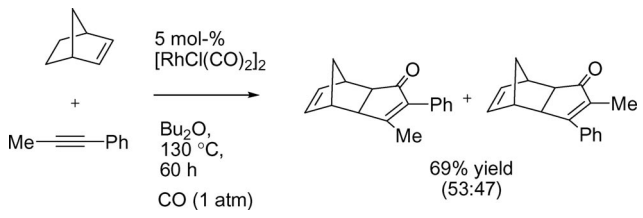
Entry	Inter-PKR	Intra-PKR	Catalyst system	*p*(CO) [atm]	TON[a]	Ref.
1	+	+	$[Co_2(CO)_8]$ + R_3PS	1	15 (4–16)	[36]
2	+	+	$[Co_2(CO)_7 PPh_3]$	1.05	6–10 (5–9)	[37]
3	+	–	$[Co_2(CO)_6\{P(Ph)_3\}_2]$	27.2	3–47	[9]
4	+	+	$[Co_2(CO)_8]$ + (*S*)-BINAP	1	(1–2)	[15,16]
5	–	+	$[Co_2(CO)_8]$ + $P(OPh)_3$	3	(2–15)	[5]
6	–	+	$[Co_2(CO)_8]$ + bisphosphite ligand	1	(1–8)	[20]
7	–	+	$[Co_2(CO)_8]$ + *hv*	1	(7–10)	[38]
8	–	+	$[Co_2(CO)_8]$ + $CyNH_2$	1	(4–10)	[39]
9	–	+	$[Co_2(CO)_8]$ + DME	7	(36–50)	[40]
10	+	+	$[Co_3(CO)_9(\mu^3\text{-CH})]$	7	14–16 (3–16)	[41]
11	+	–	$[Co_4(CO)_{12}]$	10	38–50	[42]
12	–	+	stabilized Co nanoparticle[b]	20	n.a.	[33]
13	+	+	PEG-stabilized Co nanoparticle[c]	23–35	14–29 (24–29)	[14]
14	+	+	Raney cobalt[d]	23–35	3–5 (15–16)	[13]
15	+	+	Co_2Rh_2[e]	1	n.a.	[30,31]
16	+	+	$Ru_3(CO)_{12}$/CNC	0	n.a.	[29]
17	+	–	$[Co_4(CO)_{11}P(OPh)_3]$[f]	5	2–7	[7]
18	+	+	$[Co(acac)_2]$ + $NaBH_4$	30–40	6–100 (5–18)	[43]
19	+	+	Indenyl cobalt(I)	15	10–97 (32–47)	[6]
20	+	–	$[Co_2(CO)_8]$ + PuPHOS/CamPHOS	1–3	1–10	[22–26]
21	–	+	$[Co_2(CO)_8]$ + CTAB[g]	0	n.a.	[34]
22	+	+	$[Co_2(CO)_8]$[h]	0	1–3 (2–3)	[12]

[a] TONs calculated with respect to the number of mol of Co_1; TONs in parentheses are turnover numbers of intramolecular PKRs. [b] PKR catalysed by stabilized cobalt nanoparticles in aqueous medium, recycled up to six runs. [c] With 2-pyridylmethyl formate as CO source. [d] Recycled up to three runs. [e] Recycled up to six runs. [f] Reaction run in supercritical ethene. [g] Cobalt-mediated PKR with addition of cetyltrimethylammonium bromide (CTAB). [h] Cobalt catalyst was mixed with paste containing molecular sieves (4 Å) and *tert*-butyl alcohol treated with CO.



Scheme 28.

of the $[RhCl(CO)_2]_2$ complex for catalysing intramolecular cycloadditions, Narasaka et al. further applied this rhodium complex to intermolecular Pauson–Khand-type cyclization.[45] They demonstrated that in the reaction between norbornene and 1-phenylpropyne, the cyclic enones were obtained as a mixture of regioisomers in 69% yield (Scheme 29). Additionally, they disclosed that the reaction could be accelerated by reducing the CO partial pressure to less than 1 atm.



Scheme 29.

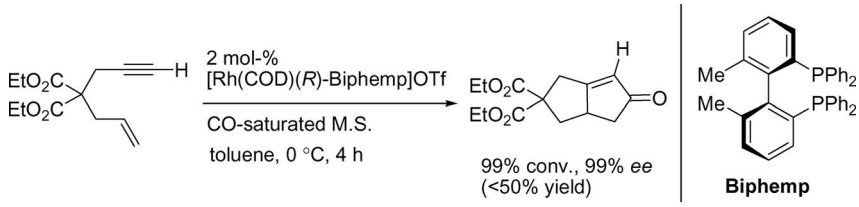
Chung and coworkers recently established a recyclable Pauson–Khand-type protocol assisting by entrapped Rh complexes, prepared by a sol/gel process.[46] In particular, the metal complexes could be recovered and reused at least 10 times without loss of catalytic activity. However, the stereoinduction offered by these catalytic systems was poor: only a 13% *ee* was obtained in an intramolecular Pauson–Khand-type cyclization of an aromatic 1,6-enyne. In 2003, the same research group demonstrated a relatively more environmentally friendly Rh-catalysed PKR in a water/dioxane mixture. A surfactant (SDS) was necessary for a successful transformation.[47]

Recently, Consiglio et al. reported an interesting system for Pauson–Khand-type chemistry.[48] They reported that CO-saturated molecular sieves could be used as a CO reservoir for carbonylative cyclization. Notably, their protocol represented the lowest temperature so far achieved for a Pauson–Khand-type reaction (Scheme 30). At 0 °C, the desired product was obtained in 99% conversion with 99% *ee*.

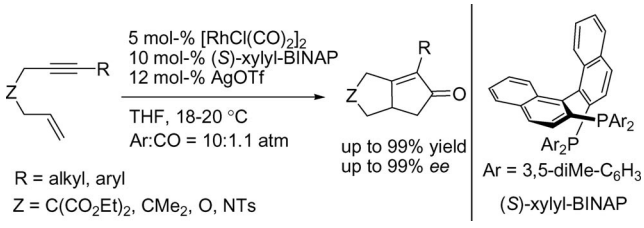
In 2008, Ratovelomanan-Vidal, Genêt and Jeong reported an efficient asymmetric Pauson–Khand-type reaction system mediated by Rh^I catalyst at ambient temperature (18–20 °C in general).[49] They employed (*S*)-xylyl-BINAP and $[RhCl(CO)_2]_2$ as the catalytic system with 0.1 atm CO partial pressure to yield bicyclic cyclopentenones with excellent yields and enantioselectivities (Scheme 31).

In addition to enyne substrates, the authors also reported the asymmetric desymmetrization of dienynes through enantioselective Pauson–Khand-type reactions at around room temperature (Scheme 32).

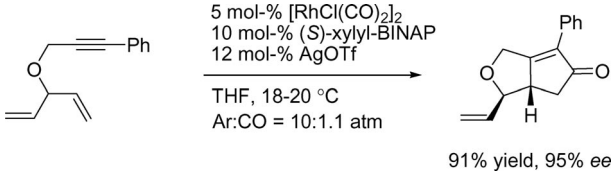
To demonstrate the applicability of the Pauson–Khand reaction in the synthesis of natural compounds, the same research group reported an efficient asymmetric desymmetrization of the prochiral acetal **13** (Scheme 33). They re-



Scheme 30.

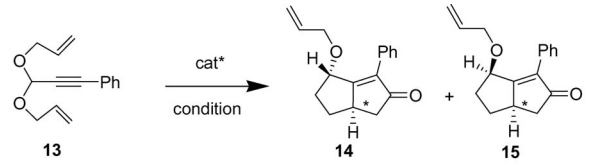


Scheme 31.



Scheme 32.

ported that the desymmetrization of the acetal was sensitive to the reaction conditions. Decomposition of the acetal was observed under their previously reported thermal reaction conditions. Interestingly, cinnamaldehyde can be used as a surrogate to generate the CO component[57,62,63] for the carbonylative cycloaddition to afford products with satisfactory yields and moderate % *ee* values.[50]



Entry	Condition	**14** Yield/*ee* (%)	**15** Yield/*ee* (%)
1	**a**	– (decomposition of **13**)	
2	**b**	41/86	25/70

a: $[Rh(CO)_2Cl]_2$ (3 mol-%), (*R*)-BINAP (9 mol-%), AgOTf (12 mol-%) in THF at 90 °C under CO (1 atm)
b: $[Rh(CO)_2Cl]_2$ (5 mol-%), (*R*)-BINAP (12 mol-%) in cinnamaldehyde (20 equiv.) at 120 °C under Ar (1 atm)

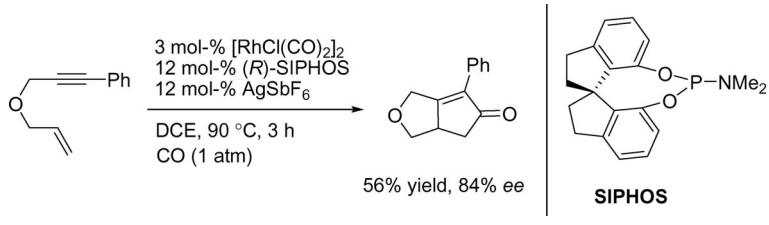
Scheme 33.

As an alternative to chiral bidentate phosphane ligands, Zhou and coworkers recently demonstrated the new monodentate phosphoramidite **SIPHOS** ligands (Scheme 34), which were effective in the asymmetric carbonylative cyclization.[51] This finding represented the first example of a successful chiral monodentate ligand in an asymmetric Rh-catalysed PKR, indicating that monodentate ligands have high potential for further utilization in related enantioselective reactions.

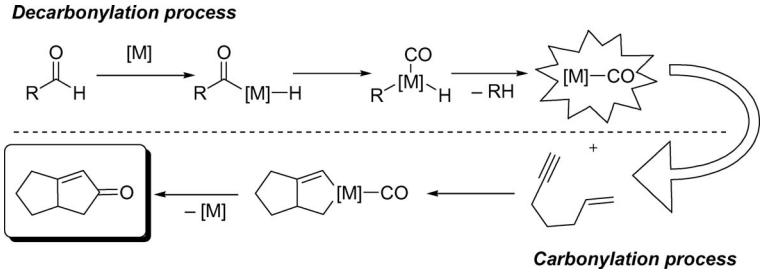
Transition-metal-catalysed carbonylation has been successful in the area of organic synthesis, and is recognized as a powerful protocol for the direct synthesis of a wide variety of carbonyl-containing compounds.[52] However, the use of the highly poisonous carbon monoxide constitutes a drawback to these methodologies. Recently, Morimoto and Kakiuchi[53] and Shibata[54] independently reported a conceptual evolution on the use of metal carbonyl systems to allow PKRs in the absence of gaseous carbon monoxide.[55,56] This approach involved an aldehyde decarbonylation process and a subsequent CO transfer reaction (Scheme 35).

The Morimoto–Kakiuchi group reported that pentafluorobenzaldehyde was an efficient CO surrogate for Pauson–Khand-type cyclization, whereas the Shibata group found that cinnamaldehyde was the best CO donor (Scheme 36). Moreover, Shibata et al. later developed a protocol that used chiral BINAP ligands for the asymmetric Pauson–Khand-type reaction to give *ee*s of up to 92%.[57]

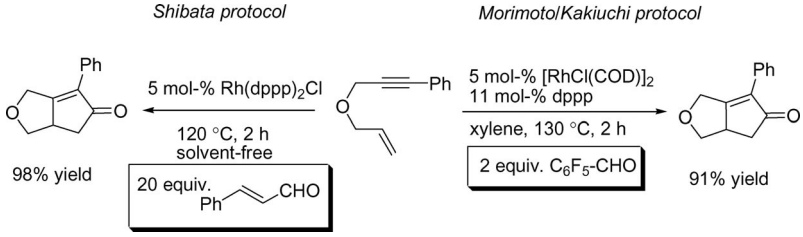
The Morimoto/Kakiuchi group further reported that, in addition to aromatic aldehydes, formaldehyde (in water) was also an effective CO reservoir for the PKR.[58] They used a mixed-phosphane catalytic system (i.e., a water-soluble and an organic-solvent-soluble ligand) for this catalysis. The authors proposed micelle formation during the course



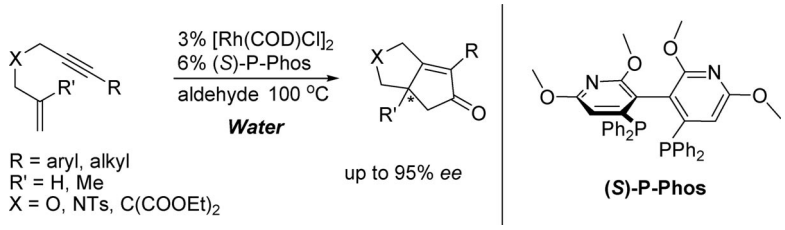
Scheme 34.



Scheme 35.



Scheme 36.



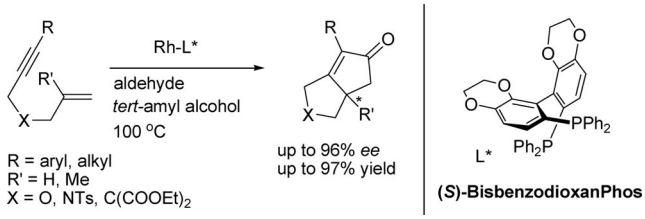
Scheme 37.

of the reaction.[59] In 2004, the same research group disclosed an enantioselective version of this reaction employing BINAP-class ligands, giving good to excellent enantioselectivities in the products.[60]

Recently, tremendous attention has been given to aqueous transition-metal-catalysed reactions.[61] However, no catalytic asymmetric systems permitting the use of water as the only solvent (without a surfactant) in the PKR had been developed prior to 2005, when we presented a Rh-catalysed asymmetric PKR in water based on the use of the chiral dipyridyl diphosphane ligand P-Phos (Scheme 37).[62] A variety of 1,6-enynes were transformed into the corresponding cyclopentenones with *ee*s of up to 95%.

In addition to the aqueous system, we also developed a homogeneous asymmetric PKR using an environmentally benign alcoholic solvent. In the presence of (*S*)-Bisbenzodioxan Phos [named (*S*)-SYNPHOS by Genet et al.] and Rh precatalyst, the bicyclic cyclopentenones were obtained with *ee* values of up to 96% (Scheme 38).[63]

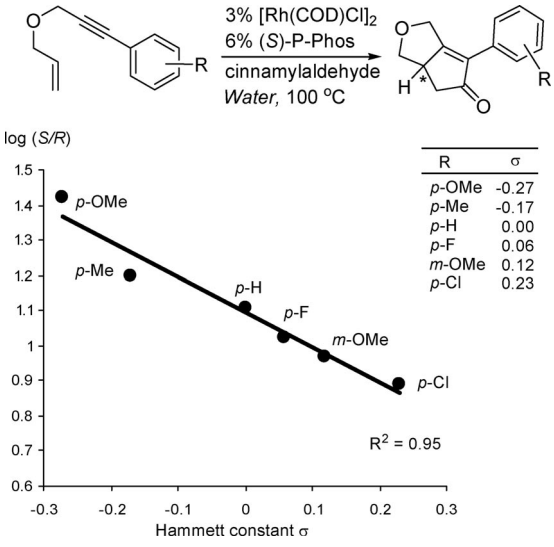
Electronic effects in asymmetric catalysis are an important parameter for control of the stereooutcome in the desired products.[64] In fact, electronic factors relating both to substrate and to catalyst (ligand) can significantly alter the



Scheme 38.

enantioselectivity. We recently reported substrate electronic effects capable of affecting the levels of enantioselectivity of the desired products (i.e., bicyclic cyclopentenones) in 1,6-aromatic enynes (Scheme 37).[62] Higher enantioselectivities were obtained when an electron-rich substituent was attached to the aromatic ring. A Hammett study showed that a linear free energy relationship was obeyed (Scheme 39).[65]

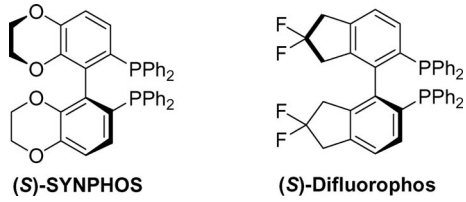
Moreover, we also proposed a structure for the metal complex leading to the desired cycloadducts. It was suggested that the electron-rich enynes bound the Rh metal centre more closely and thus gave better stereoinduction, whereas electron-poor enynes were loosely coordinated (Scheme 40).[66]



Scheme 39.

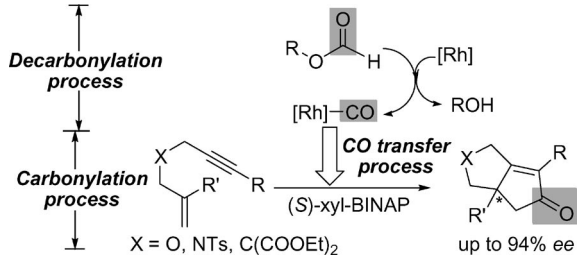
As well as substrate electronic effects, Ratovelomanan-Vidal, Genêt and Jeong also reported a ligand electronic effect in the Rh-catalysed PKR.[67] They demonstrated that both the rate and the enantioselectivity were significantly dependent on the electronic densities in the axially chiral BINAP class ligands. With ligands bearing relatively electron-deficient phosphorus donors [i.e., with *p*-electron-withdrawing substituent(s) on the phosphorus-attached aromatic rings], the reaction rates were slower, but the PKR products were obtained with higher enantioselectivity.

The same research groups recently carried out a detailed study on the effect of the catalyst (ligand) dihedral angle on the enantioselectivity in the PKR cycloadducts.[68] They found that the steric properties of the biaryl backbone of the ligand, especially the value of its dihedral angle, played a crucial role in the stereochemical outcome of the Rh-mediated PKR. Chiral ligands such as **SYNPHOS** (named as BisbenzodioxanPhos by Chan et al.) and **Difluorophos**, with narrower dihedral angles than BINAP-type ligands, gave improved reactivity and enantioselectivity for most enyne substrates (Scheme 41). On the basis of the influences of electronic properties of ligands and substrates on the enantioselectivities of cycloadducts, they developed an efficient kinetic resolution system for racemic 1-arylallyl propargyl ethers.[69]



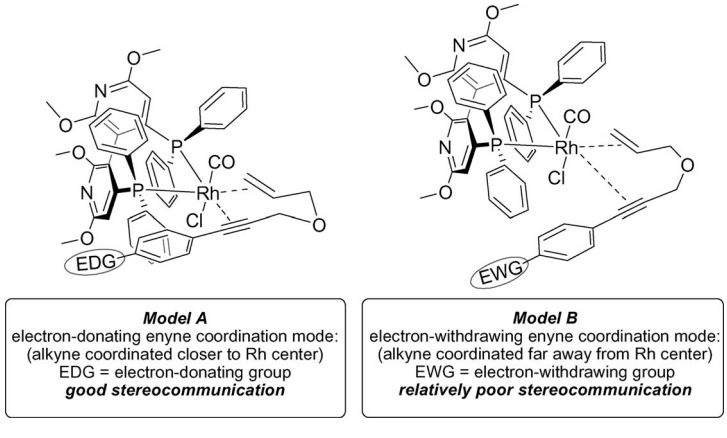
Scheme 41.

In addition to the use of aldehydes as CO surrogates, our group recently reported that benzyl formate could serve as a CO source for cooperative dual catalysis.[70] The cascade decarbonylation of formate by the Rh complex and carbonylation of the enyne offered the carbonylative cycloadduct effectively (Scheme 42).

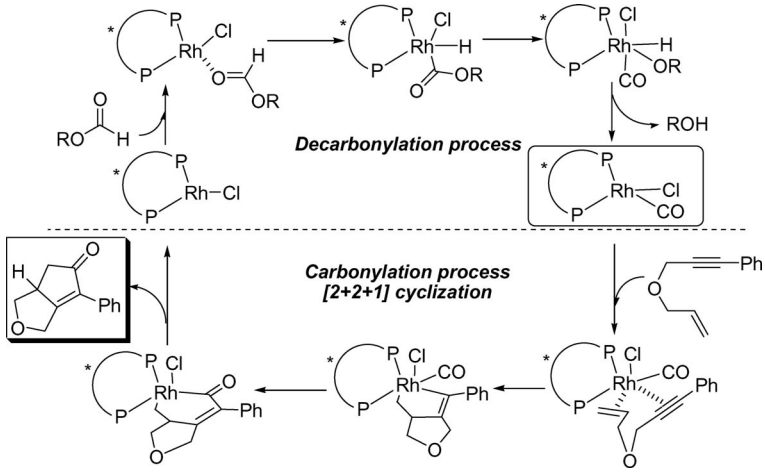


Scheme 42.

We proposed the cooperative catalytic cycle shown in Scheme 43. The formate coordinates to the Rh centre and subsequent C–H oxidative addition gives the Rh^{III} complex. The decarbonylation of the Rh-acyl complex yields the Rh carbonyl species. The Rh–CO complex enters into the enyne carbonylation process to generate the cyclopentenone by

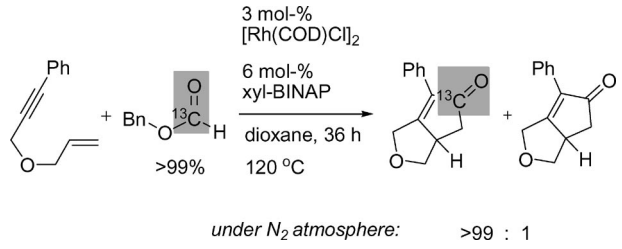


Scheme 40.



Scheme 43.

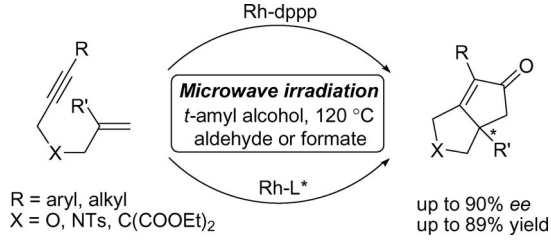
the usual PKR mechanism. In addition to the suggested mechanism, we also performed experiments with labelled substrates to indicate the source of the CO moiety (Scheme 44).



Scheme 44.

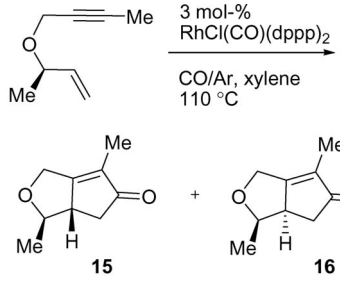
Microwave heating has penetrated many different areas of chemical research in the last decade.[71] Since the pioneering reports on microwave-accelerated organic transformation by the groups of Gedye and of Giguere and Majetich in 1986,[72] the application of microwave dielectric heating to microwave-assisted organic synthesis (MAOS) has attracted considerable attention.[73] In 2008, we reported dual catalysis by microwave assistance and by a Rh-diphosphane complex.[74,75] This cooperative process provided [2+2+1] cycloadducts through sequential decarbonylation of aldehyde or formate and carbonylation of enynes within short times. Various *O*-, *N*- and *C*-tethered enynes were transformed into the corresponding products in good yields. In fact, this catalysis represented the first enantioselective version of a microwave-accelerated cascade cyclization. In the presence of chiral Rh-(*S*)-BisbenzodioxanPhos complex, up to 90% *ee*s were achieved in the bicyclic cyclopentenones (Scheme 45).

Recently, Evans and Baik reported a mechanistic study on the diastereoselective Rh-catalysed PKR and the role of coordination number for governing the stereocontrol.[76] They figured out a theoretical analysis of the Rh-catalysed PKR that could provide two mechanistic scenarios for the



Scheme 45.

origin of diastereoselectivity, in which the optimum selectivity could be attributed to a five- rather than a four-coordinate organorhodium complex (Scheme 46). These findings offer a foundation for determining relevant controlling factors to improve the stereochemical outcome of the PK reaction.



CO pressure	Ar pressure	% yield	*dr* (**15**/**16**)
1.00	0.00	88	>99:1
0.10	0.90	51	58:1
0.05	0.95	44	57:1

Scheme 46.

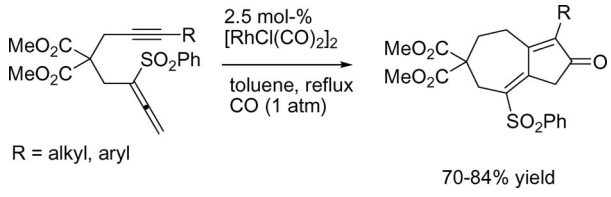
The Pauson–Khand-type cyclization with an allene moiety in the presence of an Rh complex was successfully achieved in 2002.[77,78] Through the use of the appropriate

Table 2. A brief summary of rhodium catalysts and activities.

Entry	Inter-PKR	Intra-PKR	Catalyst system	*p*(CO) [atm]	TON[a]	Ref.
1	–	+	$[Rh(dppp)_2Cl]$[b]	0	(11–20)	[54]
2	–	+	$[Rh(dppp)_2Cl]$[c]	0	(7–10)	[53]
3	–	+	$[Rh(COD)Cl]_2$ + (*S*)-PPhos[c]	0	(8–15)	[62]
4	–	+	$[Rh(COD)Cl]_2$ + (*S*)-BisbenzodioxanPhos[c]	0	(10–16)	[63]
5	–	+	$[Rh(COD)Cl]_2$ + (*S*)-Xyl-BINAP[d]	0	(1–7)	[70]
6	–	+	$[Rh(COD)Cl]_2$ + dppp[e]	0	(3–15)	[74]
7	–	+	$[Rh(COD)Cl]_2$ + dppp[f]	0	(3–7)	[75]
8	–	+	[Rh(COD)Biphemp]X[g] {X = BF_4^-, PF_6^-, OTf^-}	0	(16–25)	[48]
9	–	+	$[Rh(COD)Cl]_2$ + dppp + TPPTS + SDS[h]	0	(6–9)	[58]
10	–	+	$[Rh(COD)Cl]_2$[i]	5	(7–9)	[46]
11	+	+	$[Rh(CO)_2Cl]_2$	1	4–6 (7–28)	[45]
12	–	+	$[Rh(CO)_2Cl]_2$ + (*R*)-SIPHOS	1	(5–12)	[51]
13	–	+	$[Rh(CO)(dppp)Cl]_2$[j]	1	(7–15)	[76]
14	–	+	$[Rh(CO)_2Cl]_2$ + (*S*)-BINAP	1	(6–16)	[44]
15	–	+	$[Rh(CO)_2Cl]_2$[k]	1	(3–10)	[49]

[a] TONs calculated with respect to the number of mol of Rh_1; TONs in parentheses are turnover numbers of intramolecular PKRs. [b] With pentafluorobenzaldehyde as CO source. [c] With cinnamaldehyde as CO source under conventional heating conditions. [d] With benzyl formate as CO source under conventional heating conditions. [e] With cinnamaldehyde as CO source under microwave irradiation conditions. [f] With *p*-chlorobenzyl formate as CO source under microwave irradiation conditions. [g] With CO entrapped in molecular sieves (4 Å). [h] With formaldehyde as CO source in aqueous medium. [i] Rh catalyst entrapped with silica sol gel. [j] Under Ar/CO, demonstrating the effects of CO pressure on product yields. [k] Under Ar/CO (10:1, 1 atm).

allenyne substrate, the construction of seven-membered ring systems was also possible (Scheme 47). Mukai recently reported an Rh-catalysed reaction of allenenes.[79] Intramolecular coupling of an allene-alkene, tethered by three or four atoms, afforded a bicyclic cyclopentenone with either a 6–5- or a 7–5-fused ring system, respectively, along with the isomerization of the carbon–carbon double bond.

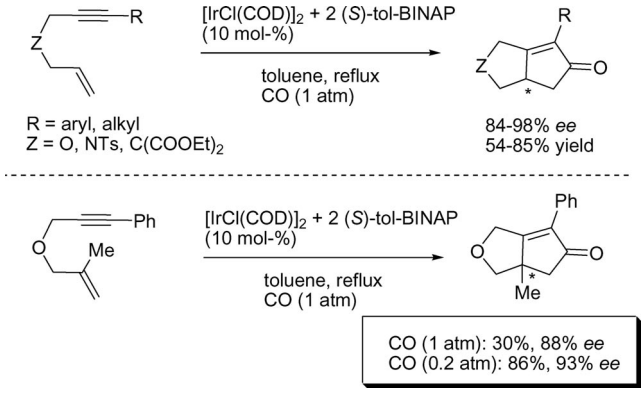


Scheme 47.

To offer a better picture for comparison between rhodium catalysts, we have summarized the turnover activity of each catalyst in Table 2.

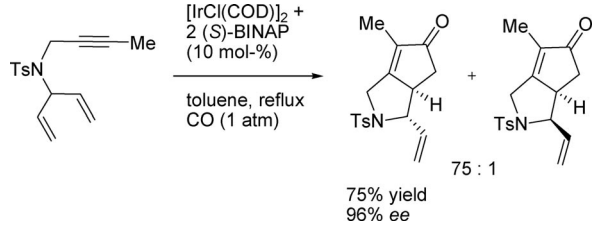
4. Iridium-Catalysed Pauson–Khand-Type Cyclizations

In 2000, Shibata and coworkers reported the first Ir-catalysed asymmetric Pauson–Khand-type reaction,[80] employing $[Ir(COD)Cl]_2$ and (*S*)-tol-BINAP as the catalytic system (Scheme 48). Excellent *ee* values were obtained in the cycloadducts. Notably, higher yields and enantioselectivities were achieved when the CO pressure was less than 1 atm.



Scheme 48.

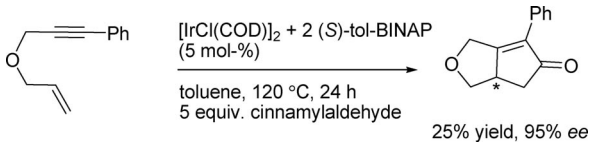
The chiral iridium catalyst was also applied in the desymmetrization of *meso*-dienynes.[81] A highly enantio- and diastereoselective Pauson–Khand-type reaction proceeded to afford vinyl-substituted bicyclic cyclopentenones containing two chiral centres (Scheme 49).



Scheme 49.

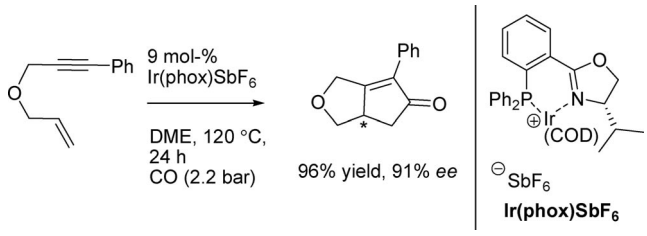
Shibata further demonstrated that the iridium complex was efficient for decarbonylation of aldehyde and that the corresponding metal carbonyl could be used for the PK re-

action (Scheme 50).[82] They reported that the enantioselectivity was higher than that afforded by the rhodium complex. Our group also independently reported a similar protocol to access a series of optically active bicyclic cyclopentenones in the presence of (*S*)-BINAP-iridium complex.[83]



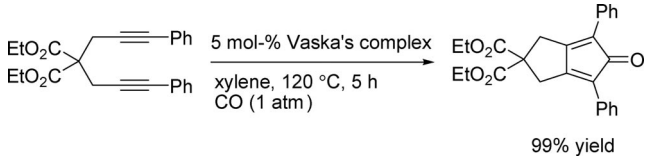
Scheme 50.

Recently, Pfaltz reported a chiral cationic Ir(phox) complex that was effective in asymmetric Pauson–Khand-type reactions (Scheme 51).[84] Under optimized reaction conditions, high yields and enantioselectivities of >90% *ee* were obtained. The influence of the anion was also studied: it was found that the hexafluoroantimonate anion was the most suitable counter anion for the complex to effect this catalysis.



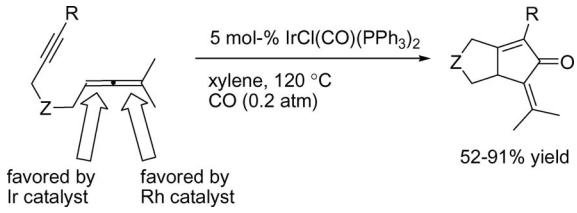
Scheme 51.

As well as carbonylative alkene-alkyne coupling, Shibata et al. achieved effective alkyne-alkyne coupling with carbon monoxide (Scheme 52),[85] using Vaska's $IrCl(CO)(PPh_3)_2$ complex for this intramolecular [2+2+1] cycloaddition. In addition to trapping of CO moiety, they also reported that isocyanides could be inserted to these intermediates.



Scheme 52.

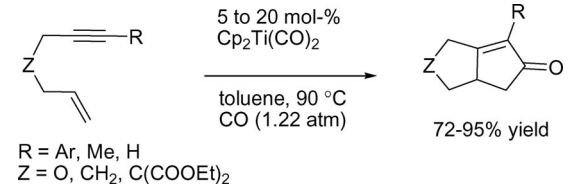
Interestingly, Ir- and Rh-catalysed Pauson–Khand-type reactions showed different regioselectivities in allenyne cyclization. When an allenyne with two substituents on the allene terminus was used under a low partial pressure of carbon monoxide, the internal π-bond of the allene moiety was the major reaction site and the bicyclic cyclopentenone with an alkylidene substituent was obtained (Scheme 53).[86] In contrast, when $[RhCl(CO)(PPh_3)_2]$ was used {instead of $[IrCl(CO)(PPh_3)_2]$} as the catalyst under the same reaction conditions, the reaction through the external π-bond of the allene moiety was the major pathway. The Shibata group also demonstrated the enantioselective version of this protocol by use of a chiral BINAP supporting ligand.[87]



Scheme 53.

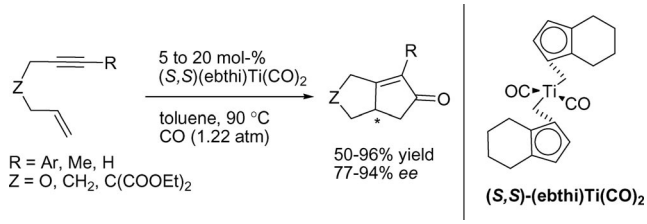
5. Titanium-Catalysed Pauson–Khand-Type Cyclizations

In 1996, Buchwald and coworkers reported a Ti-catalysed intramolecular coupling of various enynes under carbon monoxide, leading to the formation of bicyclic cyclopentenones in good to excellent yields (Scheme 54).[88,89] In another approach to the preparation of the bicyclic cyclopentenones from enynes, Negishi also demonstrated a related Zr-mediated transformation.[90]



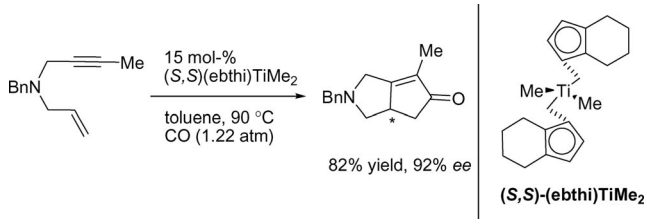
Scheme 54.

Diastereoselective Pauson–Khand reactions based on enynes with chiral auxiliaries on the alkyne or alkene terminus or tethers have been reported, as well as enantioselective reactions in the presence of stoichiometric amounts of chiral cobalt complexes (as stated in the previous sections). However, a genuine catalytic and enantioselective PK reaction had to wait until Buchwald's report in late 1996.[91,92] An effective enantioselective reaction under CO with the aid of a transition metal catalyst with a chiral ligand was in fact rather difficult in that instance, because the chiral ligand can be easily dissociated from the metal centre by excess CO and so part of the reaction might take place in an achiral environment. Notably, Buchwald tackled this difficulty by employing a chiral Ti complex in which the metal centre and chiral scaffold were connected by a σ-bond (Scheme 55). A variety of enynes were transformed into chiral cyclopentenones. However, this PK reaction must be conducted in a glovebox because the low-valent Ti complex with a Ti–C σ-bond is highly sensitive to air and moisture.

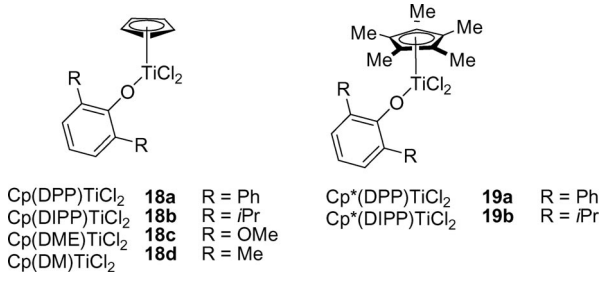


Scheme 55.

In addition to *C*- and *O*-tethered enynes, Buchwald also reported the use of a modified Ti catalyst in the Pauson–Khand-type cyclization of *N*-tethered enynes (Scheme 56).[93] Good enantioselectivity was obtained in nitrogen-containing cyclopentenones. Although various kinds of 1,6- and 1,7-enynes could be converted into their corresponding products, the application of dicyclopentadienyltitanium dicarbonyl complex in cases of sterically hindered alkynes or olefins was unsuccessful. Buchwald and coworkers therefore introduced new monocyclopentadienyltitanium aryloxide complexes into the Pauson–Khand reaction (Scheme 57).[94]



Scheme 56.

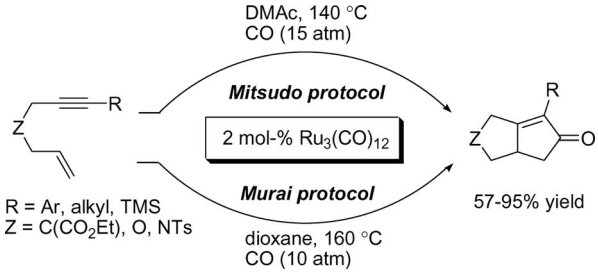


Scheme 57.

They found that the pentamethylmonocyclopentadienyl complex **19a** failed to react with enynes to form metallocycles, but that the monocyclopentadienyl complex **18a** was feasible (Scheme 57). A series of complexes **18a**–**d** were then investigated in terms of their conversion into metallocycles. Interestingly, their catalytic activities were specific toward different enynes. Complex **18a** was found to mediate cyclocarbonylation of trimethylsilyl-substituted enynes effectively, complex **18b** assisted the cyclocarbonylation of trisubstituted olefins, complex **18c** efficiently mediated the cyclocarbonylation of phenyl-substituted enynes, and complex **18d** was employed to mediate diene cycloisomerization.

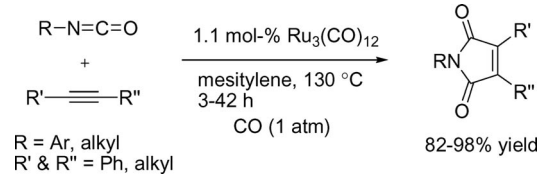
6. Ruthenium-Catalysed Pauson–Khand-Type Cyclizations

In 1997, Mitsudo[95] and Murai[96] independently reported that Ru complexes were effective in promoting Pauson–Khand-type cyclizations. Under high pressures of carbon monoxide and at high temperatures, the intramolecular PK reaction was found to be feasible (Scheme 58). Interestingly, the related Cp*RuCl(COD), which was an effective catalyst for [2+2] cycloaddition of norbornenes with alkynes,[97] was totally ineffective in the carbonylative [2+2+1] reaction.



Scheme 58.

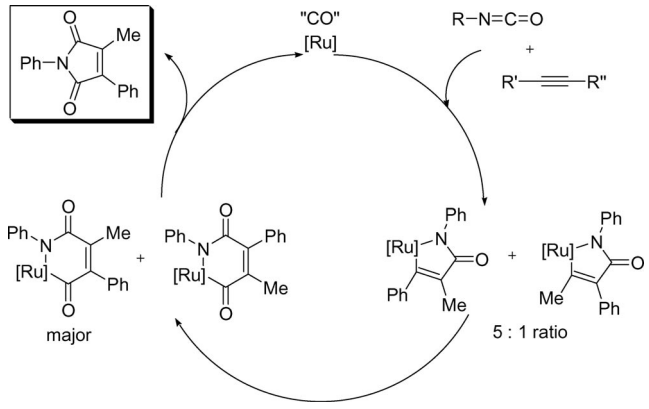
In 2006, Kondo demonstrated the first Ru-catalysed [2+2+1] co-cyclizations of isocyanates, alkynes and CO.[98] This process allows a rapid and atom-economical protocol to generate a series of unsymmetrically polysubstituted maleimides in one-step fashion (Scheme 59).



Scheme 59.

Kondo and coworkers also postulated a mechanism for this newly developed co-cyclization (Scheme 60). From the results of a ^{13}C-labelling experiment, they suggested the formation of azaruthenacyclopentenones as mixtures of regioisomers. The formation of the α-phenyl-substituted intermediate was verified to be more favourable than that of the α-methyl-substituted intermediate, as judged by ^{13}C NNE spectroscopy. The insertion of CO into a Ru–C(sp^2) bond rather than a Ru–N bond predominantly occurred to give azaruthenacyclohexenediones, followed by reductive elimination to give maleimides and regeneration of the Ru catalyst.

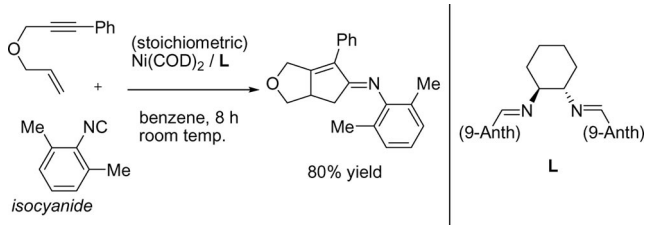
Mastrorilli and Braunstein recently also showed that tri- and tetranuclear Ru clusters of formula $NEt_4[RuCo_3(CO)_{12}]$ were effective as precatalysts for Pauson–Khand-type reactions.[99]



Scheme 60.

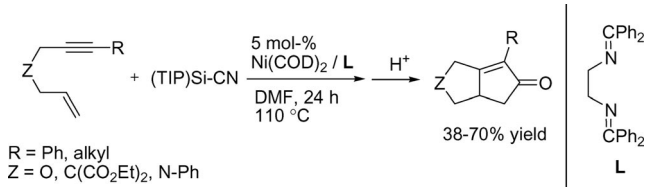
7. Nickel- and Palladium-Catalysed Pauson–Khand-Type Cyclizations

Nickel-catalysed Pauson–Khand-type [2+2+1] cyclization of enynes was achieved by Buchwald and coworker in 1996.[100] They showed that a stoichiometric amount of Ni complex was required to cyclize an enyne and an isocyanide to produce an iminocyclopentene (Scheme 61). Tuning of the supporting ligand from a phosphane to a nitrogen-donor ligand revealed that the *rac*-diimine **L** was superior in this reaction.



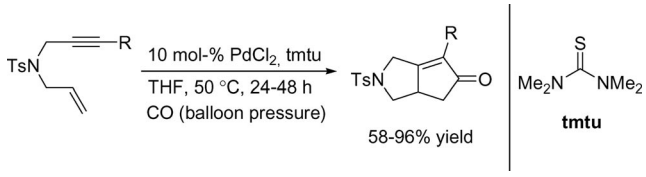
Scheme 61.

Buchwald demonstrated that the above reaction failed in its catalytic form, because of the formation of a nickel-isocyanide complex, preventing further coordination and hence enyne cyclization. With use of other isocyanide sources, such as trialkylsilyl cyanides, effective transformation of enynes into bicyclic cyclopentenones (after acid hydrolysis) was accomplished (Scheme 62). It was hypothesized that trialkysilyl cyanides generate sufficient yet relatively low equilibrium concentrations of the trialkylsilyl isocyanide isomer ($K \approx 0.01$).[101]



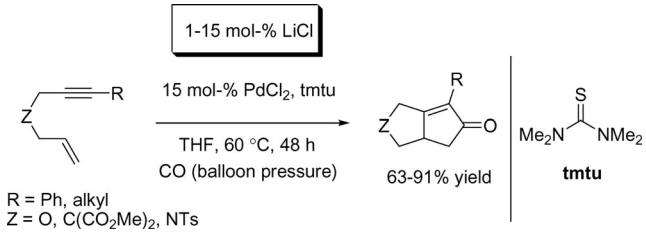
Scheme 62.

The carbonylative cyclization of diynes was reported in 2003.[102] In 2005, the first successful Pd-catalysed Pauson–Khand-type cyclization was reported.[103] Chen and Yang and coworkers showed that the thiourea ligand was necessary and important for this PKR achievement (Scheme 63). They pointed out that *C*- and *O*-tethered 1,6-enynes were ineffective under these reaction conditions. In contrast, *N*-tethered enynes were efficiently transformed into the corresponding bicyclic products in good yields (up to 96%).



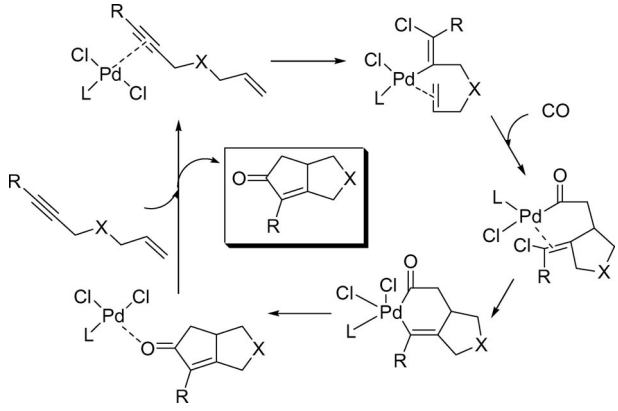
Scheme 63.

The same research group later reported that the addition of LiCl to the reaction mixture could enhance the PKR product yield significantly (Scheme 64).[104] This catalytic system was found to be more general than the previously developed Pd system.



Scheme 64.

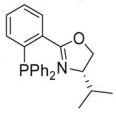
In 2009, Wiest, Yang and Wu and coworkers proposed a mechanism for the Pd-catalysed Pauson–Khand-type reaction, based both on DFT calculations and on experimental studies.[105] It is suggested that the first step involves the *cis*-halometallation of the alkyne moiety and is then followed by sequential alkene and carbonyl insertions. The rate-determining step is an intramolecular C–Cl oxidative addition, generating the Pd^{IV} species (Scheme 65). The final step is, as usual, reductive elimination to give the desired product.



Scheme 65.

Table 3 summarizes other transition metal catalysts and their activities.

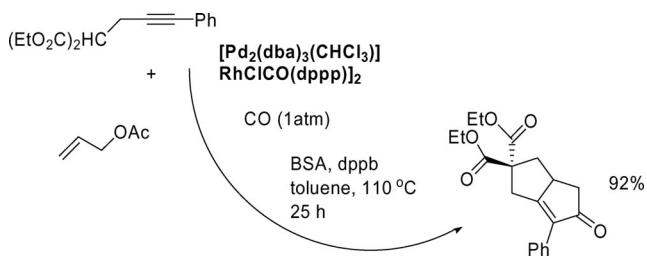
Table 3. A brief summary of other transition metal catalysts and activities.

Entry	Inter-PKR	Intra-PKR	Catalyst system	*p*(CO) [atm]	TON[a]	Ref.
1	–	+	$[Cp_2Ti(CO)_2]$	1.22	(9–19)	[88,89]
2	–	+	$[Ru_3(CO)_{12}]$	10–15	(16–7)	[96]
3	–	+	$[RuCo_3(CO)_{12}]X$ X = NEt_4, bmim, H	8	(32–46)	[99]
4	–	+	$Ni(COD)_2$ + L[b] L = 	0	(8–17)	[101]
5	–	+	$PdCl_2$-tmtu tmtu = 	1	(2–4)	[102]
6	–	+	$PdCl_2$-tmtu + LiCl	1	(3–30)	[104]
7	–	+	$[Ir(COD)Cl]_2$ + phox phox = 	2.2	(9–11)	[84]
8	–	+	$[Ir(COD)Cl]_2$ + (*S*)-tol-BIANP[c]	1	(2–9)	[80]
9	–	+	$[Ir(COD)Cl]_2$ + (*S*)-tol-BIANP[d]	0	(2–5)	[82]
10	–	+	$[Ir(COD)Cl]_2$ + (*S*)-BINAP[e]	0	(2–7)	[83]

[a] TONs calculated with respect to the number of mol of metals; TONs in parentheses are turnover numbers of the intramolecular PKR. [b] Insertion of 2,6-dimethylphenyl isocyanide followed by hydrolysis to obtain the desired cyclopentenones. [c] Under Ar/CO (8:2, 1 atm). [d] With cinnamaldehyde as CO source. [e] With nonylaldehyde as CO source.

8. Tandem Reactions and Selected Applications of Carbonylative Cyclization in Complex Organic Synthesis

Pauson–Khand-type reactions have been successful as effective methods for the construction of cyclopentenone frameworks in the synthesis of many pharmaceutically useful and scientifically interesting molecules.[106,107] Tandem reactions based on the principle of atom economy have become one of the hot topics of recent years. In 2000, Jeong and coworkers reported a mixed catalytic system consisting of $[Pd_2(dba)_3(CHCl_3)]$ and $[RhCl(CO)(dppp)]_2$ for conversion of malonates and allyl acetate into desired cyclopentenones (Scheme 66).[108]

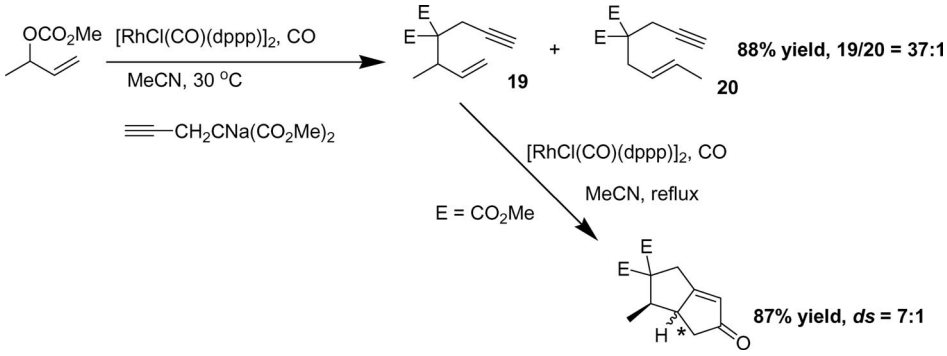


Scheme 66.

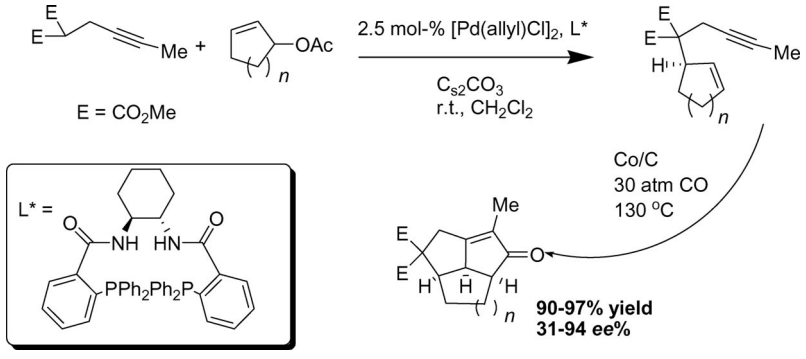
Evans and coworkers employed $[RhCl(CO)dppp]_2$ as catalyst for the reactions of allylic carbonate and the sodium salt of an α-branched malonate under carbon monoxide to furnish the desired cyclopentenone with good yields and selectivities (Scheme 67).[109] Chung's research group attempted to utilize a combined chiral Pd^{II} and Co/C catalytic system for asymmetric allylic alkylation and cascade carbonylative cyclization (Scheme 68).[110] Surprisingly, tricyclic compounds can be also obtained in good yields and with moderate *ee*s. Afterwards the same research group reported a Pauson–Khand reaction between acrolein and alkynes in the presence of Co_2Rh_2 as catalyst to afford the desired substituted cyclopentenones (Scheme 69).[111]

Earlier applications reported by Schreiber based on a Co-mediated protocol for synthesizing (+)-epoxydictymene were noteworthy.[112,113] Evans and coworkers recently described a Pauson–Khand product that was an important intermediate for further hydrogenation to generate an allylic alcohol (Scheme 70).[114,115] They used the Co-mediated PKR and subsequently reduced the cycloadduct with $NaBH_4$. Moreover, isomerization of the C=C double bond was effected with the aid of Crabtree's catalyst.

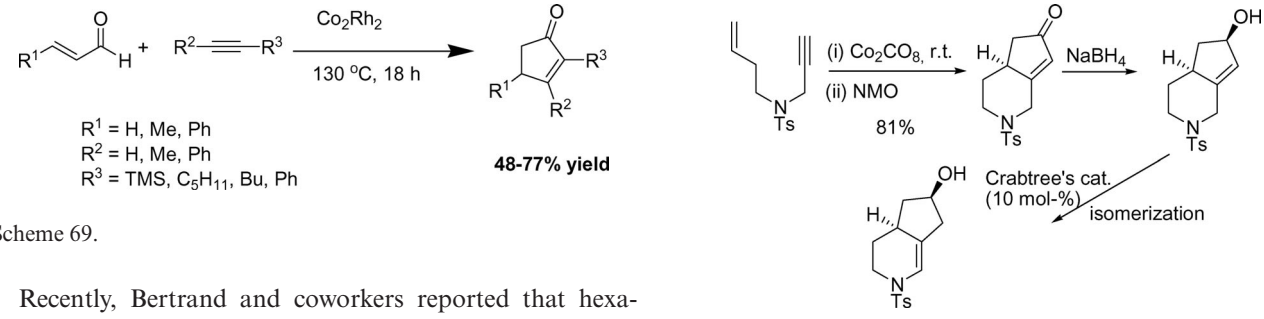
A Pauson–Khand method was used as a protocol for an estrone E-ring extension synthesis (Scheme 71).[116] A series of alkynes could be used under these reaction conditions. This system required microwave irradiation to promote the desired PK reaction.



Scheme 67.



Scheme 68.

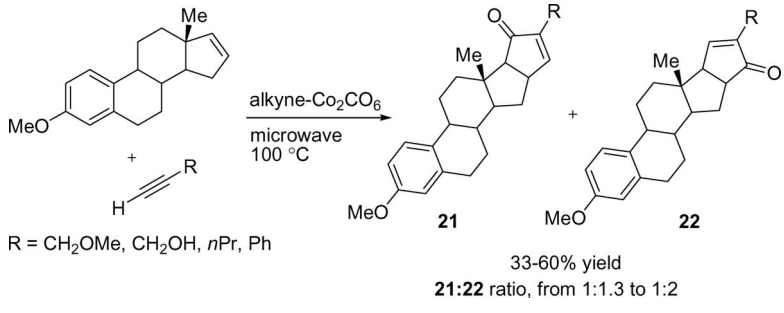


Scheme 69.

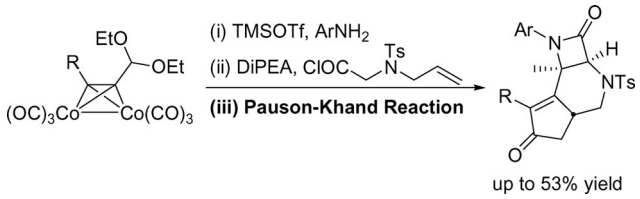
Recently, Bertrand and coworkers reported that hexacarbonyldicobalt complexes of alkynyl imines could be used for a sequential Staudinger/Pauson–Khand process to generate a variety of structurally novel fused tricyclic β-lactams (Scheme 72).[117]

Honda and coworkers employed dicobalt octacarbonyl complexes in an intramolecular Pauson–Khand reaction to synthesize (–)-incarvilline, an analgesic monoterpene piperidine alkaloid.[118] The (–)-incarvilline intermediates **24** and **25** were obtained through an intramolecular Pauson–Khand reaction of enyne **23** as a key step (Scheme 73). The rate of reaction could be enhanced by introducing *tert*-butyl methyl sulfide into the reaction system: in the presence of *tert*-butyl methyl sulfide (3.5 equiv.) under carbon mon-

Scheme 70.



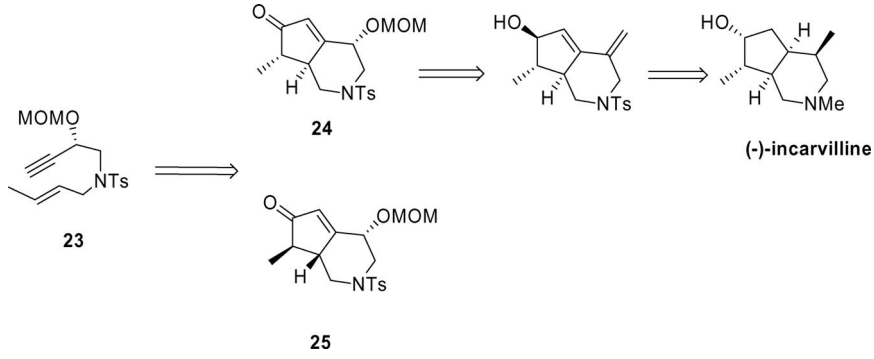
Scheme 71.



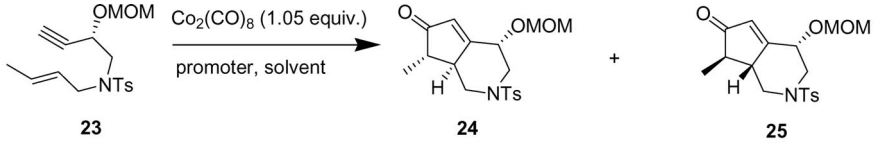
Scheme 72.

oxide, the desired bicyclic compounds **24** and **25** were obtained in 73% and 8% yields, respectively (Scheme 74). It was reported that the diastereoselectivity could be explained in terms of a cyclization that would proceed through the sterically favoured intermediate **A** (Scheme 75), leading to the compound **24** because of steric repulsion between the MOM group and the dicobalt complex.

To explore other synthetic pathways relating to incarvilline, the same group attempted to synthesize skytanthine,[119] which is structurally similar to incarvilline (Scheme 76). The proposed synthetic pathway was shorter than that for incarvilline. Starting from multiple condensations between an alkenyl alcohol, an alkynyl alcohol and 2-nitrobenzenesulfonamide, enyne **26** was generated. A diastereoselective Pauson–Khand reaction was used as a key step to afford the corresponding bicyclic compounds (Scheme 76), and subsequent stereoselective reduction by epimerization provided the desired α-skytanthine. When the previous reaction conditions[118] were applied to convert the enyne **26** into its cycloadducts, four isomers were formed in poor yields (Scheme 77). Surprisingly, only the reductive bicyclic products **28** and **30** were obtained after addition of *tert*-butyl methyl sulfide to the reaction medium. The reac-

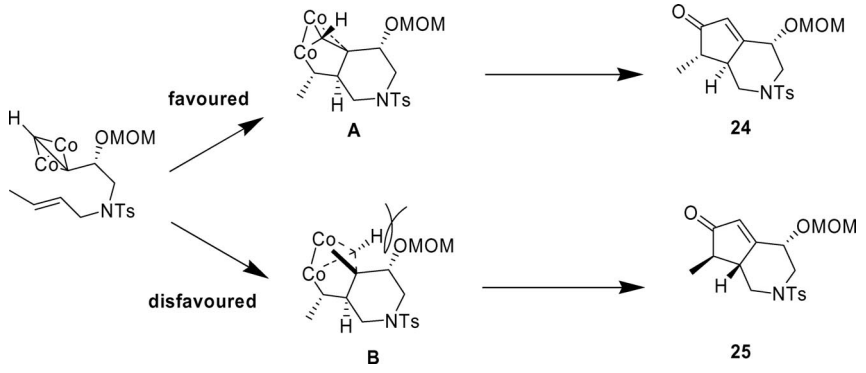


Scheme 73.

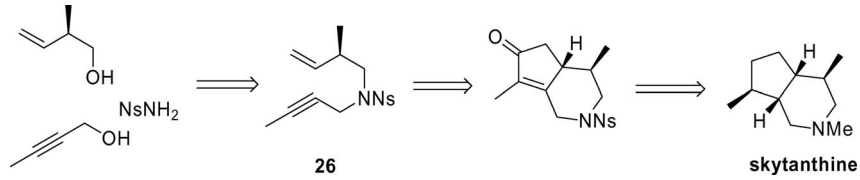


Entry	Promoter	Solvent	Atmosphere	*T* (°C)	Time (h)	**24**/Yield (%)	**25**/Yield (%)
1	none	toluene	Ar	110	2	54	7
2	***t*BuSMe (3.5)**	**DCE**	**CO**	**83**	**2.5**	**73**	**8**

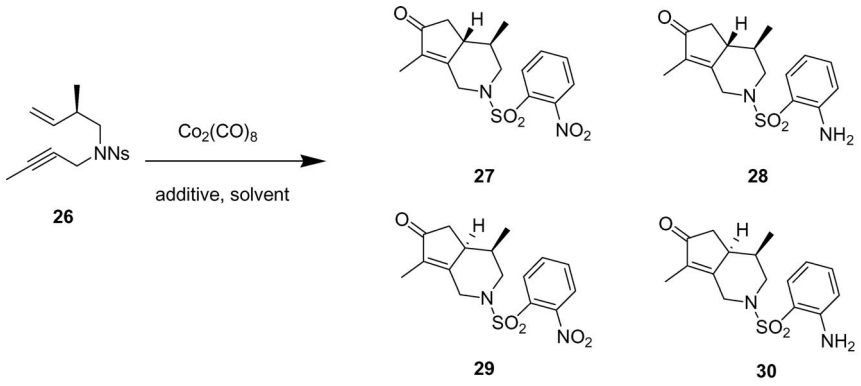
Scheme 74.



Scheme 75.



Scheme 76.

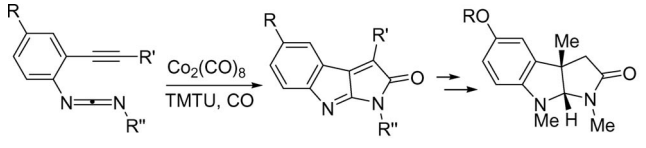


Entry	Additive (equiv.)	Solvent	Atmosphere	Temp. (°C)	Time (h)	Yield (%) 27	28	29	30
1	none	Toluene	CO	60	24	27	32	7	6
2	*t*BuSMe (3.5)	DCE	CO	83	3	–	49	–	7
3	**TMANO·2H$_2$O (5)**	**THF/H$_2$O (3:1)**	**–**	**0 to r.t.**	**7**	**6**	**71**	**–**	**8**

Scheme 77.

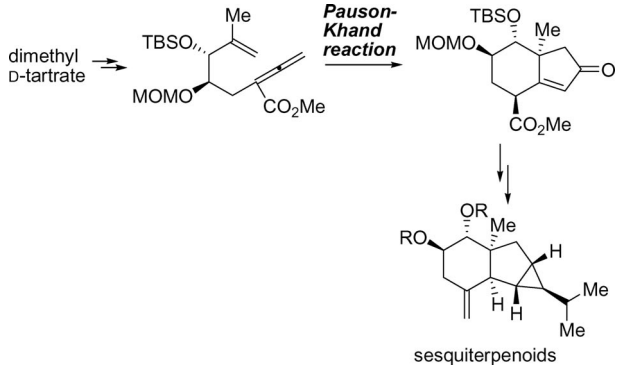
tion performance was further enhanced when trimethylamine *N*-oxide (5 equiv.) was added, to give the desired product **28** in 71% yield.

In 2006, Mukai reported the first successful Co-mediated hetero-Pauson–Khand reaction for an efficient synthesis of physostigmine (Scheme 78).[120] They applied the key alkynecarbodiimide as the initial substrate for target molecule synthesis.



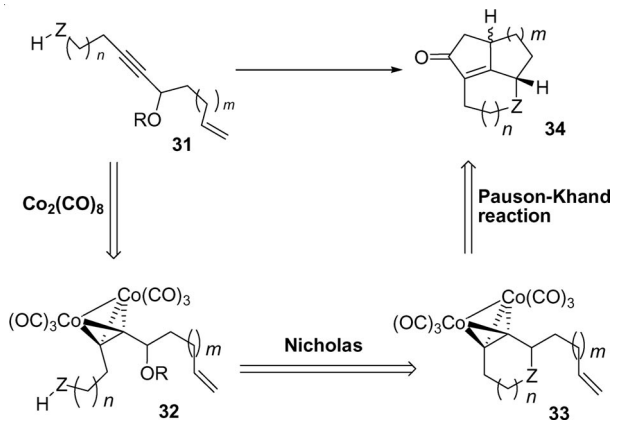
Scheme 78.

In 2008, Mukai further demonstrated the significance of Pauson–Khand chemistry, utilizing a Pauson–Khand protocol as one of the key steps for the total synthesis of uncommon sesquiterpenoids (Scheme 79).[121]



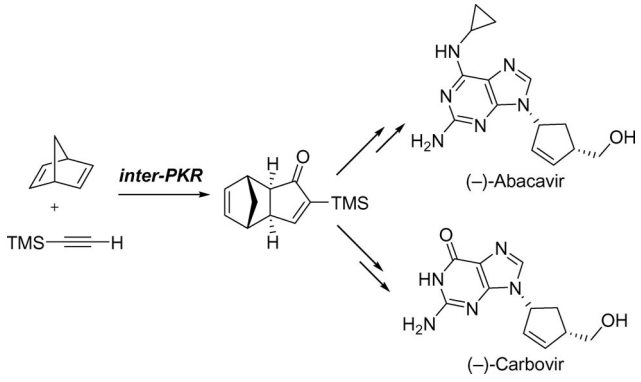
Scheme 79.

Shea and coworkers recently demonstrated the utility of intramolecular Nicholas and Pauson–Khand reactions in the synthesis of tricyclic heterocycles.[122] The acyclic enynes **31** were first chelated onto dicobalt octacarbonyl complexes to form the cobalt-alkyne complexes **32**, followed by a Nicholas reaction to provide the heterocycles **33**, and were then finally cyclized through intramolecular Pauson–Khand reactions to afford the desired tricyclic heterocycles **34** (Scheme 80).



Scheme 80.

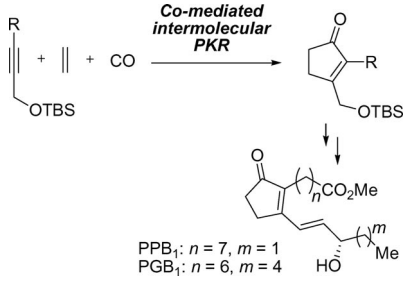
Verdaguer and Riera recently reported the application of the Co-mediated intermolecular Pauson–Khand reaction for the enantioselective synthesis of carbanucleosides (Scheme 81).[123] The chiral cyclopentenone intermediate was accessible in an enantiomerically pure form through an intermolecular PK reaction between TMS-acetylene and norbornadiene in the presence of *N*-benzyl-*N*-diphenylphosphanyl-*tert*-butyl-sulfinamide as a chiral *P,S* ligand. The target molecules, carbovir and abacavir, are synthetically useful five-membered-ring carbanucleosides. They have shown major antiviral and anticancer activities; indeed, abacavir has been approved and launched for the treatment of HIV.



Scheme 81.

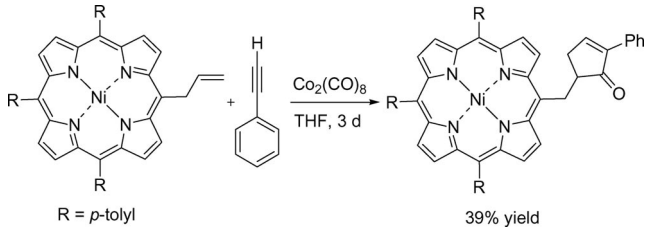
In 2009, the same research group reported a new approach to the synthesis of prostaglandin and phytoprostane B_1 by Pauson–Khand chemistry (Scheme 82).[124] The key step in this total synthesis was an intermolecular PK reaction between a silyl-protected propargyl acetylene and ethylene.

Pauson–Khand-type reactions can also be applied to prepare other scientifically interesting molecules. Recently, intermolecular Pauson–Khand reactions of *meso*-substituted porphyrins were reported.[125] Senge and Horn performed the PK reaction with an allyl-substituted porphyrin and phenylacetylene to afford the desired product in moderate yield (Scheme 83). In addition, they showed that the

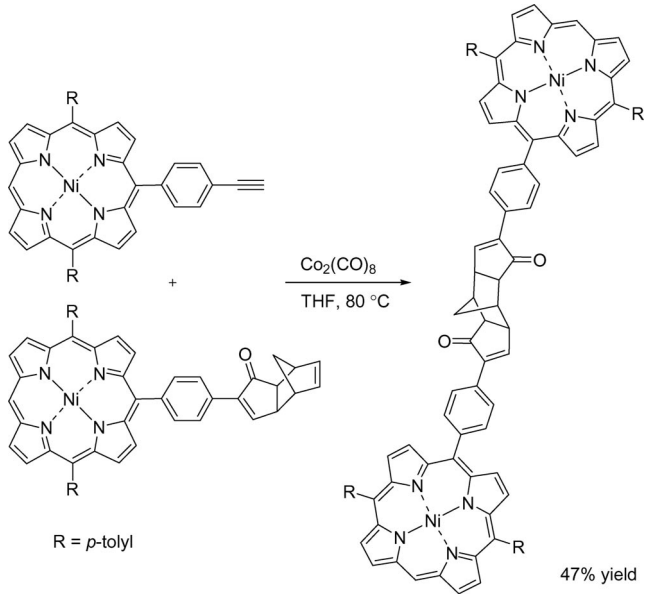


Scheme 82.

porphyrin dimer could also be obtained (Scheme 84). These results have potentially enriched the application of PK chemistry to the preparation of structurally novel macromolecules.

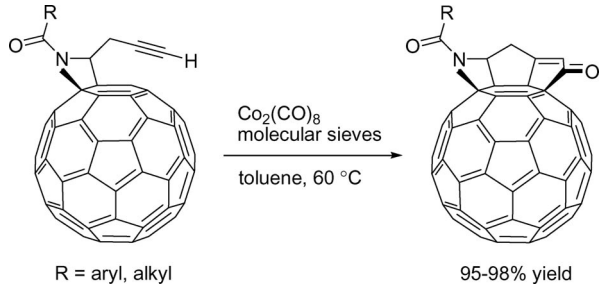


Scheme 83.



Scheme 84.

Martín and coworkers recently demonstrated a highly efficient Pauson–Khand reaction with C_{60}.[126] This report represented for the first time a new [2+2+1] cycloaddition reaction on the fullerene core, regioselectively affording a new class of *cis-1* bis-cycloadducts with three fused pentagonal rings (Scheme 85). These interesting results, especially in view of the reactivities of fullerenes, provided a new avenue in fullerene chemistry.[127]



Scheme 85.

9. Conclusion

This microreview illustrates current developments in catalytic Pauson–Khand-type reactions and the recent catalyst advancements in these reactions. Although some significant improvements have been achieved in the intramolecular PK reaction, the perfect intermolecular PK reaction, especially with regard to the features of environmental friendliness, asymmetry and low catalyst loadings, is still far away. We hope that the summary of the TONs in the tables for each type of catalysts might provide insights for authors to choose appropriate catalysts in using this reaction type for relevant synthetic applications, as well as offering information for future catalyst design.

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