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Cascade Reactions Involving Pauson–Khand and Related Processes

Javier Pérez-Castells

Dpt. Chemistry, Fac. Farmacia, Universidad San Pablo CEU., Boadilla del Monte,
28668 Madrid, Spain
jpercas@ceu.es

Abstract The Pauson–Khand [2 + 2 + 1] cycloaddition is one of the best ways to construct a cyclopentenone. It implies the formation of three new bonds and one or two cycles in the intermolecular or intramolecular versions, respectively. Furthermore some groups have enhanced the synthetic power of this transformation by combining the PKR with other processes. In addition, some unexpected results imply that successive events have occurred, usually after the cycloaddition process. This review aims to point out the most recent advances in cascade reactions in which the Pauson–Khand and PK-type reactions are involved. The non-specialist reader will have an introduction section to outline the state of the art of this chemistry. This will involve, the reaction mechanism, the most useful reaction conditions, the scope of the inter- and intramolecular PKR and the development of asymmetric and catalytic versions.

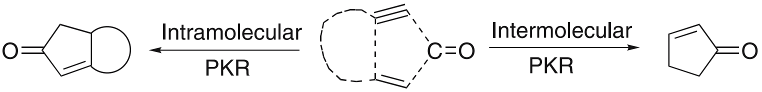
Keywords Catalysis · Cycloaddition · Cyclopentenones · Pauson–Khand reaction · Transition metal complexes

Abbreviations

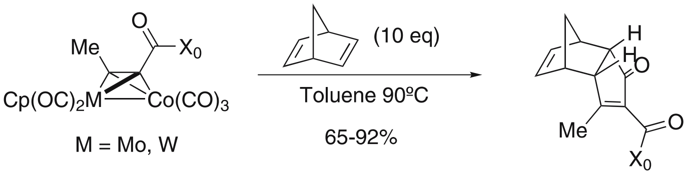
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BSA	Bis(trimethylsilyl)acetamide
BOC	*tert*-Butoxycarbonyl
cod	Ciclooctadiene
dba	Dibenzylidenacetone
DCM	Dichloromethane
DME	Dimethoxietane
DMF	*N*,*N*-Dimethylformamide
dppe	Bis(diphenylphosphino)ethane
dppp	Bis(diphenylphosphino)propane
DSAC	Dry state adsorption conditions
EWG	Electronic withdrawing group
NMO	4-Methylmorpholine *N*-oxide
PKR	Pauson–Khand reaction
RCM	Ring-closing metathesis
SDS	Dodecyl sulfate, sodium salt
TBS	*terc*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilyl
TMANO	Trimethylamine *N*-oxide
TolilBINAP	2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TON	Turnover number
TPPTS	Triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt

1
Introduction. What is the Pauson–Khand Reaction, Its Origin and an Outline of the General State of the Art

The Pauson–Khand reaction (PKR) is among the most powerful transformations in terms of molecular complexity increment [1]. Only a few of other reactions like the Diels–Alder, or the cyclotrimerization of alkynes can compete with the PKR, which consists formally of a [2 + 2 + 1] cycloaddition in which a triple bond, a double bond and carbon monoxide form a cyclopentenone [2–12]. This constitutes one of the best ways to construct cyclopentenones, which upon further transformations can be converted into structures present in numerous natural products (Scheme 1).



Scheme 1 The PKR: an inter- or intramolecular [2 + 2 + 1] cyclization



1 **2**

Scheme 2 Heterobimetallic complexes mediate the PKR

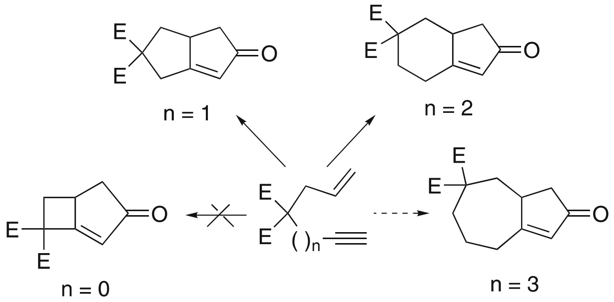
This reaction was first reported in the early 1970s as an unexpected result in search for the synthesis of new organometallic cobalt complexes [13–18]. Dicobalt octacarbonyl was the only cluster used in its beginnings, although now, many cobalt species and other metal complexes are able to mediate or catalyze this reaction. Thus, the stoichiometric reaction has been performed with Zr, Ni, Fe, Ti, W and Mo derivatives. In addition, heterobimetallic Co – W and Co – Mo complexes (**1**), are suitable precursors for the PKR and impart a high degree of selectivity in the process giving exclusively *endo* adducts **2** (Scheme 2) [19, 20].

The catalytic version is actually carried out with Co, Ti, Ru, Ir, and Rh complexes being the latter the more promising ones in terms of scope and efficiency [21].

1.1
Scope and Limitations

PKRs can be performed inter- or intramolecularly. The latter reactions, although developed later, avoid regioselective problems and work with more types of double bonds. The first intramolecular PKR was reported by Schore and allows the formation of 5,5- and 5,6-fused bicycles, and more recently even some 5,7-bicycles. In general, good conversions are achieved only with *gem*-disubstituted enynes (Scheme 3) [22–24].

With the exception of propynoic acid derivatives, all alkynes undergo the reaction. On the other hand, generally, only strained olefins react efficiently in the intermolecular PKR whereas electron deficient alkenes give the reaction only in limited examples. With respect to regioselectivity, the bulkier substituent of the alkyne is placed adjacent to the carbonyl in the cyclopentenone product. Unsymmetrical olefins usually give mixtures of regioisomers

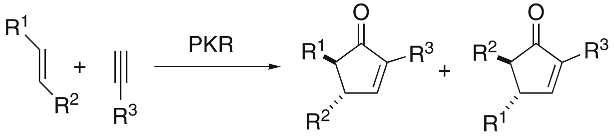


Scheme 3 The scope of the intramolecular PKR with regard to ring size

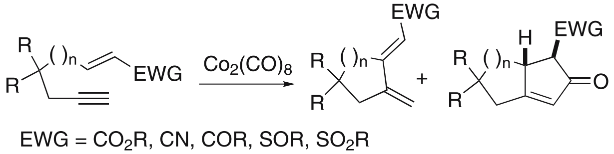
(Scheme 4) [25]. Substitution at the double bond is restricted as disubstituted olefins usually fail to react.

The idea that alkenes possessing electron-withdrawing groups are not adequate substrates for Pauson–Khand reactions has in recent years turned out not to be precise. Carretero has reported several examples involving electron-deficient alkenes **3**), such as α,β-unsaturated ketones, esters, nitriles, sulfoxides and sulfones. In these reactions they reach good yields of PK products (**4**) and isolate small amounts of dienes **5**, that come from a β-elimination competitive reaction (Scheme 5) [26, 27].

In terms of functional group compatibility, ethers, alcohols, tertiary amines, acetals, esters, amides and heterocycles are compatible with the Pauson–Khand reaction. In the intramolecular version, relatively few carbon skeletons undergo the cyclization. Most intramolecular PKRs use systems derived from hept-1-en-6-yne (**6**) or propargyl allyl ethers (**7**) or amines (**8**). Other interesting and more recent substrates are enynes connected through aromatic rings like **9–11**, which have allowed us and other groups to obtain aromatic polycycles (Fig. 1) [28–31].



Scheme 4 Regioselectivity in the intermolecular PKR



3 **4** **5**

Scheme 5 PKR with electron deficient alkenes

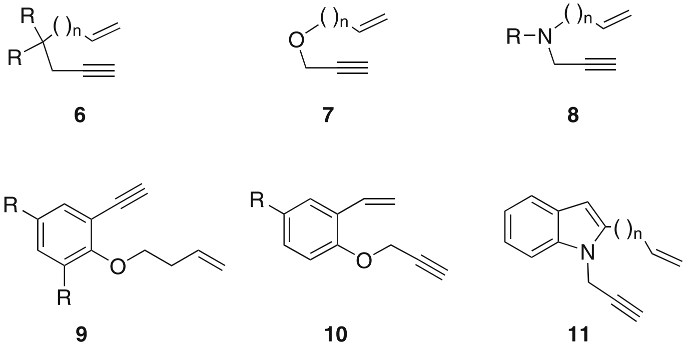
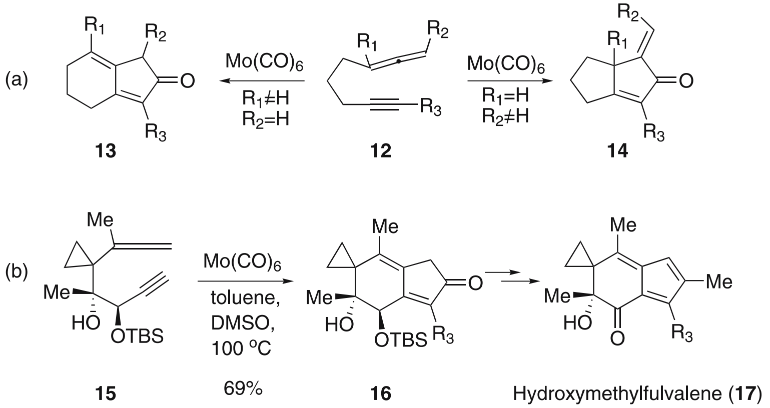


Fig. 1 Some aliphatic and aromatic substrates used for intermolecular PKR

In addition, allenes can act as the olefinic part of the reaction [32]. Allenynes like **12** may react with both double bonds. Brummond established the substitution patterns for the reaction with either the external or the internal bond of the allenic fragment, that give products with different ring sizes (**13**–**14**) [33]. This group has applied these studies to the synthesis of hydroxymethylfulvalene (**17**), a potent anticancer agent related with illudines, a natural sesquiterpene family. The key step was the synthesis of **16** from **15** with a PKR mediated by molybdenum carbonyl (Scheme 6) [34,35]. In addition they have developed an asymmetric version of the reaction. They have transferred efficiently chirality from a non-racemic allene to an α-alkylidene and an α-silylidene cyclopentenone in a molybdenum mediated reaction [36–38].

The synthesis of medium-sized rings is very interesting and has been an important limitation for the intramolecular PKR. It is only possible if certain

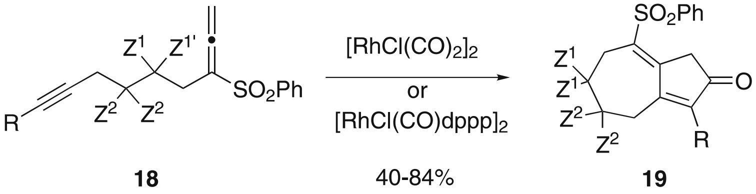


Scheme 6 The allenic PKR: **a** Study on the substitution patterns that make either double bond react; **b** Application in synthesis of an illudine derivative

structural features allow the increase in the population of the reactive conformation. This has happened with several aromatic substrates [28–31, 39].

On the other hand, the intramolecular allenic PKR has allowed the efficient synthesis of seven membered rings. Mukai has synthesized bicyclo[5.3.0]decenones (**19**) from allenynes **18**, using several rhodium catalysts. The process tolerates hydroxy and silyloxy groups and generally reaches good yields (Scheme 7) [40, 41].

Exocyclic olefin fragments are among the few disubstituted double bonds that react efficiently in PKRs. Several examples have appeared in the literature and include methylenecyclohexanes (**20**), methylenecyclopropanes (**21**) and methylenepyranes (**22**) [42, 43]. Cyclopropyl tethered methylenecyclopropanes can give the expected PK products or rearranged hydroindenones in which neither of the two carbon atoms of the alkyne form part of the cyclopentenone ring in the final product [42]. Other substrates like enamines (**23**) and ynamines (**24**) undergo readily this reaction (Fig. 2) [44–47].



$Z^1 = H, CO_2Me$; $Z^{1'} = OH, OTBS$
$Z^2 = H, CO_2Me$
$R = H, Ph$

Scheme 7 The allenic PKR allows the synthesis of medium sized rings

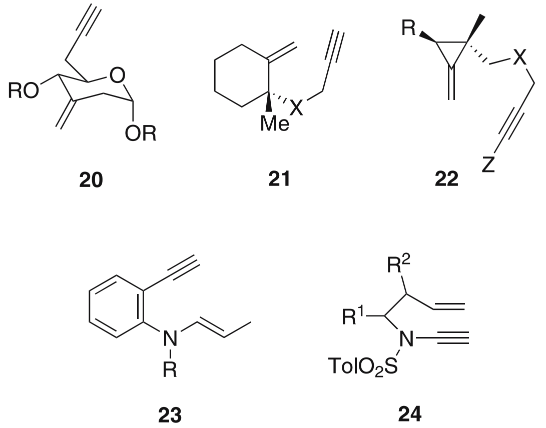
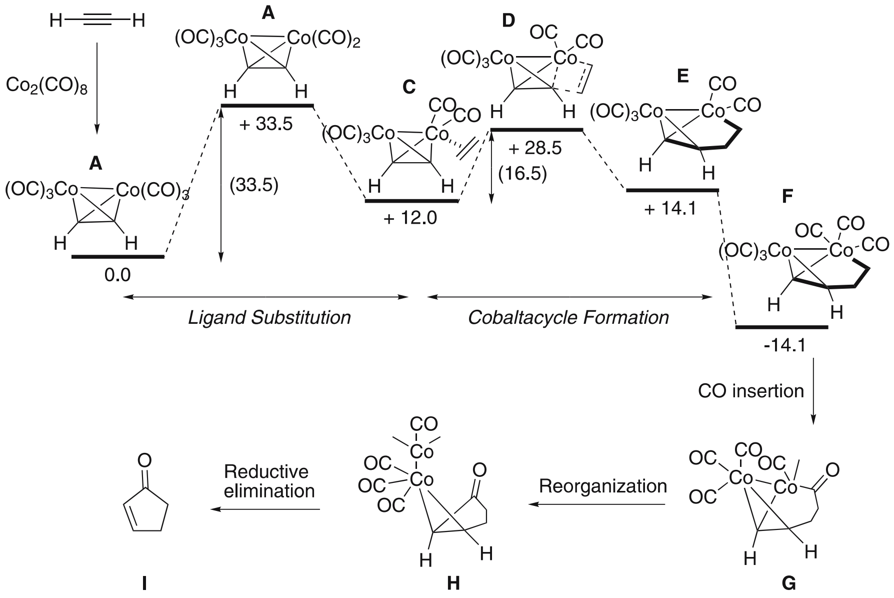


Fig. 2 Some recently introduced substrates: Exocyclic alkenes, ynamides and enamines

1.2
Reaction Pathway and Promotion

Mechanistically, the pathway proposed by Magnus is generally accepted as it explains most experimental results (Scheme 8) [48, 49]. The main problem with the demonstration of this mechanism is that beyond the cobalt-hexacarbonylalkyne complex (**A**), it is difficult to detect further intermediates.

Starting from the initial complex **A**, the first step would be the loss of one CO in a dissociative manner. This step, which is strongly endothermic, is the rate-determining step and, consequently, acceleration of the process usually involves the use of promoters that act at this point, labilizing one of the CO ligands [50]. Pericàs has isolated sulfur-ligated decarbonylated type **B** intermediates that support the dissociative mechanism [51]. Then, the olefin coordinates with the cobalt (**C**) and is inserted into a Co – C bond forming cobaltacycle **E** which recovers one CO to give **F**. This is the other important stage in the reaction course as it determines its stereochemical outcome. DFT calculations show the importance of facilitating CO dissociation but point out that the energy of the second step is also important and this is the reason why strained olefins react so well [51]. In this second step, the strain of cyclic olefins is liberated, favoring the process [52]. Several other theoretical stud-



Scheme 8 The commonly accepted reaction pathway for the PKR of acetylene and ethylene. Energy profile for the important stages of the mechanism

ies support this mechanism while it explains the regio- and stereochemical results of numerous examples. Thus, Nakamura [53] and Milet and Gimbert [54] have performed high-level theoretical calculations on the cobalt-acycle formation step, showing that the insertion of the olefin is the critical stereo- and regiochemical-determining step of the PKR.

Continuing with the reaction pathway, from complex **F**, insertion of CO follows giving **G**, and a subsequent complex reorganization forms **H**. Finally a reductive elimination leads to the cyclopentenone **I**.

Several reports show different ways to accelerate the reaction. These are important for the aims of this chapter as sometimes they lead to unexpected results that involve cascade reactions occurring after the PKR. For instance, the first important finding on the promotion of the PKR was by Smit and Caple, who effected the reaction with the reagents adsorbed in several solid supports (Dry State Adsorption Conditions, DSAC) observing reduced products and other unexpected results in many cases (*vide infra*) [55]. Actually, promotion of the PKR usually involves the use of chemical additives. Amine *N*-oxides [56, 57] act oxidizing one CO ligand, which is transformed into CO_2, thus forming a vacant in the cobalt cluster. Other possibilities include addition of sulfides and sulfoxides [58] or cyclohexylamine [59, 60]. These additives probably act helping the displacement of a CO ligand and stabilizing reaction intermediates. We have shown the positive effect of molecular sieves in both the catalytic and the stoichiometric version of the reaction. These zeolites probably retain CO molecules, increasing conversions even with non favorable substrates, such as substituted olefins [61, 62].

Other ways of labilizing CO ligands consist of irradiating the complex with ultraviolet light [63], ultrasounds [64] or microwaves [65, 66]. The latter conditions seem to shorten reaction times remarkably, though results are not spectacular with respect to conversions.

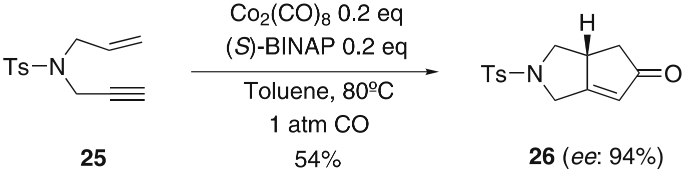
1.3
Catalytic PKR

With the focus on green chemistry, it is actually impossible to think on an industrial chemical reaction, which involves transition metal complexes, that is not efficiently catalytic. The chemical industry demands atom economical reactions, that is, those in which substrates are transformed into products with the only aid of catalytic amounts of the rest of reactants. Although really catalytic PKR appeared only in the mid-1990s, developments from recent years allow us to be moderately enthusiastic. The literature gives a good deal of catalytic protocols that use different cobalt and other metal complexes. Still, a lack of scope is generally observed in these reports. In addition there are few examples of intermolecular reactions performed in catalytic conditions [21].

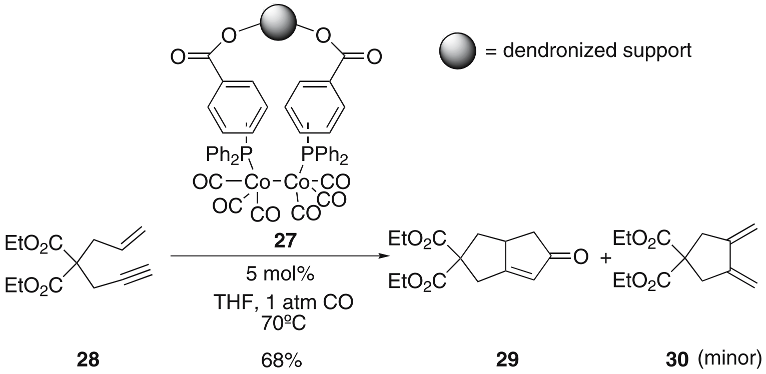
The first important advances in the development of a catalytic PKR were by the groups of Livinghouse [67, 68] and Krafft [69, 70] who reported reaction conditions using only 1 atmosphere of CO. Soon afterwards other groups observed that addition of certain ligands enhanced the efficiency of the process. Thus, the addition of phosphines and phosphites may avoid the formation of inactive cobalt species, stabilizing intermediate active clusters [71, 72]. When adding chiral phosphines such as BINAP to the reaction of **25**, **26** was formed with good enantiomeric excesses and moderate chemical yields. Substitution patterns in the skeleton of the substrate affect dramatically the stereochemical outcome of the reaction and, in general, they need high catalyst loadings (Scheme 9) [73, 74]. Chiral phosphites, used by Buchwald, reached good ee values only in certain substrates [75].

Modified carbonylcobalt complexes can catalyze the PKR. One or more CO can be substituted by phosphines, and these can be immobilized in resins thus giving anchored cobalt complexes (**27**), that were able to catalyze the reaction of **28** giving **29** with good yield and minor amounts of **30** (Scheme 10) [76]. Other cobalt metal clusters like $Co_4(CO)_{12}$ [77] or methylidynetricobalt nonacarbonyl [78] have exhibited high reactivity in the catalytic PKR.

With regard to PK-type reactions, Buchwald studied titanium species as efficient catalysts in the PKR and in PK-like reactions with cyanides. Following preliminary results with $[Cp_2Ti(PMe_3)_2]$ and $[Cp_2TiCl_2]$ [79–81], they reported a more practical procedure which improved the TON using commercial titanocene dicarbonyl (**33**) [82, 83]. This complex is able to catalyze the



Scheme 9 Formation of chiral catalysts *in situ* by addition of chiral phosphines

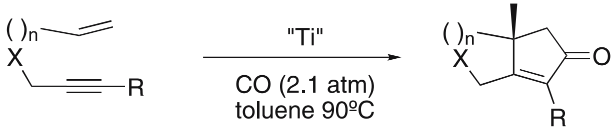


Scheme 10 PKR with anchored cobalt complex catalysis

reaction of different 1,6 and 1,7-enynes (**31**) with excellent functional group tolerance and under low CO pressure, but fails to react with sterically hindered olefins and alkynes. In an enantioselective version of this methodology, Buchwald has used chiral titanocenes like **34** to effect the PKR. These catalysts have reached good chemical yields of **32** with moderate enantiomeric excesses (72–96%) [84–86]. This group has prepared recently a series of aryloxide complexes (**35**) that are able to promote cyclisations with some sterically hindered enynes (Scheme 11) [87].

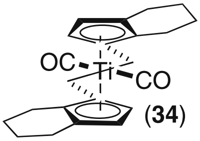
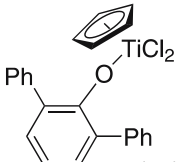
A couple of reports used [$Ru_3(CO)_{12}$] as catalyst. Both studies, by Murai [88] and Mitsudo [89], used enynes bearing disubstituted alkynes and needed severe reaction conditions with high CO pressures.

Rhodium complexes are effective catalysts for the PKR and are receiving much attention. In addition to the studies by Narasaka with [RhCl $(CO)_2]_2$ [90], Jeong has introduced several species as new catalysts. Some of these rhodium complexes need activation with AgOTf. The reaction works well with non-terminal alkynes (**36**) and the scope and efficiency is dependent on the catalyst used. In the case of chiral species, a careful choice of conditions, including CO pressure, activation, solvent and ligands, is essential to obtain **37** with high enantioselectivity (Scheme 12) [91].

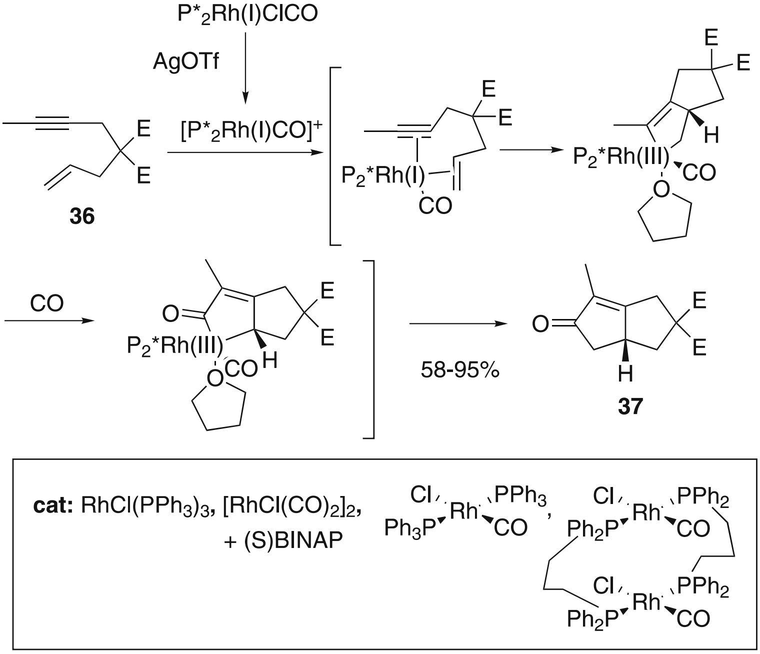


X = O, $(EtO_2C)_2$, CH_2.NBn R = H, Aryl, Alkyl, TMS

31 **32**

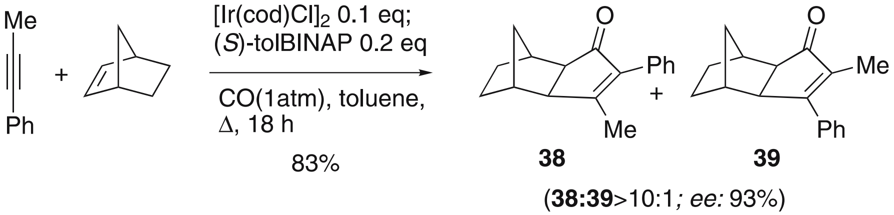
"Ti"	Yields	*ee*
$Cp_2Ti(CO)_2$ (**33**)	83-95%	-
 (**34**)	80-93%	72-96%
 (**35**)	75-81%	-

Scheme 11 Titanocene derivatives as catalysts in PK-type reactions



Scheme 12 The use of several rhodium complexes for [2 + 2 + 1] cyclizations. The role of AgOTf activation

Although first results with iridium complexes were disappointing in terms of conversions with typical substrates, when adding phosphanes yields improved. This observation prompted Shibata to use chiral phosphanes like *S*-tolylBINAP, reaching high chemical yields and enantioselectivities. Impressively, the first example of an asymmetric intermolecular PKR was reported using these conditions. The reaction was not totally regioselective, reaching a mixture of **38** and **39,** but ee was 93% (Scheme 13) [92].



Scheme 13 The best (and almost unique) example of an asymmetric catalytic intermolecular PK-type reaction

1.4
Asymmetric PKR

There are several possibilities to induce asymmetry in the PKR, which are summarized in Fig. 3.

These are: (1) The chiral substrate approach. This approach involves using chiral precursors that transfer their chirality to the final cyclopentenone. This implies the synthesis of chiral substrates, which has generally been made from classic chiral pools. Examples include carbohydrate derivatives like **40** that give **41** with variable yields depending on the substitution pattern. **41** is transformed into cyclopenta[*c*]pyrane **42**, which is the skeleton of iridoids [93]. In another example epichlorhydrin (**43**) is used to construct chiral enyne **44** which gives cyclopentenone **45** [94] (Scheme 14).

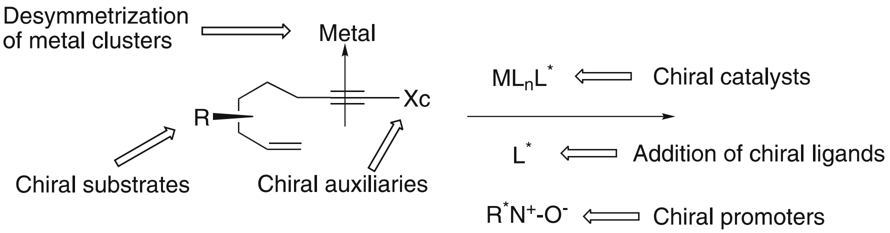
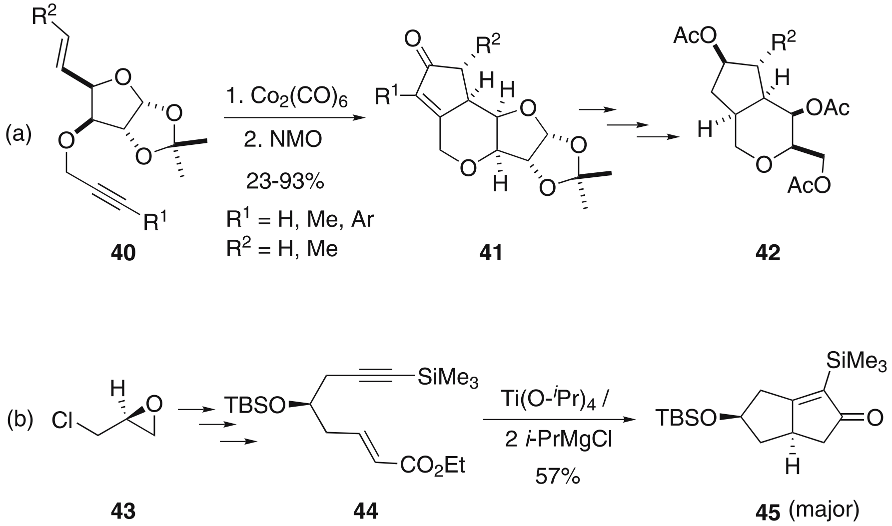


Fig. 3 Inducing asymmetry in the PKR. A wide variety of possibilities

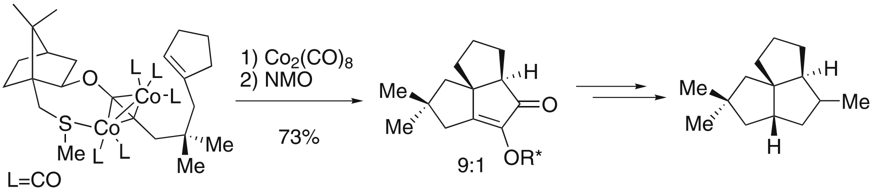


Scheme 14 Two examples of the chiral substrate approach: **a** carbohydrates as starting materials for the construction of chiral enynes; **b** epichlorhydrin as source of chirality in assymetric PKRs

(2) The chiral auxiliary approach. Pericàs' group has worked with chiral sulfur moieties like 10-methylthioisoborneol, Oppolzer's camphorsultam or chiral oxazolidinones which gave excellent results in stereocontrol and yields [95–100]. Recently they have reported that chiral alkynylthiols like **46** exhibit excellent diastereoselectivities in both inter- and intramolecular PKR, and have used this approach for the synthesis of **47**, an intermediate in the synthesis of (+)-15-nor-pentelenene (**48**) (Scheme 15) [101, 102].

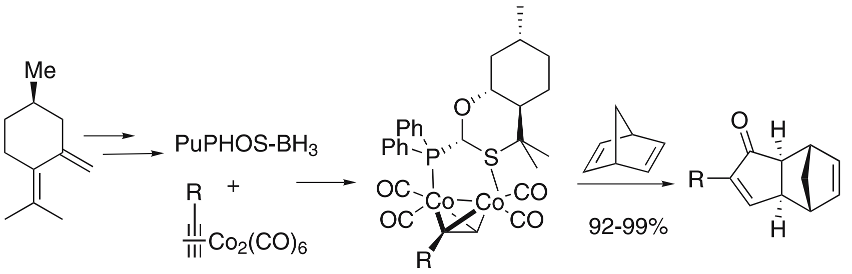
Carretero used chiral sulfoxides attached at the olefin that are efficient auxiliaries due to the proximity of the chiral sulfur to the reaction centre. Reductive cleavage of the sulfoxide is carried out by treatment with activated zinc [103, 104].

(3) The chiral metal complex approach. We have shown in the previous section several methodologies included in this approach. They go from the addition of chiral ligands to metal species that form in situ chiral aggregates, to the synthesis of complexes including chiral ligands or non-symmetrical heterobimetallic clusters. As an example, Pericàs has recently obtained different chiral complexes (**50**) using bidentate (P,N) and (P,S) ligands. The most effective result was achieved using a ligand called PuPHOS, which is readily obtained from natural product (+)-pulegone (**49**). The reaction of these complexes with norbornadiene gave **51** with high yields and ees (Scheme 16) [105].



46 **47** (+)-15-nor-pentelenene (**48**)

Scheme 15 Synthesis of (+)-15-nor-pentelenene with a PKR of an enyne bearing a chiral auxiliar



(+)-pulegone (**49**) **50** **51** *ee:* 97-99%

Scheme 16 An example of synthesis and application of chiral metal clusters in assymetric PKRs

(4) The chiral promoter approach. Chiral promoters, generally natural alkaloid *N*-oxides, might be able to make a selective decarbonylation of one carbonyl of the cobalt cluster. Nevertheless they gave poor results in terms of ee in all the reports appeared to date [106–109].

We have seen in this first section the state of the art in the PKR. In following sections this chapter will deal with those single synthetic steps in which multiple reactions are combined, being one of them a PKR or a PK-type reaction. This will include those processes named *domino* or *cascade* reactions in which a substrate suffers at least two transformations in a single step, and also sequential reactions in which additional reagents or changes in the reaction conditions are involved during the process but without isolation or purification of the intermediates (what is usually called a *one pot* procedure). Some of the transformations will be stoichiometrically mediated by one or several metal complexes, others will constitute concurrent tandem catalyzed reactions, that is, reactions that involve two or more catalytic cycles in which the same or different catalysts perform successive transformations. In general the reactions that are added to the PK transformation may occur before the cycloaddition, generally implying the formation of the enyne, or the formation of CO from a decarbonylation reaction, or after the PKR involving a myriad of simple transformations such as reductions, double bond shifts or cleavage of carbon–heteroatom bonds (Fig. 4).

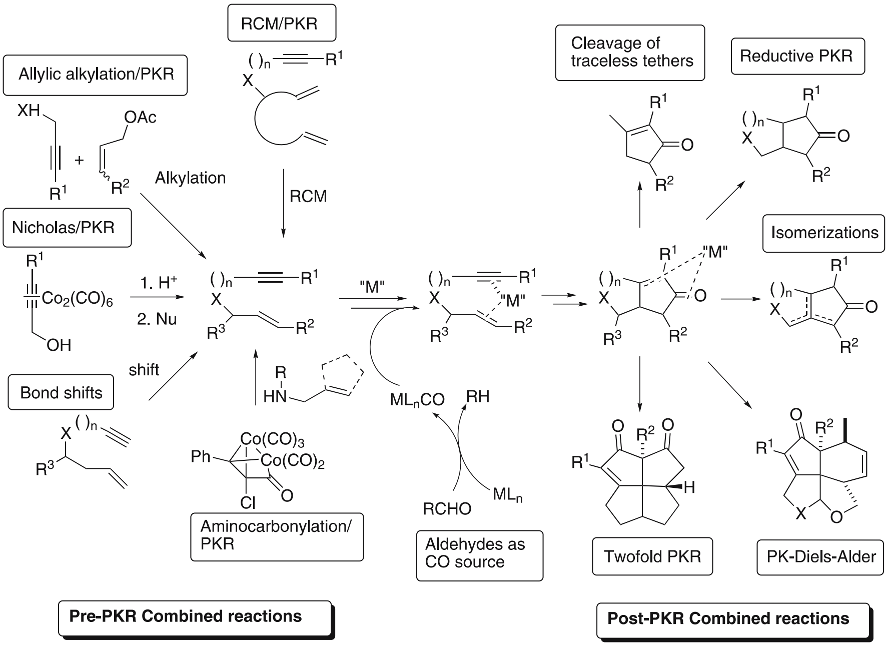


Fig. 4 Summary of main pre- and post-PKR processes

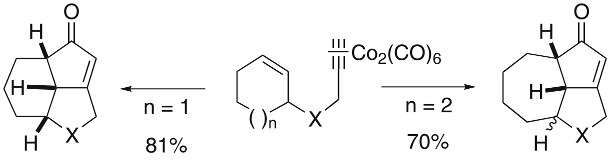
2
Cascade Synthesis of Enynes/Pauson–Khand Reaction

The synthesis of enynes is not always trivial. Some synthetic reactions have functional group compatibility problems, others give poor yields due to instability of the products. Transition metals can be useful in reactions that give enynes which can suffer subsequent PKRs.

2.1
RCM-PKR

Our group has used a combined metathesis-PKR for the synthesis of tricyclic compounds in one step. The process starts from pure cobalt complexed dienynes **52**. The cobalt cluster acts first as a protecting group to avoid undesired enyne metathesis processes. The methodology allows the formation of tricyclic [6.5.5] (**53**) and [7.5.5] (**54**) structures including, in some examples, oxygen or nitrogen. Tricycles **53** are obtained in a total stereoselective manner, while compounds **54** are formed as mixtures of two diastereomers (Scheme 17) [110].

In a complementary contribution to this chemistry, Young assembled a [9.5.5] system by sequential metathesis reaction on a diene linked by a cobalt hexacarbonyl complexed alkyne followed by domino Nicholas-PKR which we will comment later [111].



53 **52** **54**

Conditions: i) $Cl_2(Cy_3P)_2Ru{=}CHPh$, 5%, DCM. ii) NMO (6 eq.)
X = O, N-BOC

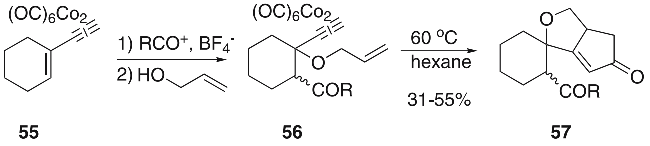
Scheme 17 Tandem RCM-PKR for the synthesis of tricyclic compounds in one step

2.2
Nicholas-PKR

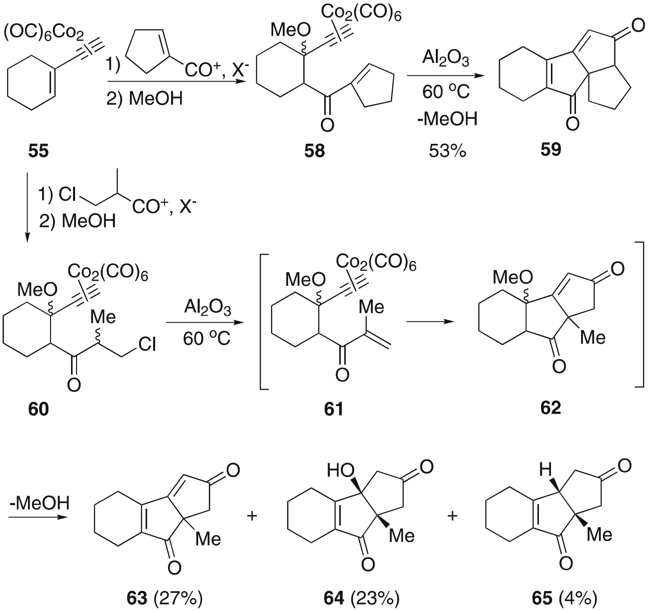
Complexation of an alkyne to dicobalthexacarbonyl is a well-known way to stabilize carbocationic charges generated in the carbon α to the alkyne. These carbocations react with different nucleophiles. This process, the Nicholas reaction [112], has been used to generate enynes that undergo, in a domino fashion, a PKR.

In a very early example, Smit and Caple generated the stabilized cation from a conjugated enyne (**55**) by electrophilic attack followed by incorporation of a nucleophile to give **56**. When they used allyl alcohol as nucleophile they generated an enyne that underwent a PK cyclization giving tricyclic spirocompounds **57** (Scheme 18) [55]. The complementary approach using an unsaturated electrophile did not work as it implied the reaction of an electron deficient double bond. In this case they transformed the ketone into an alcohol by reaction with a Grignard reagent and performed the PKR independently.

Some years later the same group succeeded in performing their second approach, that is the PKR of a 1,6-enyne-3-one, prepared via a Nicholas reaction. In that case they used cyclic conjugated enynes which were reacted with an alkanoyl tetrafluorborate to give enynes like **58** which, under DSAC conditions, gave the corresponding PK products. Scheme 19 shows two interesting



Scheme 18 Spirocompound synthesis in a *one pot* procedure using a Nicholas-PKR sequence

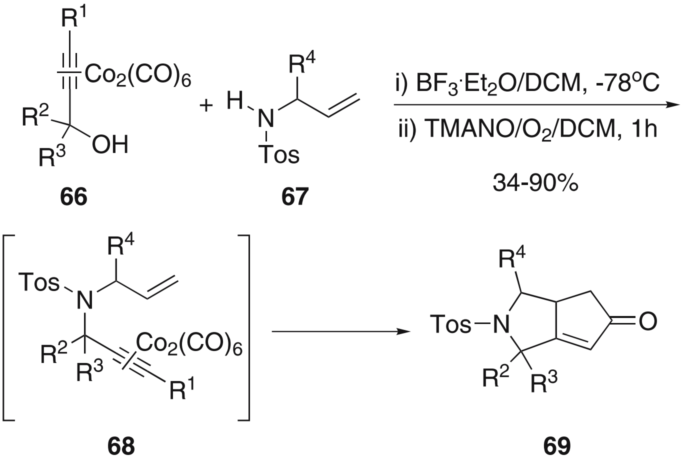


Scheme 19 The first published PKR of an unsaturated ketone. A combination of several pre- and post-PKR in one synthetic step

examples of this chemistry. The first leads to tetracyclic product **59** and includes a post-PKR elimination of methanol. In the second case the complexed enyne **61** is obtained in situ by means of a HCl elimination in **60** previous to the PKR. The authors expected the formation of the enyne **61**, when they found that it was directly transformed into the cyclization products **63** and **64** in the reaction conditions. Thus, after formation of **62**, a methanol elimination followed and, in the case of **64**, further addition of water to the emerging double bond occurred. A small amount of reduced product **65** was also isolated. This was the first example in which a conjugated ketone underwent the PKR [113, 114].

Another one pot Nicholas-PKR strategy was reported by Jeong using amidic nitrogen nucleophiles in the Nicholas step. Thus, a series of tosyl and CBz amides (**67**) were effectively propargylated using cobalt complexed propargylic alcohols **66** as precursors of the corresponding cations. The Nicholas process was quenched with triethylamine giving **68**, and upon addition of a promoter (generally TMANO), PKR followed giving bicyclic enones **69** with moderate to good yields (Scheme 20) [115].

Later on, Schreiber used consecutively these two reactions in the key step for the synthesis of diterpene (+)-epoxydictimene (**73**), starting from natural (*R*)-pulegone [116, 117]. This approach was built on their preliminary studies on Lewis acid mediated intermolecular Nicholas reactions [118]. They prepared functionalized enyne **70** bearing a mixed acetal. This compound was transformed into its dicobalt-hexacarbonyl complex and, in the presence of a carefully selected Lewis acid, it formed a stabilized carbocation by release of the more accessible ethyl moiety. This cation reacted intramolecularly with the allylsilane giving the central eight membered ring of the natural product

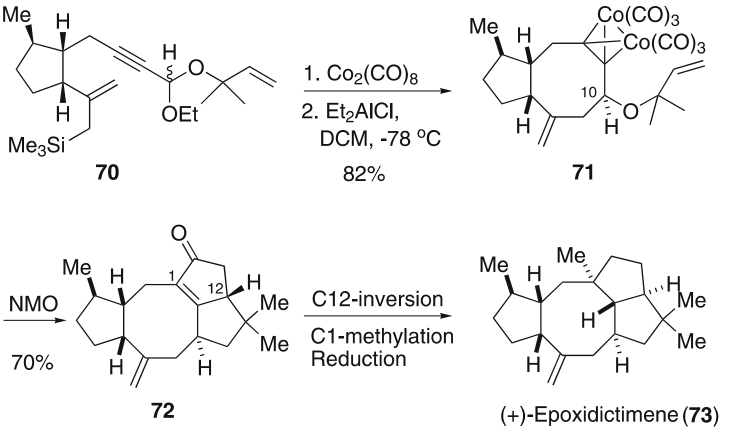


Scheme 20 Nicholas-PKR for the synthesis of propargyl allyltosylamides and subsequent cyclization

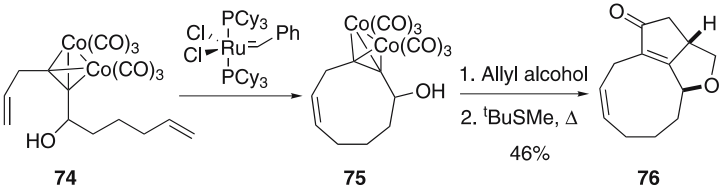
with the desired configuration at C10 (**71**). This intermediate is transformed without purification into the PK product **72**. The conditions that gave better results in terms of yield and diastereoselection at C12 were NMO promotion in dichloromethane (Scheme 21).

As commented above, Young has reported one example of a Nicholas/PKR starting from cobalt complex **74**, prepared by means of a RCM reaction [111]. The reaction of **74** with allyl alcohol in the presence of BF_3Et_2O gave enyne **75** which cyclized with *t*-BuSMe promotion to give tricycle **76** (Scheme 22).

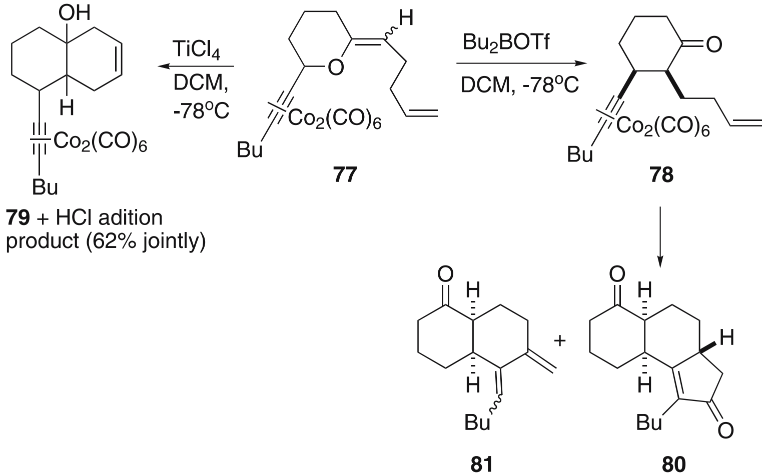
The stabilization of positive charges adjacent to a cobalt hexacarbonyl complex is the base of a rearrangement of an enol ether complex described by Harrity [119]. They used enolether **77** with a pending alkene, which, when treated with dibutylboron triflate, gave *cis*-complexed enyne **78**. The selection of the Lewis acid was essential to avoid an undesired ene/Prins side reaction that formed **79**. Complex **78** gave the corresponding PK product **80** under several reaction conditions. Isomeric mixtures of diene **81** were found also in the reaction mixtures. This by-product appears frequently in PKRs and comes from the *β*-elimination of the metallacyclic intermediate. Best results were achieved using Kerr's polymer supported sulfide resin (Scheme 23) [120].



Scheme 21 Synthesis of natural sesquiterpene (+)-epoxidictimene using a tandem Nicholas-PKR as the key step



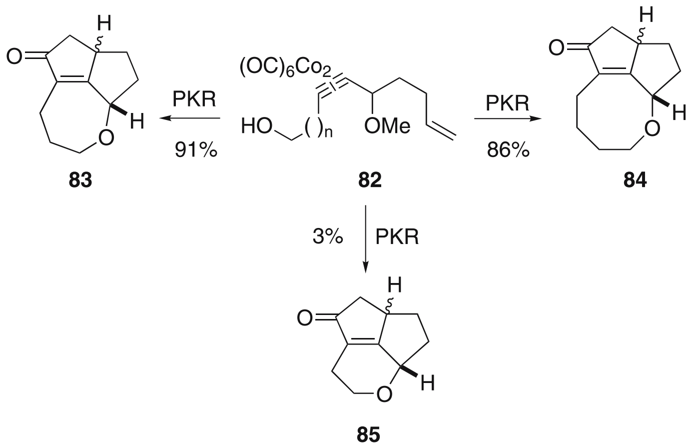
Scheme 22 Cyclic alkynes in the PKR. Tandem Nicholas-PKR for a tricycle construction



	81	80
Toluene, 0°C, Mol sieves	42%	13%
1,2-DCE, 83 °C	71%	21%
Toluene, 110 °C	-	72%

Scheme 23 Tandem rearrangement and PKR for the synthesis of polycycles

The most recent contribution in this area is by Shea who prepared tricyclic oxygen containing heterocycles from acyclic enynes **82** using a combination of intramolecular Nicholas and PKRs. They constructed [5.7.5] and [5.8.5] (**83–84**) systems involving the formation of a complexed cyclic alkyne. They used several PKR conditions that give different yields and diastereoselectivities. Due to the strain of the intermediate, [5.6.5] systems (**85**) were obtained in poor yields (Scheme 24) [121].

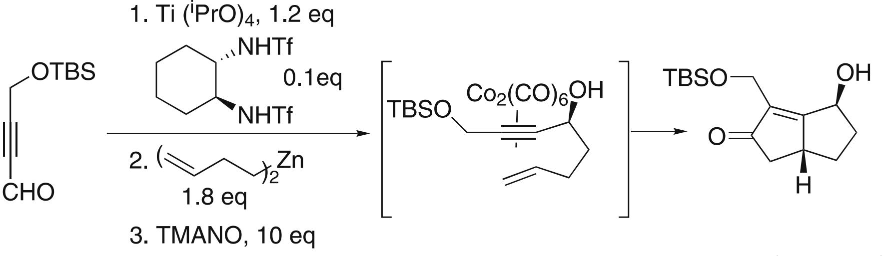


Scheme 24 Tandem intramolecular Nicholas-PKR for the synthesis of tricycles

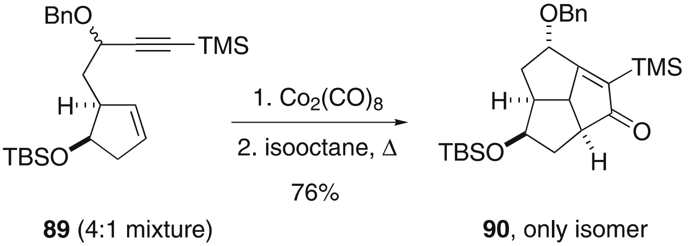
Complexation of propargyl aldehydes to cobalt also enhances the reactivity and enantioselectivity of the addition of alkylzinc reagents. This fact was used to create non-racemic enyne-ol **88** reacting the aldehyde **86** with *bis*-homoallylzinc in the presence of a chiral *bis*-(sulfonamide) and $Ti(O^iPr)_4$. The resulting complexed substrate **87** underwent the PKR promoted by TMANO in a *one pot* fashion (Scheme 25) [122].

In connection with this, an unusual isomerization of the propargyl chiral centre in **89** was observed during a PKR in which **90** was obtained as an only isomer. This result shows the transition formation of positive charges at the propargylic position during the cycloaddition (Scheme 26) [123].

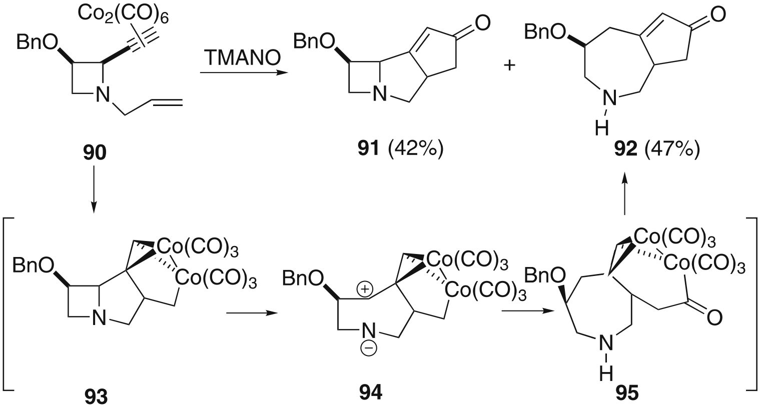
Finally, a Nicholas-type reaction is presumably responsible for an unexpected result reported by Alcaide. During their work devoted to the application of the PKR in the field of *β*-lactams and azetidines they reacted complexed azetidine **91** with TMANO, isolating a mixture of the expected PK product **92** and by-product **93**. The formation of **93** is believed to be a consequence of the ionization of the propargylic C – N bond at the cobalt-acycle step. The crowded metallacycle formed after the insertion of the olefin (**93**), would prompt the cleavage of the C – N bond, forming an ionic species (**94**) that would trap a hydride, possibly from a cobalt hydride giving **95**, which then would follow the usual pathway towards the cyclopentenone (Scheme 27) [124].



Scheme 25 *One pot* asymmetric addition of dialkyl zinc to a cobalt complexed propargyl aldehyde followed by PKR



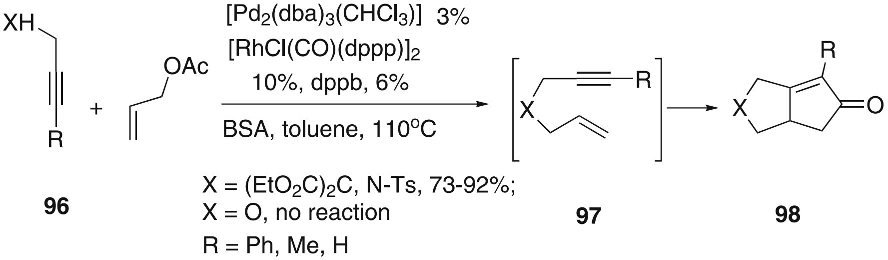
Scheme 26 Epimerization at the propargylic position during a PKR



Scheme 27 Unexpected formation of azepine in the PKR of azetidines. Mechanistic hypothesis

2.3
Allylic Alkylations

An excellent example of concurrent tandem catalysis involving PK-type reactions is that in which different catalysts perform successively the synthesis of an enyne by means of an allylic alkylation followed by the PKR. Jeong used a combination of [$Pd_2(dba)_3(CHCl_3)$] with [$RhCl(CO)(dppp)]_2$ to convert derivatives **96** and an allylacetate into the cyclopentenone **98** [125]. It was necessary to perform a detailed investigation of Pd and Rh catalyst precursors, ligands and reaction conditions as the PK step was in principle problematic, and interferences between catalysts had to be avoided. The ratio of the Rh(I)/Pd catalyst was optimized by 2–3 to 1 in order to avoid undesired reactions, reaching high yields of the final product. The formation of the intermediate enyne **97** was detected following the reaction by gas chromatography. The reaction is highly dependent on the substrate and while malonyl derivatives and amides reacted smoothly, propargyl alcohols did not react (Scheme 28).



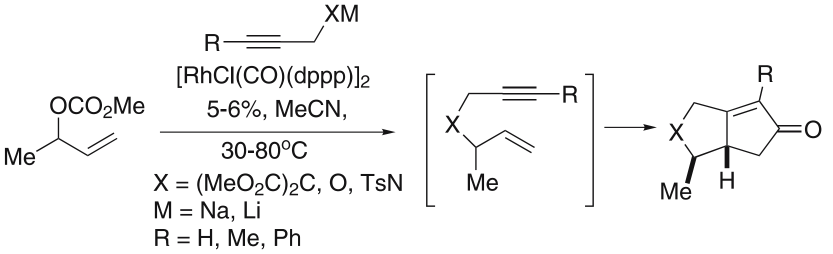
Scheme 28 Tandem action of different catalysts in allylic alkylation-PKR

Evans used a single catalyst for an allylation-PKR sequence that only required changing the reaction temperature for each step. Thus, they synthesized cyclopentenone **101** from allylic acetate **99** and diethyl propargylmalonate salt in the presence of [RhClCO(dppp)]$_2$ with high yield. When formation of intermediate **100** was complete they just heated the reaction to 80 °C to get **101** (Scheme 29) [126].

Several non-carbonyl cobalt sources used recently show high efficiency in the catalysis of the PKR. Chung has reported different reusable catalysts like cobalt supported on mesoporous silica or on charcoal that work under high CO pressures [127]. Most recently they have described milder conditions with the use of colloidal cobalt nanoparticles, which react at lower CO pressures and can be used in aqueous media [128].

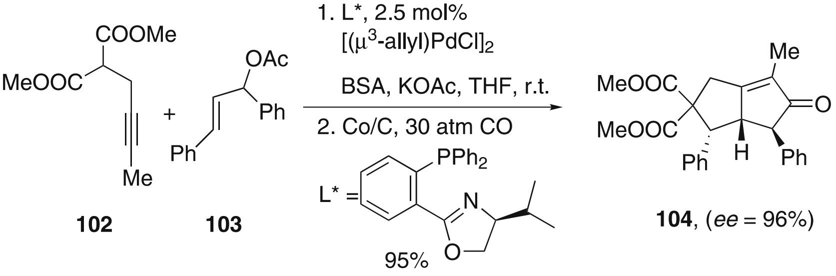
The combination of cobalt with other metals like Pd increases the synthetic utility of this methodology. Thus, a concurrent tandem catalysis reaction of **102** and **103** using first an homogeneous chiral palladium complex, followed by the action of heterogeneous cobalt/C led to high enantioselective synthesis of PK products **104** (Scheme 30) [129].

More recently this group has prepared a combination of palladium and cobalt nanoparticles immobilized on silica (PCNS) to form bicyclic enones after domino allylic alkylation-PKR [130].



99 73-87% **100** **101** (ds = 3:1 to >19:1)

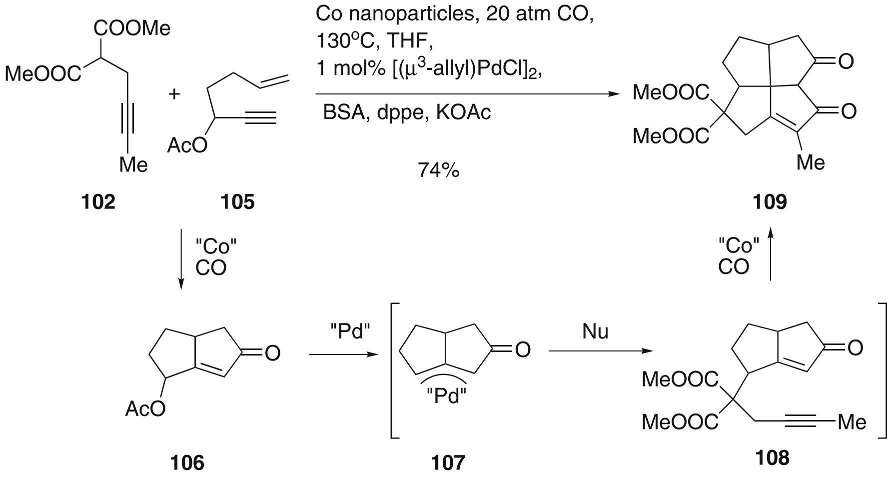
Scheme 29 Tandem rhodium catalyzed allylic alkylation-PKR



102 **103** **104**, (*ee* = 96%)

Scheme 30 Tandem action of chiral Pd(II) and Co/C catalyst for the asymmetric synthesis of cyclopentenones from propargyl malonate and allylic acetates

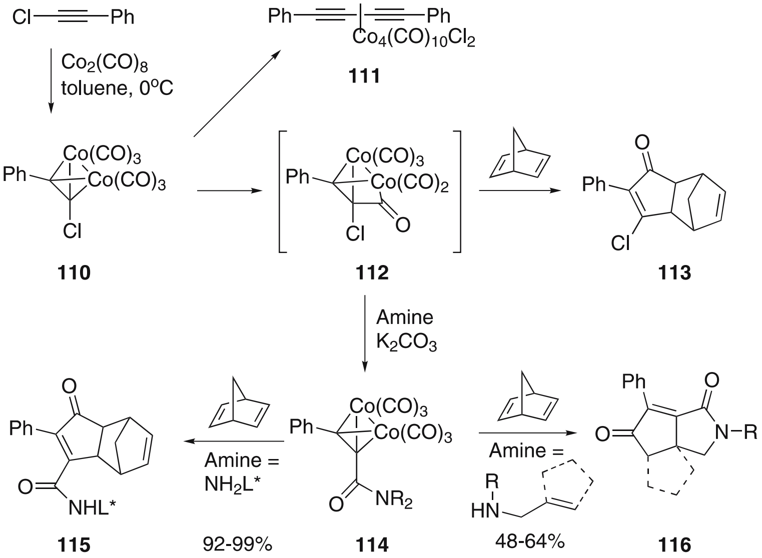
A spectacular application allowed the synthesis of fenestranes by a three-step sequential action of cobalt nanoparticles and a palladium catalyst [131]. The cascade reaction started with a PKR of enyne **105**, accomplished by the cobalt catalyst giving **106**, followed by the formation of allyl-π^3 palladium complex **107** which reacted with a nucleophile derived from diethyl malonate, to give enyne **108**. The final step was a second PKR that gave **109** in good yield. They used cobalt nanoparticles as with Co/charcoal the third step did not take place, apparently due to damage in this catalyst after the allylation step (Scheme 31).



Scheme 31 Three-step one pot synthesis of fenestranes from an enyne and an alkyne

2.4
Aminocarbonylation

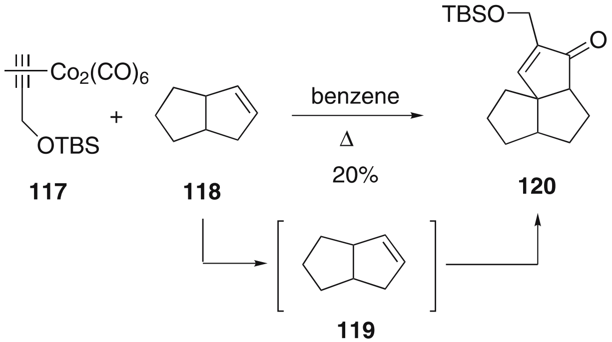
Pericàs group reported an interesting case of a tandem process in which dicobalt hexacarbonyl complexes of haloacetylenes suffered an aminocarbonylation followed by a PKR. They reacted de dicobalt hexacarbonyl complex of 1-chloro-2-phenylacetylene (**110**) and observed its decomposition into two new species. One of them was apparently a dichloro tetracobalt decacarbonyl complex of 1,4-diphenyl-1,3-butadiyne (**111**) while the other was assigned to acyl cobalt complex **112** that was able to cyclize with norbornadiene to give **113**. On the other hand **112** was trapped with different amines and the resulting complexes (**114**) were submitted to PKR with norbornadiene. When they used chiral amines, they obtained non-racemic compounds **115** with high yields, whereas when using allylic amines, the corresponding intramolecular PKR afforded bicyclic amides **116** with moderate to good yields (Scheme 32) [132].



Scheme 32 Tandem aminocarbonylation/PKR of haloacetylenes

2.5
Other Pre-PKR Processes

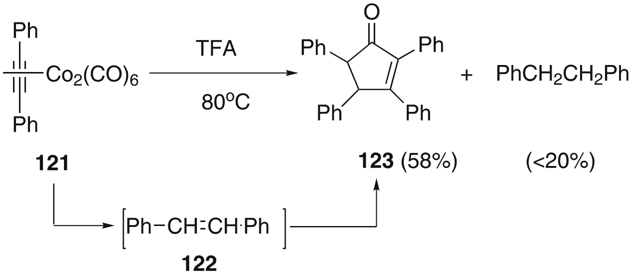
Some double-bond shifts and isomerizations have been observed previous to the PKR. Sometimes 1,6 enynes have reacted partially as 1,7 enynes, or 1,8-enynes have isomerized to 1,7-enynes prior to the PKR [59, 60, 133]. In some intermolecular examples strained alkenes have isomerized totally before the cyclization giving unexpected products. An example, in the synthesis of triquinanes like **120**, depicted in Scheme 33, the starting alkene **118** was isomerized to **119** prior to the reaction with **117** [134, 135].



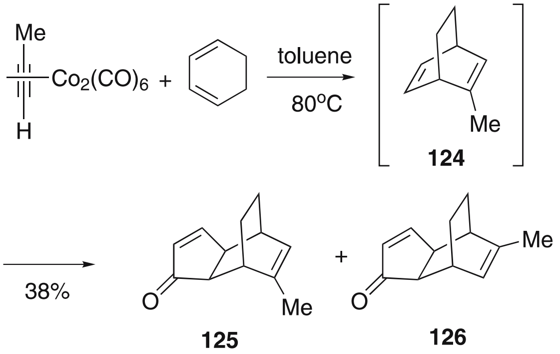
Scheme 33 A pre-PK double bond shift. Synthesis of triquinanes

Other reactions that may occur before the PK are hydrogenolysis, reductions of the alkyne complex and, when using dienes as the alkene part, a Diels–Alder reaction. When hydrogenolysis is observed in enynamides or enynethers, the resulting products usually do not cyclize, so no PK products are obtained [136]. One interesting case of previous reduction of a cobalt-hexacarbonyl complex, shown in Scheme 34, implied that in the presence of TFA, part of complex **121** was reduced to alkene **122** which reacted further with other complex molecules to give the PK product **123** [137].

The dienyl PK-type catalytic reaction, introduced recently by Wender's group, is an interesting variant as it allows low rhodium catalyst loadings and mild conditions both in the intramolecular [138] and the intermolecular version [139]. These authors have optimized the reaction conditions to avoid competitive [4 + 2] cycloadditions that occurred in their preliminary studies. In an early example Pauson described a cascade Diels–Alder-PKR with 1,3-cyclohexadiene and the dicobalt hexacarbonylcomplex of phenylacetylene. The cobalt complex has to be active in the [4 + 2] reaction as this diene does not give Diels–Alder products in similar conditions with usual dienophiles. The resulting adduct **124** undergoes the PKR giving **125–126** mixtures in moderate yield (Scheme 35) [140].



Scheme 34 Partial reduction of the alkyne-cobalt hexacarbonyl complexes under PK conditions in the presence of TFA

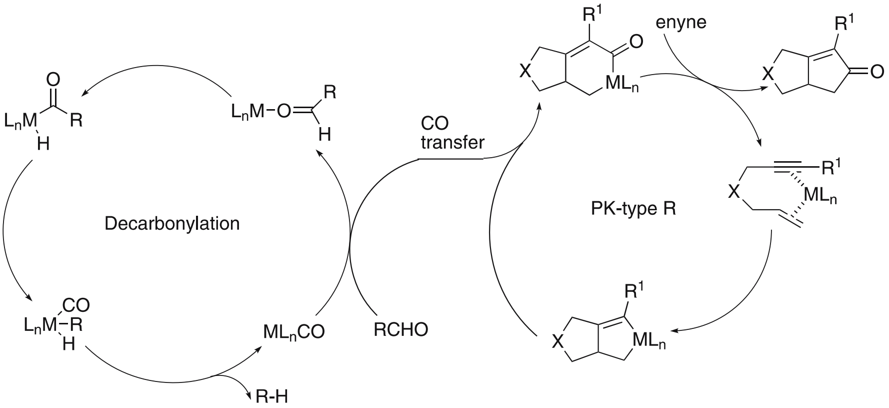


Scheme 35 A Diels–Alder-PKR cascade

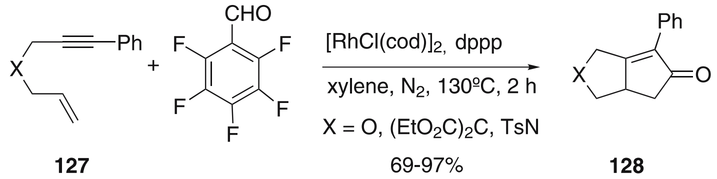
3
Previous Decarbonylations as a Source of CO

The major drawback in the development of efficient catalytic PK protocols is the use of carbon monoxide. Many groups probably refuse to use this reaction in their synthetic plans in order to avoid the manipulation of such a highly toxic gas. Carbonylation reactions without the use of carbon monoxide would make them more desirable and would lead to further advances in those areas. Once the use of rhodium complexes was introduced in catalytic PKR, two independent groups realized these species were known for effecting decarbonylation reactions in aldehydes, which is a way to synthesize metal carbonyls. Thus, aldehydes could be used as a source of CO for the PKR. This elegant approach begins with decarbonylation of an aldehyde and transfer of the CO to the enyne catalyzed by rhodium, ruthenium or iridium complexes under argon atmosphere (Scheme 36).

Morimoto studied several aldehydes and concluded that the best conditions were using two eqs of C_6F_5CHO in xylene, in the presence of $[RhCl(cod)]_2$ (5%) and dppp (11%) at 130 °C under N_2. The conversion of **127** into **128** was high yielding. $[IrCl(cod)]_2$ and $Ru_3(CO)_{12}$ were able to transfer CO from the aldehyde although in lower efficiency (Scheme 37) [141].



Scheme 36 The two catalytic cycles in the decarbonylation-PKR methodology



Scheme 37 PKR with aldehydes as a CO source

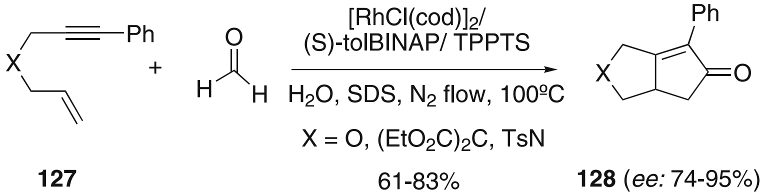
In two recent communications this group has used formaldehyde as the CO source in aqueous media and has introduced chiral ligands in the rhodium complex reaching high yields and enantioselectivities. A hydrophilic phosphine (TPPTS) and a surfactant (SDS) are also added to enable the reaction (Scheme 38) [142, 143].

Shibata reported soon afterwards a solvent-free reaction in which the transferring aldehyde was cinnamaldehyde and the catalyst $[Rh(dppp)_2Cl]_2$.

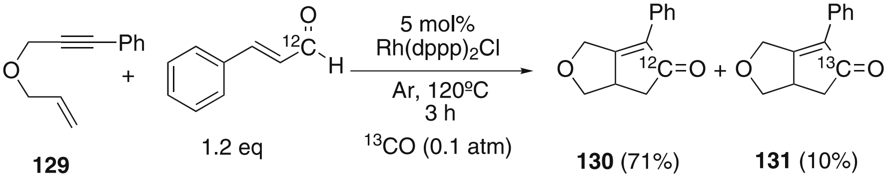
The authors show there is no free CO in the reaction medium that is used to form the PK product, as they perform reactions of **129** in ^{13}CO atmosphere observing very little incorporation of ^{13}C in the final product (**130** : **131** = 7 : 1). The enantiomeric excess reached when using a chiral ligand is higher with this methodology than when using CO atmosphere in the absence of the aldehyde (Scheme 39) [144, 145].

Following their works on immobilized heterobimetallic nanoparticle catalysts, Chung's group has synthesized Ru/Co nanoparticles immobilized in charcoal and shown the ability of this system to catalyze a PKR-type reaction in the presence of pyridylmethyl formiate as a CO source. They used these conditions with intra- and intermolecular reactions and showed that the catalyst can be reused without loss of catalytic activity (Scheme 40) [146].

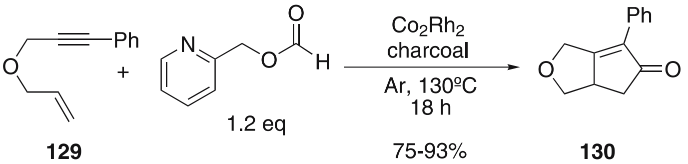
In addition, the same authors showed that α,β-unsaturated aldehydes **132** could act both as CO and alkene source and give the PK products **134** upon reaction with different alkynes (**133**) (Scheme 41). As part of their study, they performed a cross reaction of cinnamaldehyde and a substituted styrene with phenylacetylene, isolating two PK products coming from both alkenes. This is a proof for a decarbonylative-[2 + 2 + 1] reaction pathway [147].



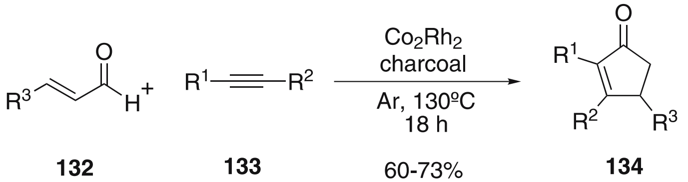
Scheme 38 Aqueous asymmetric PKR with formaldehyde as CO source



Scheme 39 Cinnamaldehyde as a CO source. Studies on the CO transference from the aldehyde to the cyclopentenone



Scheme 40 Ru/Co nanoparticles as catalysts for the PKR in the presence of pyridylmethyl formiate



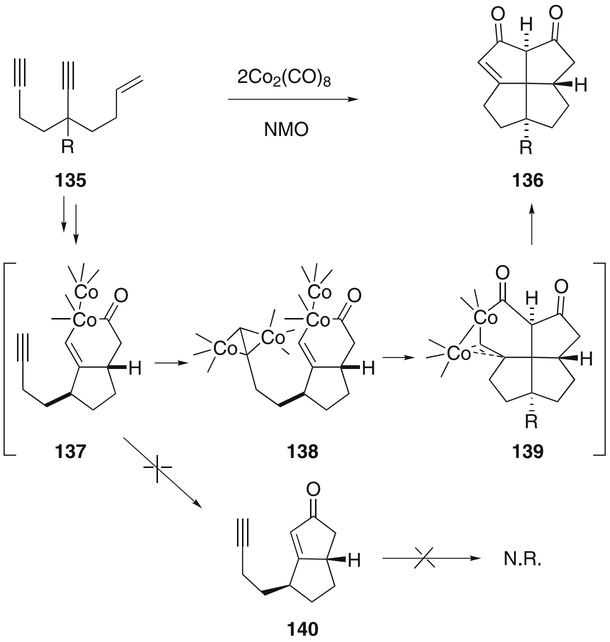
Scheme 41 An olefinic aldehyde as an olefin and CO source

4
Tandem Carbocyclizations Involving [2 + 2 + 1] Reactions

Several groups have developed the combination two or more PKR or PK-type reactions in the same reaction step. The multiplication of the synthetic power of this transformation has found immediate application for the synthesis of natural [5.5.5.5] systems called fenestranes. Starting materials have been enediynes that give two [2 + 2 + 1] cycloadditions. The extension of the reaction to triynes has led to interesting tandem processes that may include [2 + 2 + 2] cyclizations. Other cycloadditions like the Diels–Alder have also been combined with the PK.

4.1
Tandem PKRs

Keese envisioned the use of a tandem PKR for the synthesis of fenestranes. The second cycloaddition was in principle problematic as it involved an alkene conjugated with a ketone. They were surprised when they observed the direct formation of the tetracyclic unit **136** from the endiyne **135** although with low yield [148]. Further studies from this group led to a mechanistic proposal that explained this result. It was clear from the fact that compound **140** failed to react, that the second PKR had to start from an intermediate metallacycle rather than from the uncomplexed final cyclopentenone. Thus, cobalt complex **137** would lead to **138** were both metal clusters would interact giving intermediate **139** which would evolve in the usual way to the final product (Scheme 42) [149]. These systems have been obtained later by Chung's group using cobalt nanoparticles as commented above (Sect. 2.4) [131].

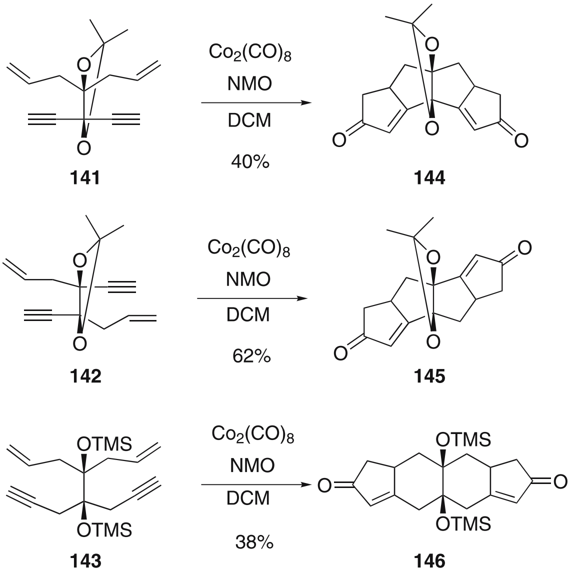


Scheme 42 Direct synthesis of [5.5.5.5]fenestrenedione via tandem PKR

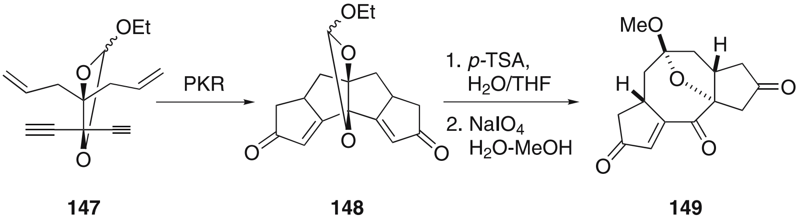
Cook has developed in recent years a tandem PKR towards the synthesis of pentalenes, that is, linear [5.5.5.5] systems. Their first studies used suitable diendiynes **141–143** that gave the corresponding tetracyclic *bis*-cyclopentenones. These were described as precursors of dicyclopenta[*a*, *d*] (**144**) and [*a*, *e*]pentalenes (**145**). The same methodology allowed the synthesis of [5.6.6.5] systems (**146**) where the central decaline system was *cis* fused (Scheme 43) [150–152]. This group succeeded in tuning up efficient photochemical catalytic conditions for these reactions [153].

As depicted in Scheme 44 some further transformations of the tetracycles such as **148** have allowed the synthesis of tryciclic cyclooctenes (**149**), present in many sesquiterpenes. For these recent studies they have used catalytic conditions for the PKR of diendiyne **147** mediated by Rh, Ir or Co complexes [154].

Impressive examples of allenic tandem-PKR depicted in Scheme 45 are the last contribution from this group. Dicyclopenta[*a*, *e*]pentalenes **152** were obtained from intermediates **151** which were synthesized using a molybdenum hexacarbonyl mediated tandem reaction of diallenediynes **150** as the key step [155–157]. An interesting unexpected product (**153**) was obtained in some reaction conditions, which included a four-membered ring. The authors showed this ring was not formed by the action of $Mo(CO)_6$ as they observed the formation of cyclobutane **154** by heating the starting allene in the ab-



Scheme 43 Tandem PKR for the construction of tetracycles

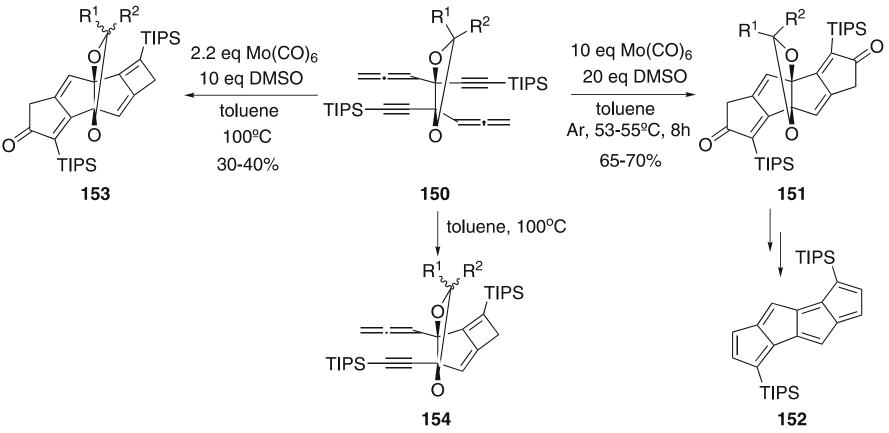


Conditions:
(a) $[Ir(cod)Cl]_2$, 20%, PPh_3, 40%, CO, 1 atm, toluene, Δ. Yield: 76%
(b) $[RhCl(CO)dppp]_2$, 20%, CO, 1 atm, MeCN, Δ. Yield: 68%
(c) $Co_2(CO)_8$, 25%, CO, 1 atm, DME, Δ. Yield: 65%
(in mixtures of isomers)

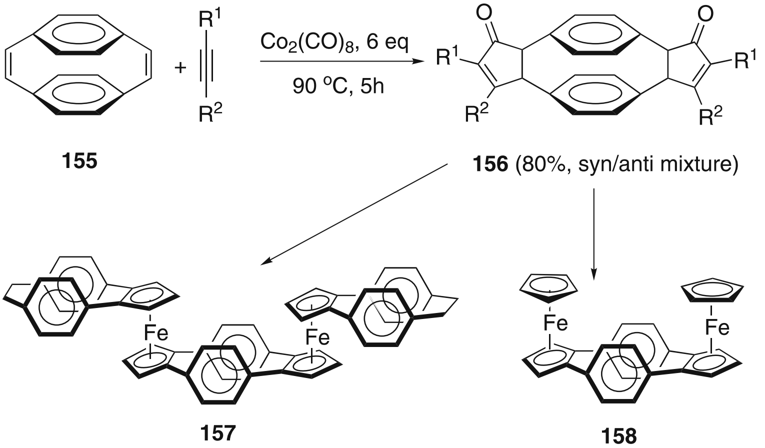
Scheme 44 Tandem PKR in the synthesis of dicyclopenta[*a*,*d*]cyclooctenes

sence of catalyst. They concluded that an unusual [2 + 2] thermal cyclization had occurred, which was possible due to the rigid geometry of the starting material.

Twofold inter- and intramolecular PKRs have found interesting applications in synthesis of *ansa*-zirconocenes. An early example illustrated the use of this approach for the synthesis of cyclopentadiene anellated[2,2]paracyclophanes **157–158**. The reaction of several paracyclophanedienes (**155**) with alkynes gave the corresponding twofold cycloaddition products **156**, which were transformed into cyclopentadienyl anions orthogonally attached to the bridges of the paracyclophane (Scheme 46) [158].



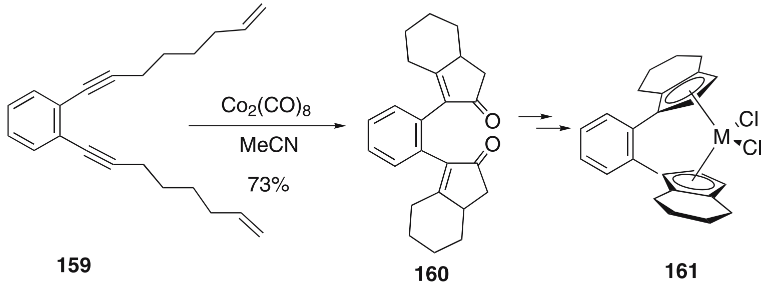
Scheme 45 The synthesis of a dicyclopenta[*a*,*e*]pentalene via molybdenum-mediated tandem allenic PKR



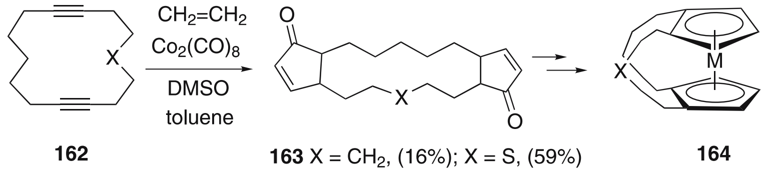
Scheme 46 Twofold intermolecular PKR for the synthesis of cyclopentadiene anellated [2.2]paracyclophanes

On the other hand, most studies on twofold PKRs deal with the use of acyclic and cyclic diynes for the synthesis of phenyl or alkyl bridged *ansa*-zirconocenes such as **161**. Scheme 47 shows an example of the reaction of a di-endiyne (**159**) that gives a twofold PKR, forming compound **160** [159, 160].

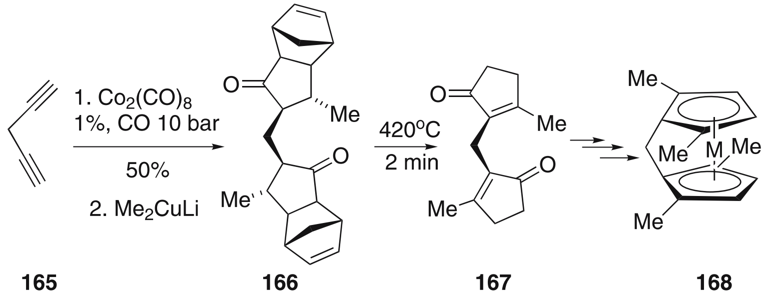
Gleiter has studied the reaction of diynes with alkenes as an intermediate step in the synthesis of *ansa*-metallocenes **164**. They have reacted acyclic diynes with ethylene [161] and cyclic diynes **162** in supercritical ethylene [162] giving tricyclic diketones **163** in low to moderate yields. The presence of coordinating heteroatoms in the link increased the reaction yields (Scheme 48) [163].



Scheme 47 Double PKR for the synthesis of *bis*-cyclopentadienes



Scheme 48 Twofold PKR of cyclic diynes in supercritical ethylene



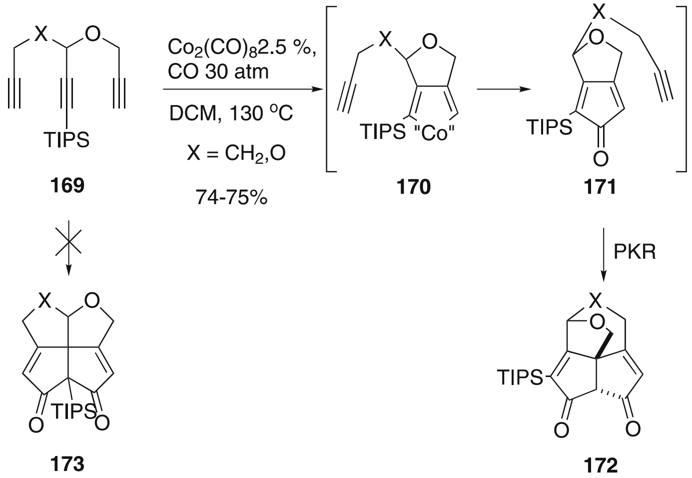
Scheme 49 Catalytic double PKR followed by a retro-Diels–Alder reaction for the synthesis of *ansa*-zirconocenes

Lee and Chung reported a different approach that avoided using ethylene for the synthesis of the same type of alkyl bridged *ansa*-zirconocenes **168.** They reacted diyne **165** with norbornadiene giving a tricyclic compound which was functionalized with Me_2CuLi to yield **166.** When **166** was heated in a quartz tube at 420 °C, **167** was formed by means of a retro-Diels–Alder reaction followed by double bond isomerization (Scheme 49) [164].

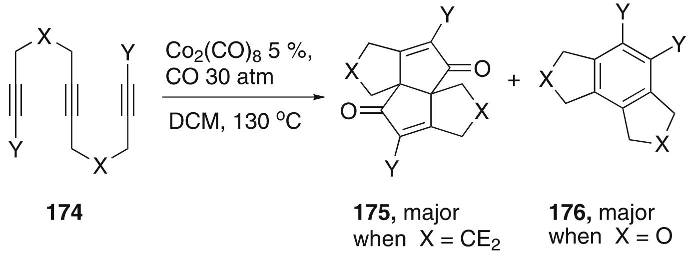
4.2
Tandem Cycloadditions of Di- and Triynes

Cobalt catalyzed double [2 + 2 + 1] cycloaddition reactions of branched triynes **169** have led to novel [5.5.5.6] tetracyclic dienone systems **172,** instead of the expected [5.5.5.5] systems **173.** These substrates underwent first a [2 + 2 + 1] cycloaddition of two triple bonds which the authors claim to go through cobaltacycle intermediate **170**. This reaction gives cyclopentadienone **171**. Due to the steric effect of the TIPS, the subsequent PKR occurred between the unsubstituted double bond an the alkyne in the pending chain, giving the final polycycles (Scheme 50) [165].

In previous works this group had observed a competition between the PKR and a [2 + 2 + 2] cyclization in the second reaction step of three triple bonds. Thus, when reacting linear triynes **174** under catalytic, high CO pressure, cobalt mediated PKR conditions, they obtained mixtures of products **175** coming from two [2 + 2 + 1] cycloadditions, and **176** from a [2 + 2 + 1]/[2 + 2 + 2] tandem reaction. When the triple bonds were ether linked, the latter was the favored reaction, while with substrates lacking oxygen atoms, the iterative PKRs was the major pathway (Scheme 51) [166]. When the reaction was performed intramolecularly between a diyne and an alkyne, the only reaction products were the result of a [2 + 2 + 1]/[2 + 2 + 2] tandem cycloaddition [167, 168].



Scheme 50 Cyclization of triynes to tetracycles catalyzed by cobalt



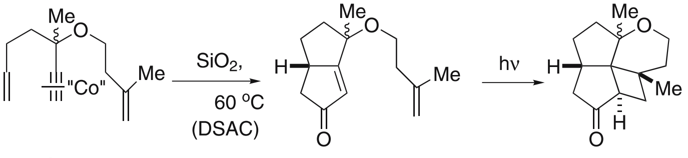
Scheme 51 Tandem [2 + 2 + 1]/[2 + 2 + 2] cycloaddition of linear triynes

4.3
Other Cycloadditions in Combination with the PKR

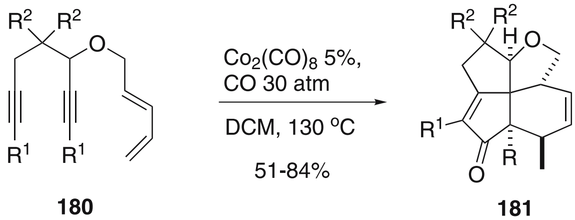
Few examples from the literature show the viability of performing a 2 + 2, 4 + 2 or 5 + 1 cycloaddition combined with the PKR. An early contribution by Smit showed a photochemical 2 + 2 cyclization performed on PK product **178** which was obtained by selective reaction of dienyne **177**. It is not clear from the work if product **179** is obtained in a *one pot* fashion or stepwise (Scheme 52) [169].

Chung has used a combined PK/Diels–Alder cascade reaction to synthesize [5.5.5.6] fenestranes and triquinanes. The first products (**181**) were obtained in high yield from diendiynes **180** upon reaction with dicobalt octacarbonyl (5%) under 30 atm of CO at 130 °C. The authors think it is more probable that the Diels–Alder reaction occurs after the PKR instead that the diene reacts first with the closer triple bond to form a 1,4-cyclohexadiene that would undergo the PKR (Scheme 53) [170].

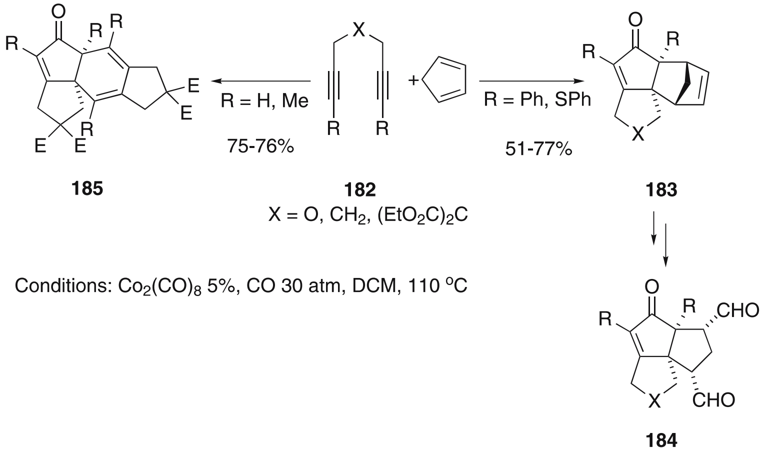
This group has used the same reaction conditions with diynes **182** and cyclic dienes like cyclopentadiene to form tetracyclic enone **183** which was transformed into triquinane **184** by means of an oxidative cleavage of the double bond. When phenyl groups at the alkyne terminus were substituted by H or Me they observed a competitive [2 + 2 + 1]/[2 + 2 + 2] process, with the participation of two diyne molecules giving compounds **185** (Scheme 54) [171]. No mechanistic hypothesis appears in this work but the formation of a norbornene derivative by means of the Diels–Alder reaction of cyclopentadiene and the diyne that would react with the other triple bond of the diyne seems attractive in this case.



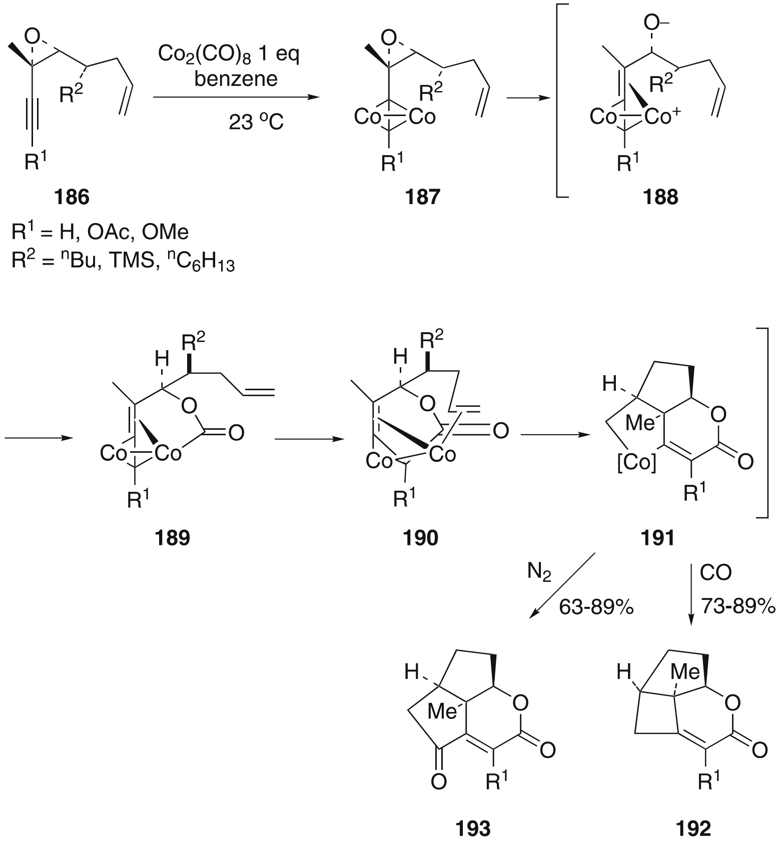
Scheme 52 Combination of a PKR with a [2 + 2] photochemical cycloaddition



Scheme 53 Tandem [2 + 2 + 1]/[4 + 2] cycloaddition of diendiynes for the *one pot* synthesis of fenestranes



Scheme 54 Cycloaddition of diynes with dienes in the synthesis of triquinanes. Tandem [2 + 2 + 1]/[4 + 2] cycloadditions



Scheme 55 Cobalt mediated tandem [5 + 1]/[2 + 2 + 1]-cycloaddition reaction

Liu has reported recently a new $Co_2(CO)_8$-mediated tandem [5 + 1]/[2 + 2 + 1]-cycloaddition reaction that gives tricyclic δ-lactones from *cis*-epoxy enynes **186**. This process possibly involves an initial opening of the epoxide in the cobalt hexacarbonyl complex **187** to from the complexed allene **189** via **188**. Further coordination of the tethered olefin leads to **190** and further oxidative cyclization gives cobaltacycle **191** which inserts CO leading to the final compound **192**. When performing the reaction under N_2, **191** suffers a reductive elimination to give cyclobutane **193** (Scheme 55) [172].

5

Reactions Occurring after the Pauson–Khand Process

Several reactions can occur after the PKR. We will comment in detail those that have synthetic utility, either because they were planned or because they have been optimized after a first unexpected finding. Those results involving minor by-products or single cases among a series, will be only mentioned. The review on unexpected results in the PKR by Krafft is a good option for obtaining more information on these latter cases [2].

5.1

Traceless Tethers

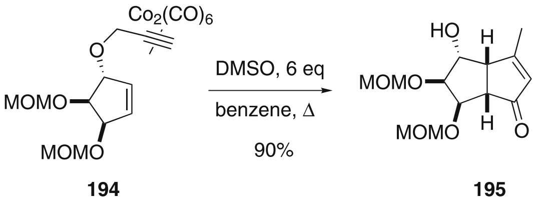
One group of interesting new substrates recently introduced for the PKR are those possessing traceless tethers. These compounds have the advantage of using the intramolecular version of the PKR, which is not limited to strained olefins and does not have regioselection problems. In a second step, which sometimes occurs in a domino fashion, they give a monocyclic compound upon cleavage of the tether.

The first tethers contained oxygen, and were cleaved during PKRs performed under DSAC conditions. These results appeared when heating the reactions and led to monocyclic cyclopentenones in moderate yields [173, 174]. Recently this approach has found synthetic utility for the construction of a 3-methylcyclopentenone (**195**) by means of a PKR and reductive cleavage of compound **194** (Scheme 56) [175].

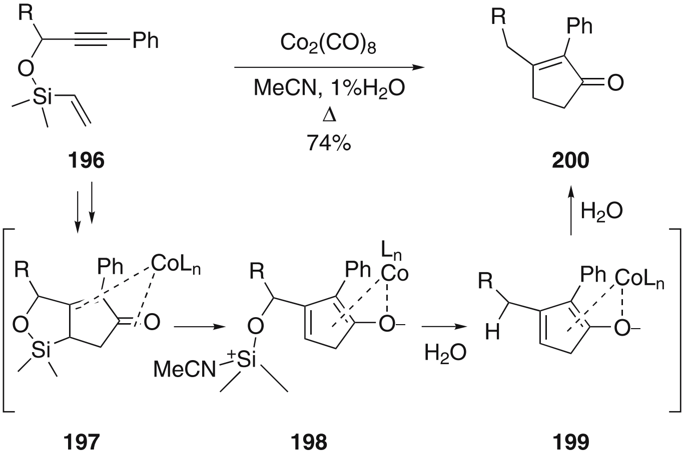
Pericàs, reported some examples in which a sulfur atom was reductively eliminated after the PKR in a stepwise manner [176].

Several recent reports use silicon as a traceless tether. Pagenkopf has succeeded in obtaining monocyclic cyclopentenones in one step, starting from a vinylsilane tethered to a propargyloxy chain (**196**). When they used longer tethers, they observed a cycloisomerization of the silane instead of the PK product. The mechanism of the reductive elimination of the silicon tether was investigated by this group. The cleavage starts from a species in which cobalt is still coordinated to the enone (**197**) and implies the participation of water in the process. When using dry solvents, cleavage of the silicon tether did not occur. Thus, wet acetonitrile was used. Simple deuterium labeling studies showed that the two new enone hydrogens came from the water present in the solvent. The reaction goes trough a cobalt dienolate (**198**) which suffers several [1, 5]-H sigmatropic rearrangements (**199**) that explain the incorporation of deuterium from the solvent at different positions of the final cyclopentenone (**200**) (Scheme 57) [177, 178].

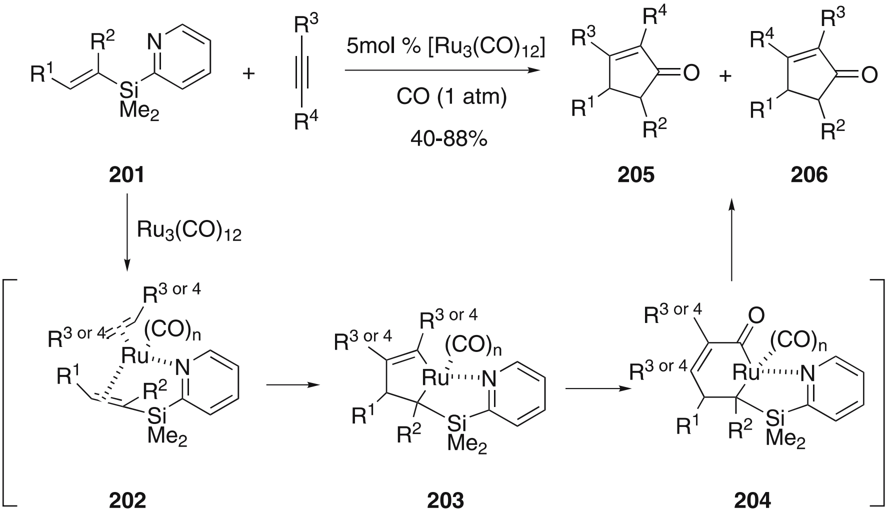
In the field of PK-type reactions, Itami and Yoshida have recently used ruthenium complexes to expand the scope of the intermolecular PKR. The strategy consists of using olefins **201** bearing a pyridylsilyl group which is readily removed after the reaction. These *α* or *β* substituted vinylsilanes are easily obtained from alkynes. The pyridyl group directs the PKR by a possible coordination of the nitrogen with the metal (**202–204**), which accelerates the process and gives complete regioselectivity. The directing group is eliminated in the reaction, giving rise directly to 4 and/or 5 substituted cyclopentenones **205–206**. This avoids the use of ethylene or strained olefins in the intermolecular PKR and is a way to solve the problem of the regioselectivity with unsymmetrical olefins (Scheme 58) [179, 180].



Scheme 56 Ether cleavage combined with a PKR



Scheme 57 The silicon tethered reductive PKR. Mechanistic considerations



Scheme 58 An expansion of the scope of the intermolecular PKR with the use of a pyridylsilyl group

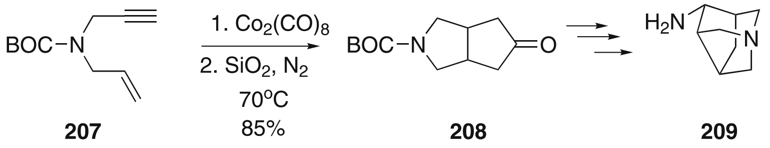
5.2
Reductive PKR

The direct synthesis of cyclopentanones from enynes under PKR conditions has been reported since early times, generally as a side reaction. This is a tandem process in which the cyclopentenone arising from the PKR is reduced. The first reports on the formation of reduced products described PKR carried out under severe conditions (high temperatures, DSAC etc.), and the reduced products were obtained along the usual cyclopentenones [181].

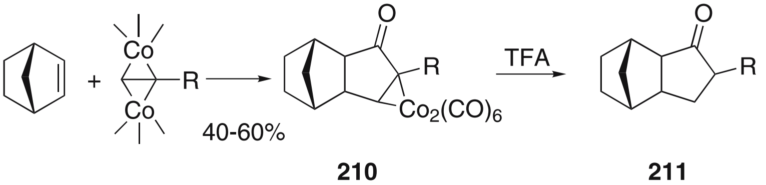
This precedents prompted several groups to develop reaction protocols that lead exclusively to the reduced products (the reductive PKR), in order to use them in synthesis. Thus, Becker obtained diazabicyclooctanones like **208** from amines (**207**) as the only reaction product when they used DSAC conditions under an inert atmosphere. The nitrogen atmosphere was essential as in air they obtained mixtures of the cyclopentanones and the cyclopentenones. This group has used this methodology for the synthesis of azaadamantanes like **209** as part of the structure of certain antagonists (Scheme 59) [182–184].

Addition of TFA to the reaction favors the formation of reduced products. A series of alkynes produced cyclopentanones as the major product when reacted with norbornene, $Co_2(CO)_8$ and TFA. The authors think TFA reacts with the cobalt complex **210**, prior to the reductive elimination that gives the final product **211** (Scheme 60) [185].

Krafft has studied modifications of the reaction conditions that can lead to variations in the result of the intramolecular PKR. Thus, they describe re-



Scheme 59 Reductive DSAC conditions

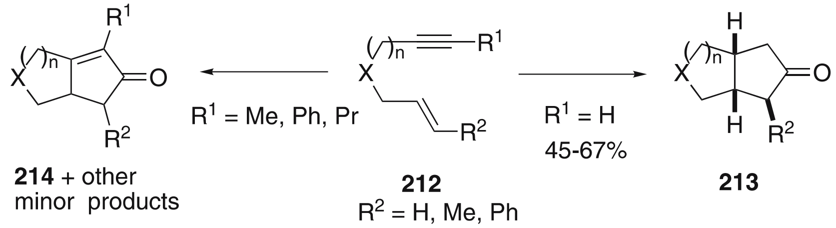


Scheme 60 The role of TFA in the reductive PKR

action conditions that allow the synthesis of cyclopentanones with certain enynes (**212**). The best results are obtained with $Co_4(CO)_{12}$ in alcohols under H_2 or N_2. The reduction of the cyclopentenone is though to be mediated by a cobalt hydride generated from residual cobalt species and takes place only with terminal alkynes. The role of the alcohol is to improve the generation of such hydrides. The hydrogen incorporated to **213** comes from the alcohol, as observed from deuterium labeling studies and not from the H_2 atmosphere, that, nevertheless, seem to have a favorable effect on yields. Non-terminal alkynes give cyclopentenones **214** in these conditions (Scheme 61) [186].

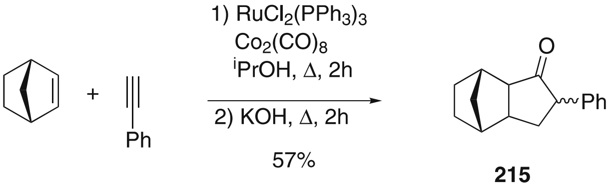
Recently, a combination of two metals has been used to perform a domino PKR-transfer hydrogenation. After a detailed study on the reaction conditions, the authors described that a mixture of $Co_2(CO)_8$ (1 eq), $RuCl_2(PPh_3)_3$ (0,1 eq) in ^{i}Pr – OH and addition of 1 eq of KOH after 2 hours of reaction were the best conditions to obtain almost exclusively the reduced PK product **215** (Scheme 62) [187].

A one-pot PKR-hydrogenation sequence was the key step in a non-racemic synthesis of (–)-dendrobine (**222**) published recently. Starting from (+)-*trans*-



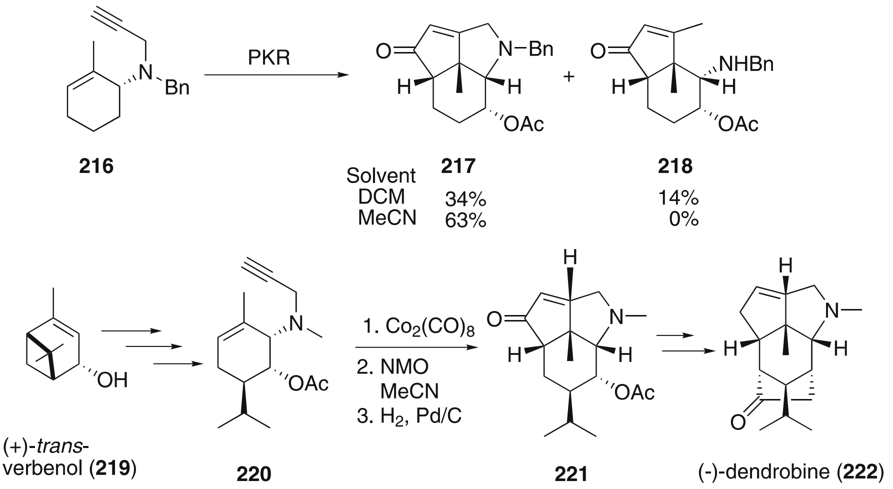
Conditions: $Co_4(CO)_{12}$, 2-propanol, H_2, 70°C

Scheme 61 The reductive PKR. Conditions and substrate dependence



Scheme 62 A reductive PKR carried out by a combination of two metals

verbenol (**219**), and using a cascade process in which a carbamoyl radical was involved, they prepared a suitable enyne (**220**). In order to adjust the conditions for the PKR of **220** they prepared compound **216** and submitted it to different reaction conditions with $Co_2(CO)_8$ using NMO as promoter. The authors observed partial hydrogenolysis of the C – N bond when using DCM as solvent, isolating **218** jointly with the PK product **217**. In acetonitrile, **218** was not formed. Reaction of **220** in the latter conditions gave an unstable cyclopentenone that was directly hydrogenated affording tricyclic compound **221** in 51% yield from **220** (Scheme 63) [188].



Solvent	217	218
DCM	34%	14%
MeCN	63%	0%

Scheme 63 The synthesis of (–)-dendrobine using a PKR/hydrogenation combination as the key step. Partial hydrogenolysis was observed when optimizing reaction conditions

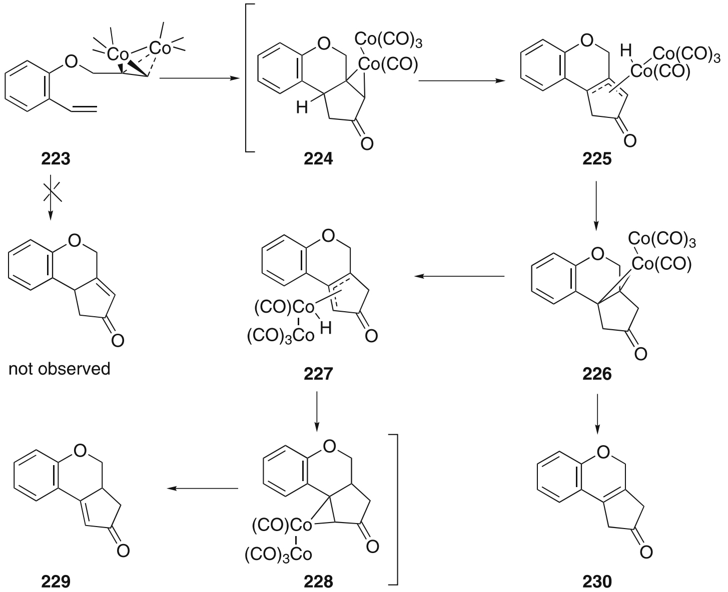
5.3
Isomerizations and Migration of Double Bonds

Migration or isomerizations of double bonds and epimerizations are frequently observed in PKRs. Several groups have studied these processes and believe they take place during the PKR or with participation of the metal species present in the reaction. We have reported several unexpected results that involve the shift of the emerging double bond. Thus, in the intramolecular reaction of styrene substrates **223**, we obtained the isomerized and more stable product **229**, and we proposed the participation of allyl cobalt complexes (**225** and **227**) arising from the intermediates of the reaction (**224**, **226**, **228**). We also isolated **230**, an intermediate in the isomerization process (Scheme 64) [28].

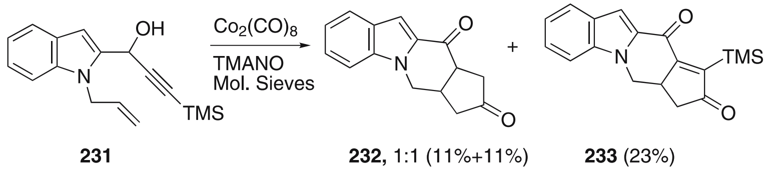
Similarly, the reaction of enynoindoles **231** bearing an unprotected hydroxy group led to mixtures of saturated diketones **232**, coming from the desilylation and double-bond migration. In addition we obtained oxidized product **233**, as a result of the oxidation of the alcohol in the PK adduct (Scheme 65) [189].

Other groups observed double-bond shifts in intermolecular reactions. As an example, in a dimethylamino directed reaction of **234** a partial double bond shift was observed, isolating mixtures of the expected product **235** and the isomer **236** (Scheme 66) [190].

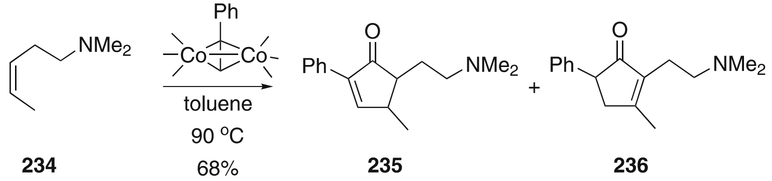
With regard to isomerizations of double bonds, sulfinyl enynes gave unexpected results when submitted to PKR. These chiral substrates were thought to give high asymmetric inductions due to the proximity of the chiral sulfur atoms to the reaction centers. Surprisingly, both *cis* and *trans tert*-butyl vinyl sulfoxides (**237**–**238**) were transformed into the same PK diastereoisomer **239** with high ee and moderate yields (Scheme 67) [103, 104].



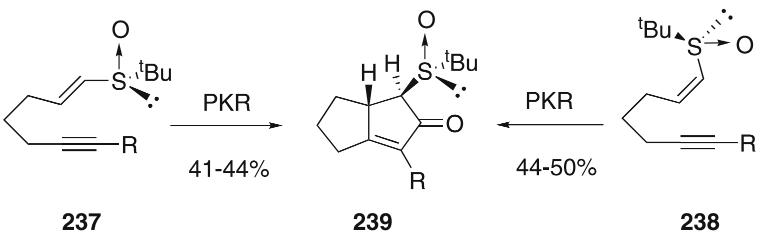
Scheme 64 Double bond shift in the PK reaction of styrenes. Mechanistic explanation



Scheme 65 Unexpected products in the PKR of indole derivatives. Double bond shifts and oxidation post-PK reactions



Scheme 66 A partial double bond shift in an intermolecular directed PKR



Conditions: 1. $Co_2(CO)_8$ 2. NMO, DCM

Scheme 67 An example of double bond isomerization during a PKR. Both *cis* and *trans* isomers gave the same reaction product

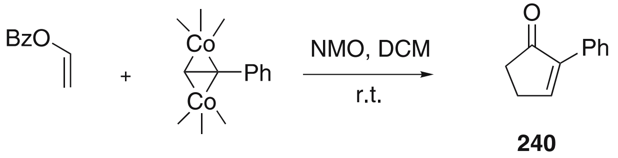
5.4
Other Post-PK Reactions (Hydrogenolysis, Oxidation, Michael, Retro-Diels–Alder)

Cleavage of C – O, C – N and other C-heteroatom bonds is a frequent side reaction observed in many PKR specially those performed under severe conditions or DSAC conditions. We have shown before how, in the synthesis of dendrobine, this reaction was observed and was strongly dependent on the solvent used. The cleavage of ether links probably happens in most cases after the PKR. It has been observed in bonds included in the link between the alkyne and the alkene and in other tethers. If the cleavage happens prior to the cyclization, the PKR becomes intermolecular and in most cases does not take place. Section 5.1 shows the synthetic utility of programmed post-cleavages in enynes bearing traceless tethers. We will show here other cases in which the hydrogenolysis of carbon–heteroatom bonds is the major or only reaction observed and does not occur in bonds included in the enyne skeleton.

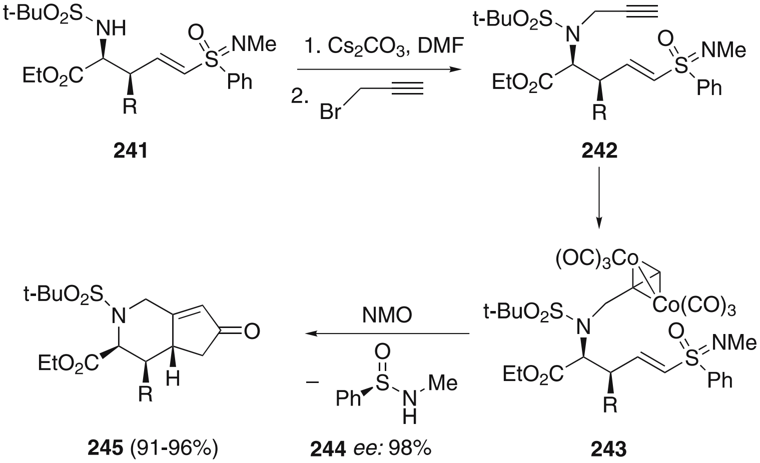
Vinyl esters and vinylethers were studied as substrates for the intermolecular PKR by Pauson's group and led to cyclopentenones **240** lacking the ether which was cleaved during the process (Scheme 68) [191].

Recently Gais has described an asymmetric synthesis of fused bicyclic amino acids having a hexahydro-cyclopenta[*c*]pyridine skeleton (**245**). The key steps of the synthesis were a highly selective allylation of a *N*-*tert*-butylsulfonyl imino ester with bis(allylsulfoximine)titanium complexes and a highly diastereoselective Pauson–Khand cycloaddition. They constructed sulfonimidoyl-substituted γ,δ-unsaturated α-amino acid esters (**241**) and introduced a propargyl group at the nitrogen (**242**). The cyclization of the corresponding cobalt complexes **243** was accompanied by a reductive cleavage of the sulfoximine group of the primary cyclization product. One interesting fact in this reaction was that the removal of the sulfoximine group proceeded with inversion of the configuration at the *S*-atom giving *N*-methylphenylsulfinamide (**244**) with > 97% ee (Scheme 69) [192].

The presence of halogens in norbornene-derived systems is a good way to control the regiochemistry of the PKR with alkynes. This has been observed with 7-oxa- and 7-azanorbornenes **246** and **249**. Thus, the carbonyl is bonded with the olefinic carbon that bore the halogen, which is eliminated in the pro-



Scheme 68 Ether cleavage in an intermolecular PKR



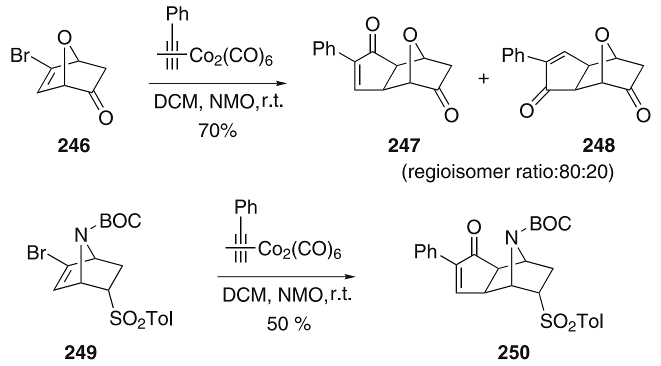
Scheme 69 Synthesis of bicyclic aminoacids via PKR with removal of a sulfoximine group

cess (products **247** and **250**). The reaction of **246** was not totally regioselective and the minor isomer **248** was detected. In both cases no traces of halogenated products appeared in the reaction mixtures (Scheme 70) [193, 194].

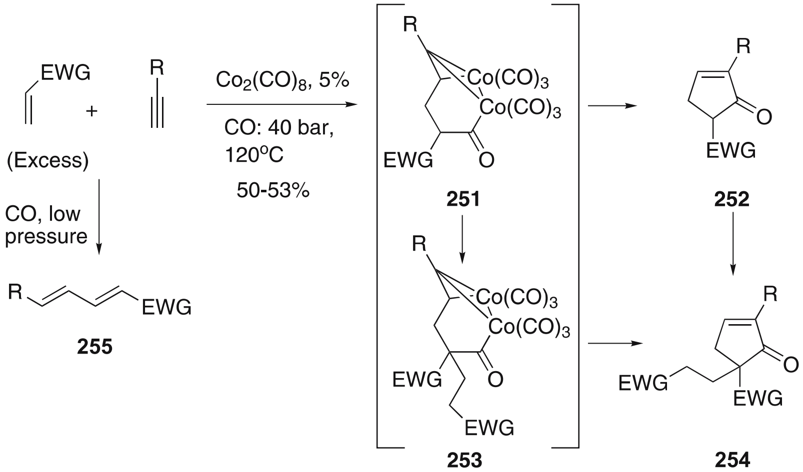
Other post-PKR processes that may happen are oxidation reactions in those cases in which final PK products may liberate part of their strain by adding water or epoxidizing the emerging double bond [195, 196]. These results appear under oxidative reaction conditions (using *N*-oxides as promoters), as in the synthesis of medium sized rings from certain aromatic enynes, where small amounts of epoxides were obtained [28].

There is only one early precedent on coupling of the PKR with a Michael-type reaction. When performing a catalytic high CO pressurized cobalt mediated reaction of alkynes with excess of olefins bearing EWGs, the authors obtained as the major product cyclopentenone **254**, which aroused from a domino PKR-Michael-type reaction. The process was regioselective both with respect to the alkene and the alkyne. The authors do not ascertain weather the Michael reaction occurs on the cobaltacycle **251** forming complex **253** or on the cyclopentenone **252**. The use of high CO pressures was essential in this case to avoid the β-hydrogen elimination, the typical competitive side reaction with this type of alkenes that gives **255** (Scheme 71) [197].

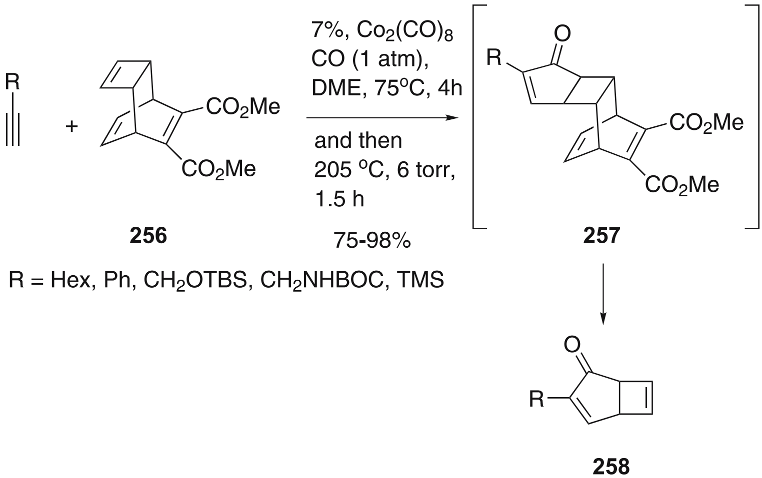
Finally, one recent report has succeeded in using a cyclobutadiene surrogate as the olefin partner in an intermolecular PKR. Cyclobutadiene is a very attractive olefin for an intermolecular PKR as it would lead to bicyclic products that cannot be obtained with the intramolecular reaction. Unfortunately it is too unstable to handle. Gibson has used cyclobutene surrogate **256**, obtained from cyclooctatetraene and dimethyl acetylenedicarboxylate, as cyclobutene equivalent in catalytic PKR with alkynes. After the cycloaddition, the resulting product **257**, that could be isolated, was submitted to thermolysis at high temperature, inducing a retro-Diels–Alder process that gave the bicyclic ketones **258** in high yields (Scheme 72) [198].



Scheme 70 Intermolecular PKR with halonorbornene derivatives. Cleavage of the C – Br bonds



Scheme 71 Tandem PKR-Michael type reaction



Scheme 72 A cyclobutadiene surrogate for the PKR. Tandem [2 + 2 + 1]/retro Diels–Alder reaction

6
Conclusions

Few organic transformations add as much molecular complexity in one step as the Pauson–Khand reaction. This reaction is one of the best examples of how organometallic chemistry is useful in modern organic synthesis, and can serve as a key tool for the synthesis of natural products, in this case those possessing cyclopentane units. The limited scope, low yields and lack of efficient catalytic procedures were serious drawbacks in the past that have been overcome in recent years with the special aid of newly developed PK-type reactions. Still, the intermolecular version is quite limited, as unstrained olefins scarcely react, although the use of traceless tethers or directing groups has circumvented this problem in certain cases. On the other hand the wide variety of catalytic protocols available generally give good results only with favorable substrates. This mature state of the art has prompted many groups to step ahead and design combined synthetic processes that increase even more the synthetic power of this reaction. We have organized these results in this chapter. Much of the work commented here has aroused unexpected results. In this sense we encourage researchers to be especially aware of strange results that can turn out to be important findings. There are many secondary reaction pathways that can appear depending on the substrates or reaction conditions. Other results included herein were planned. In particular multicomponent catalytic reactions are the most promising areas of development of this chemistry. We get closer to biosynthesis when we succeed in making several reactions in one synthetic operation, making different catalyst to work successively inside the same flask, or that the same species catalyses several reactions one after another. In this sense the most exciting future will deal with such tandem catalytic transformations, which meet perfectly the atom economy principle.

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