



Review

Transition metal-mediated routes to cyclopentenones

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Abstract

Cyclopentenones are not only key building blocks for organic synthesis, but many possess interesting biological properties in their own right. This review begins with an overview of the biological importance of cyclopentenones and a summary of the main classical routes to cyclopentenones. A detailed account of recent advances in transition metal-mediated approaches to cyclopentenones follows. The aim of the review is to draw attention to transition metal-mediated approaches to cyclopentenones that are starting to be applied in organic synthesis, and to highlight promising cyclopentenone-forming reactions that have not yet realised their full potential in a synthetic context.

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1. Introduction

The cyclopentenone ring structure is present in a wide array of natural products and interesting drug targets. Furthermore, the cyclopentenone ring structure is a very useful building block for the synthesis of other biologically active compounds composed of cyclopentane units, due to the versatility of the α,β -unsaturated carbonyl functionality. Although numerous methods already exist for the synthesis of substituted cyclopentenones, the quest for new and more efficient strategies, which increase their accessibility, is the focus of intensive synthetic efforts [1].

2. Natural product targets

For some time, prostaglandins (PGs) have attracted considerable attention, as they play an important role in the human body, controlling a wide variety of physiological responses [2]. More recently, studies on the biological activities of the so-called ‘cyclopentenone PGs’ have revealed that these compounds have the potential to become very important in a therapeutic context. Indeed recent reviews on the subject reflect the explosion of interest from biological and chemical research laboratories working in this area [3].

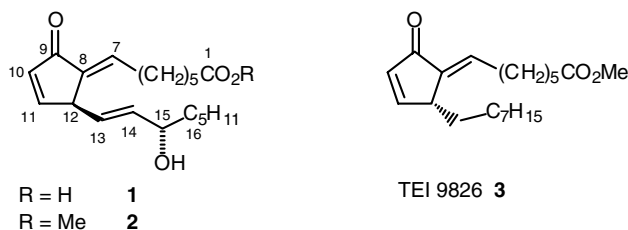
The α,β -unsaturated carbonyl group is clearly key to many of the biological actions of the cyclopentenone PGs because other PGs, devoid of this functionality, do not possess such a comparable range of biological activities. This has been confirmed in model studies, where cyclopenten-2-one has shown significant biological activity, whilst related compounds, cyclopentanone and cyclopentene, were unreactive [4].

Cyclopentenone PGs, such as Δ^7 -PG-A₁ (**1**) and its methyl ester (**2**), display significant anti-tumour activity [5]. It appears that the Δ^7 unsaturation is essential for the high anti-neoplastic activity, which may provide new opportunities

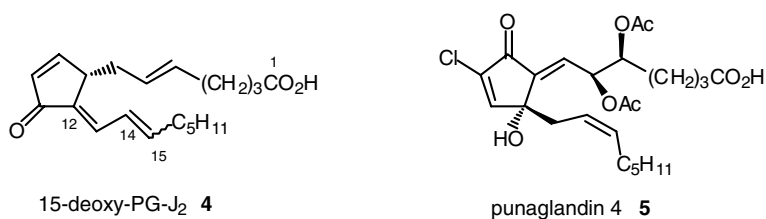
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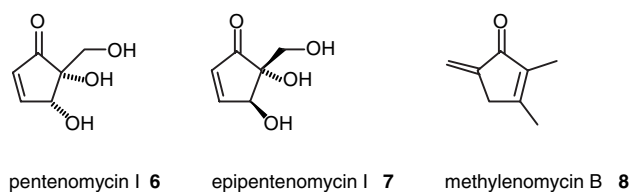
for chemotherapy, whilst the presence of the C-15 hydroxyl functionality and its stereochemistry do not affect activity. 13,14-Dihydro-15-deoxy- Δ^7 -PG-A₁ methyl ester (**3**) (TEI 9826) is active in vivo against *cis*-platin-resistant tumours and is undergoing clinical trials [6].



The PG-As and PG-Js have also been reported to inhibit a wide range of viruses, including influenza virus [7] and human immunodeficiency virus (HIV) [8]. Additionally $\Delta^{12,14}$ -15-deoxy-PG-J₂ (**4**) has been found to be a potent anti-inflammatory agent, which may open the way to a novel class of non-steroidal-based anti-inflammatory [9] and antiviral drugs [10].



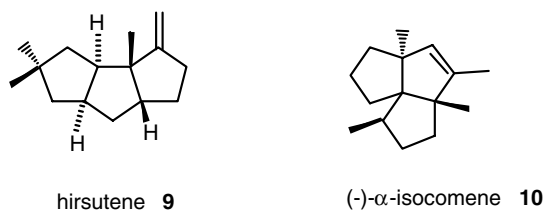
Interest in the synthesis of cyclopentenone PGs was given new impetus with the discovery of three new series of PG natural products, the punaglandins, the clavulones and the chlorovulones. This set of PGs appears to be even more potent than the PG-A and PG-J series. Of these, the halogen-containing punaglandins such as punaglandin **4** (**5**) may have the greatest therapeutic activity. In fact halogen substitution at C-10 and hydroxyl substitution at C-12 appear to increase the potency of these compounds towards anti-neoplastic activity [11].



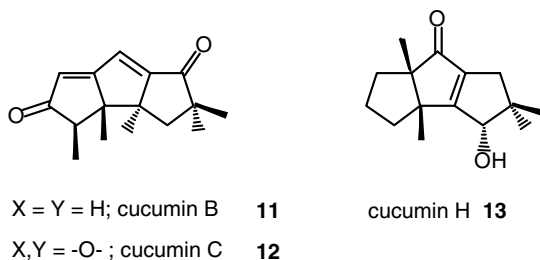
Pentenyomycins and methylenomycins **6–8** constitute a family of natural cyclopentenoids that are of increasing interest due to the variety of biological activities they display, such as glycosidase inhibitors and aminoglycosidase antibiotics. The fascinating structural and stereochemical features of these derivatives have inspired several approaches to their synthesis [12].

Triquinanes are a subgroup of the polyquinanes, which are composed entirely of fused five-membered rings. They have been discovered from plant, marine and microbial sources and exhibit significant biological activities. The complexity of the tricyclic framework along with the functional group diversity and stereochemical intricacies of this family of compounds continue to inspire synthetic chemists to devise new routes for cyclopentane annellations.

Linearly fused triquinane sesquiterpenes such as hirsutene (**9**) and angular triquinanes such as (–)- α -isocomene (**10**) have become popular targets to evaluate new methods of five-membered carbocycle annulation [13]. A great number of these natural product triquinanes often contain a substituted cyclopentenone ring in their structure, or a key step in the total synthesis strategy involves a cyclopentenone.



Linearly fused triquinane sesquiterpenes cucumins B, C and H **11–13** have been isolated recently and thus their syntheses are not yet well represented in the literature [14]. They belong to the hirsutane group and were found to exhibit high cytotoxic and antimicrobial activities. The main challenge to the synthesis of cucumins is the installation of a network of methyl groups and quaternary carbon centres.



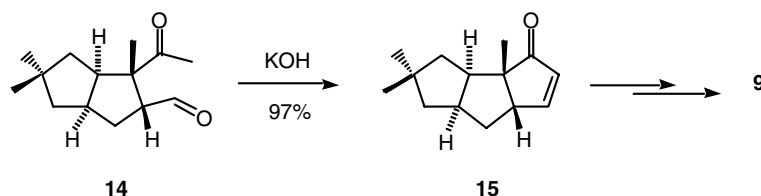
The mechanism of action of cyclopentenone natural products and their possible application as therapeutic agents remains an intriguing issue. Furthermore, scientists have concentrated mainly on naturally occurring compounds to date, yet certain well-designed unnatural analogues exhibit remarkable biological properties. The ability to further explore and understand such compounds ultimately depends upon their accessibility. Precise molecular investigations based on synthesis open the way for a rational creation of selective therapeutic agents. The development of new and versatile synthetic methodologies for the preparation of substituted cyclopentenones in large quantities, for screening, is therefore essential. The ideal route should be capable of producing both naturally occurring and unnatural cyclopentenone analogues by the same technique. The design of new enantioselective routes to substituted cyclopentenones in one step has a very significant contribution to make to this area. Consequently the design and execution of short, highly convergent approaches into this family of compounds, which satisfy the demands of industrial applicability, constitutes an important and exciting challenge for synthetic chemists.

3. Classical routes to cyclopentenones

The importance of cyclopentenones in organic synthesis has encouraged the development of many general methods for their preparation with regio- and stereochemical control [15]. A brief summary of the classical routes to cyclopentenones is provided in this section. Emphasis has been placed on synthetic methods of reasonable efficiency and general applicability. Approaches that apply only to specific natural products have been omitted.

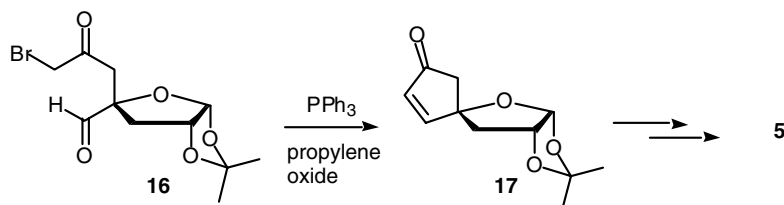
3.1. Intramolecular aldol reactions [16]

The synthesis of cyclopentenones via the aldol reaction generally involves base-catalysed intramolecular condensation of 1,4-dicarbonyl compounds. This route is flexible, as there are several routes available for the preparation of 1,4-dicarbonyl compounds. In a typical application of the reaction, an intramolecular aldol condensation of **14** led to the construction of the third ring of **15**, which was a key step in the synthesis of (\pm)-hirsutene (**9**) [17].



3.2. Intramolecular Wittig-type reactions [18]

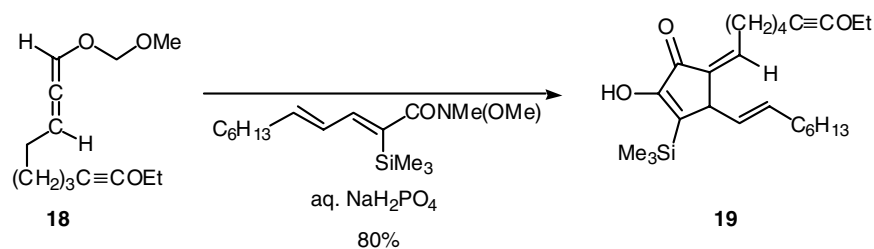
An alternative to the base-catalysed intramolecular aldol condensations is a Wittig-type reaction. Phosphoranes stabilised by an α -carbonyl group can undergo intramolecular condensations with reactive aldehyde functions. This methodology has been used to convert **16** into **17**, in studies directed towards the synthesis of the prostanoid punaglandin **45** [19].



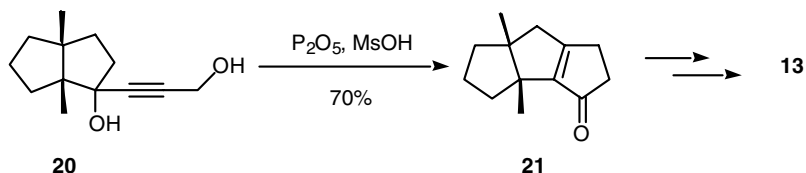
3.3. Nazarov reactions [20]

The Nazarov reaction consists of an acid-induced cyclisation of allyl vinyl and divinyl ketones to form substituted cyclopentenones (allyl vinyl ketones are first isomerised to divinyl ketones before ring closure). The reactions proceed via pentadienyl cations, which are well known to undergo conrotatory electrocyclic ring closures. Many variants on the classical Nazarov cyclisation and elegant enantioselective versions have been developed.

Allenyl ethers such as **18** have been used in a Nazarov variant to prepare the Δ^7 -PG skeleton, which was subsequently converted into various cyclopentenone PGs. Metallation of **18** with *n*-butyllithium, followed by addition of the Weinreb amide, and quenching with NaH_2PO_4 led to **19** in good yield [21].

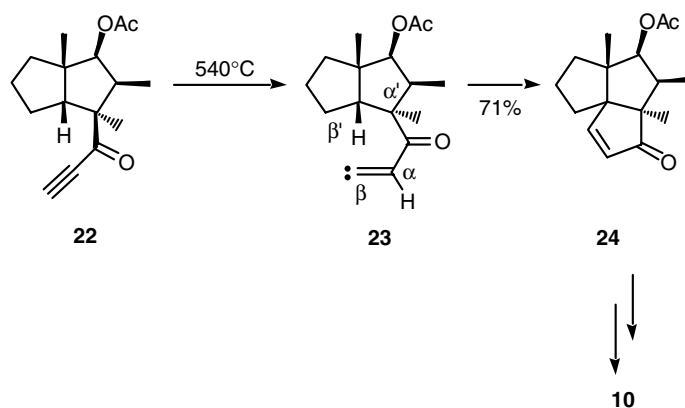


A modified Nazarov cyclisation has been used to attach a third cyclopentane ring to **20** to give **21** in a formal synthesis of sesquiterpene (–)-cucumin H (**13**), which was carried out to confirm the structure of the molecule [14].



3.4. Intramolecular 1,5-C–H insertions [22]

Alkylidene carbenes undergo regio- and stereoselective intramolecular C–H insertion reactions providing a useful method for the construction of cyclopentene skeletons. Alkylidene carbenes can be generated from alkynes under flash vacuum pyrolysis conditions by a reversible 1,2-shift. This proceeds particularly well in the case of 1-alkyn-3-ones such as **22**, and leads to the formation of cyclopentenones. The alkynone cyclisation strategy has been used to prepare **24**, a key intermediate in a formal synthesis of (±)-isocomene **10**.



Flash vacuum pyrolysis of **22** led to the formation of an alkylidene carbene intermediate **23**, which inserted into the carbon–hydrogen bond (at the β' -position) five carbon atoms away, to give **24**. The intramolecular formation of a new carbon–carbon bond between an acetylenic (β -position) and a non-activated carbon atom (β' -position) is accompanied by a [1,2]-migration of the hydrogen at the β -position to the α -position. The alkynone cyclisation offers a route to the preparation of monocyclic, bicyclic and spiro compounds containing a cyclopentenone unit [23].

4. Synthesis of cyclopentenones using transition metals

In the field of synthetic chemistry, the search for new and more efficient methods of carbon–carbon bond formation for application in the total synthesis of complex molecules, particularly of cyclic compounds, continues to be a major goal. Over the last two decades, an important area of investigation towards this end has involved transition metal-mediated and -catalysed reactions [24]. Transition metal-based methods often increase synthetic efficiency by forming several carbon–carbon bonds, with high selectivity, in a single reaction. The metals serve as suitable orienting templates and their efficiency in such systems derives from their ability to coordinate, either simultaneously or sequentially, the different components of the reaction around the metal centre. The reactivity of these components is usually altered by bonding to the metal centre and its presence is often necessary to activate the components towards the required insertion reactions. Ligand affinity and ligand activation have been found to be susceptible to modulation, and by exploiting the preferred mode of orientation of a ligand, a high degree of selectivity can be conveyed to the product. Modulation of the reactivity of a ligand can be further exploited to achieve asymmetric induction by employing suitable chiral spectator ligands. The optimal route should be direct, efficiently stereocontrolled, general and flexible.

The importance of natural products, pharmaceuticals and useful building blocks containing cyclopentenone derivatives, has stimulated much research into the development of methodologies for their synthesis. For the construction of cyclopentenone rings, there is no pericyclic reaction equivalent to the Diels–Alder cycloaddition, which results in the formation of six-membered rings. The increasing availability of metal-mediated routes to five-membered rings opens the way to new strategies for the synthesis of substituted cyclopentenones, which should considerably shorten routes to, and achieve higher selectivities in, the preparation of target cyclic products.

The following section presents the currently available synthetically useful transition metal-mediated routes to cyclopentenones, with clear emphasis on truly catalytic reactions. The aim of the review is to present these routes together to compare their utility and evaluate their application. Methods that are specific to an individual natural product are omitted, unless they are judged to have possible generality. Reactions in which the transition-metal species acts merely as a Lewis acid are generally excluded. The review is restricted to methods that result in the formation of cyclopentenones in a one-pot process.

4.1. [2+2+1] strategies

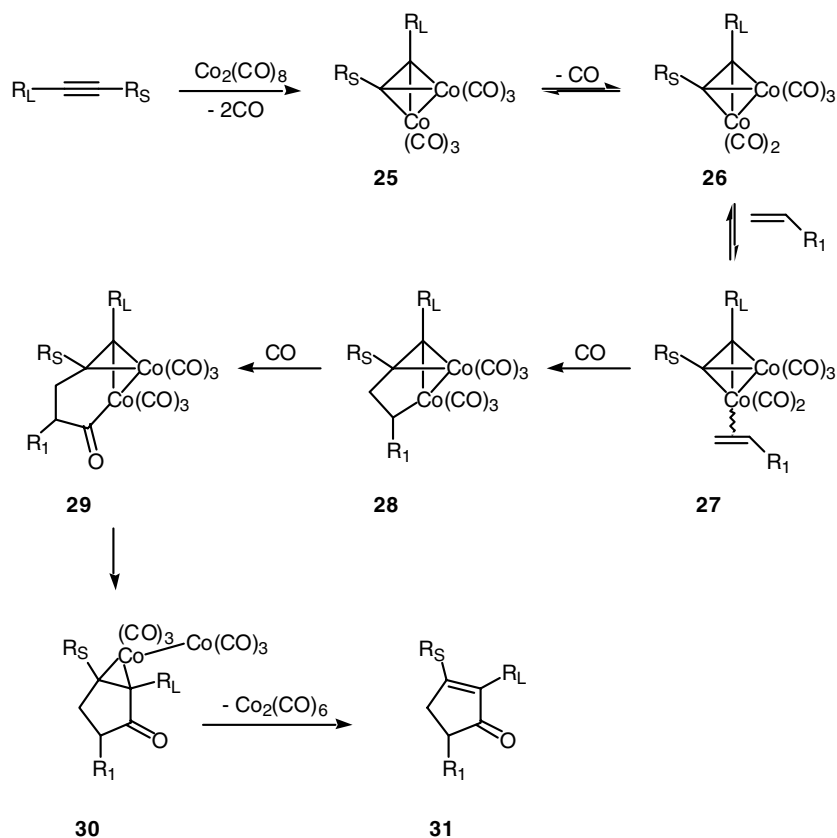
Reactions in which three or more different and independent components are assembled in a controlled, single synthetic operation are rare due to the high entropy barrier that is usually involved. However, they represent the highest chemical efficiency and atom economy for forming at least two new bonds in any designed path to the target molecule [25]. One way to overcome the disorder parameter and facilitate the formation of the necessary bonds is to use transition metals. This approach offers a simple, efficient, and highly selective method to prepare cyclopentenones from readily available starting materials.

4.1.1. The Pauson–Khand reaction

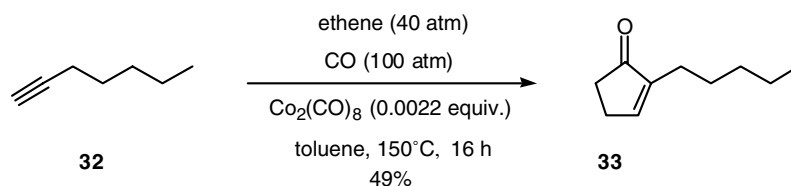
One of the most extensively studied procedures for forming cyclopentenones is the Pauson–Khand reaction (PKR). The PKR consists of a [2+2+1] ‘cycloaddition’ of an alkyne, an alkene and carbon monoxide, promoted by octacarbonyldicobalt(0), resulting in the formation of cyclopentenones. Since the first report in 1971, [26] the PKR has attracted the interest of many organic and organometallic chemists, as it is able to provide a variety of cyclopentenone systems in a single operation. The PKR has been recognised as one of the most important methodologies for the preparation of cyclopentenone derivatives and has been used in many synthetic applications, particularly of bioactive compounds [27].

Whilst a detailed mechanism has not been established, a generally accepted mechanism is outlined below [28]. The cobalt–alkyne complex **25** is usually pre-formed by reaction of an alkyne with octacarbonyldicobalt(0). This is the only intermediate that has been observed in the postulated mechanism. Loss of a carbon monoxide ligand from one of the prochiral cobalt atoms (intermediate **26**) is followed by alkene complexation to the coordinatively unsaturated metal centre, giving **27**. The first carbon–carbon bond forming reaction then takes place between the less hindered ends of the alkyne and the alkene (intermediate **28**), and it is this step that explains the good regioselectivity observed with

respect to the alkyne; regioselectivity with respect to the alkene is normally poorer. Carbon monoxide insertion into the cobaltacycle **28** takes place to form **29**. This is followed by reductive elimination to give **30** and decomplexation of the metal to release the cyclopentenone **31**.



The earliest reports of the catalytic PKR required constrained, reactive alkenes such as norbornene, a continuous flow of ethyne and varying carbon monoxide pressures [26]. A significant development in the catalytic PKR came with the use of unstrained alkenes, such as ethene, in the presence of heptyne **32**. Although a high temperature and a high pressure of carbon monoxide were necessary, the corresponding cycloadducts **33** were obtained with small quantities of catalyst [29].



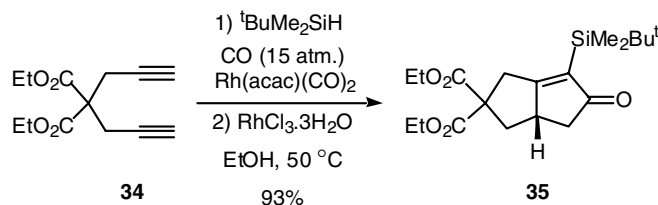
Successful catalytic PKRs have been reported using promoters, one atmosphere pressure of carbon monoxide, various sources of cobalt carbonyl and (asymmetric) additives, although the vast majority of these have been based on intramolecular reactions. Several reviews have been compiled, which provide detailed analysis of recent advances [30].

4.1.2. The rhodium-catalysed PKR

Rhodium complexes have been reported to catalyse the cocyclisation of enynes and carbon monoxide at a pressure of one atmosphere [31]. Subsequently, the chiral bisphosphine (*S*)-BINAP was used to effect a catalytic asymmetric PKR [32]. A small range of intramolecular substrates were converted to bicyclic cyclopentenones with good to excellent yields and enantioselectivities. Rhodium carbonyl complexes have also been used to successfully effect the cyclisation of alkynyl-allenes [33].

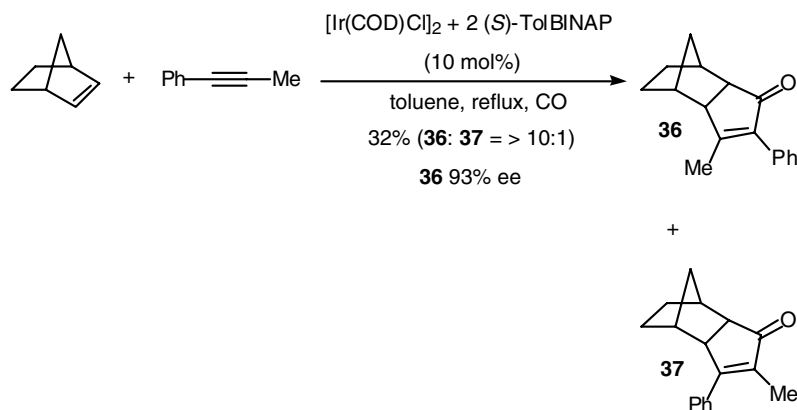
Recently, more practical procedures circumventing the use of carbon monoxide have appeared, using aldehydes as a carbon monoxide source. Rhodium complexes have been used to catalyse tandem decarbonylation of the aldehyde and carbonylative coupling of enynes, under solvent-free conditions [34]. This protocol has been further extended to the asymmetric PKR, using (*S*)-TolBINAP [34c].

Rhodium carbonyl complexes can be used to mediate the coupling of two equivalents of diphenylethyne, under high pressures of carbon monoxide, to generate a substituted cyclopentenone. The hydrogens required are supplied by the dehydrogenation of 2-propanol [35]. Rhodium complexes have also been reported to catalyse the reactions of 1,6-di-ynes **34** with *tert*-butyldimethylsilane, under carbon monoxide pressure, to form the corresponding silyl-substituted bicyclo[3.3.0]oct- $\Delta^{1,5}$ -en-3-ones. These are readily isomerised to the product **35**, in quantitative yield by adding a catalytic amount of $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ [36].



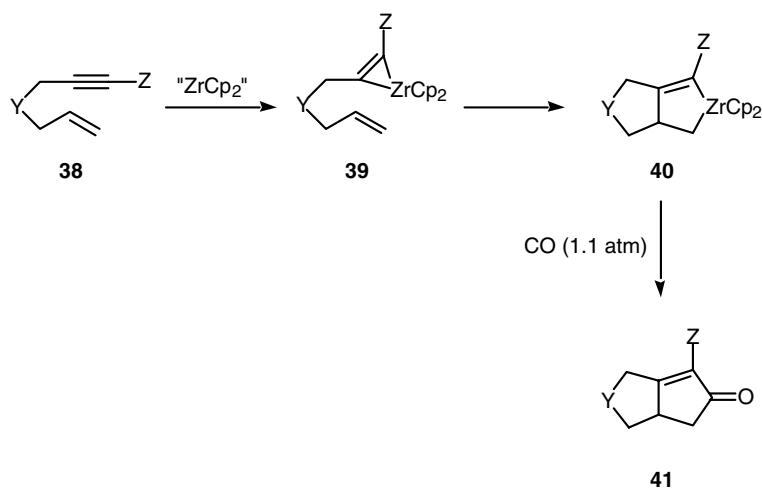
4.1.3. The iridium-catalysed PKR

An iridium(I)-chiral diphosphine complex based on (*S*)-TolBINAP, has been used to effect highly enantioselective intra- and intermolecular PKRs [37]. Use of other chiral phosphines gave lower catalytic activity and poor enantioselectivity. It is of note that this report represents the first example of a catalytic, enantioselective, intermolecular PKR. Cyclopentenone **36** is produced in high enantiomeric excess and moderate yield.



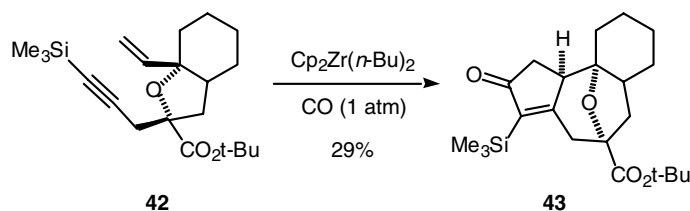
4.1.4. Titanocene- and zirconocene-promoted cyclocarbonylation

Formally related to the PKR, is the zirconium-mediated carbonylative cyclisation of enynes to bicyclo[3.3.0]octenones [38]. Enynes with various substituents on the alkyne moiety are tolerated (with the exception of hydrogen). The “ ZrCp_2 ” moiety acts as a 14 electron species that can readily react with enynes **38** at room temperature, to give initially

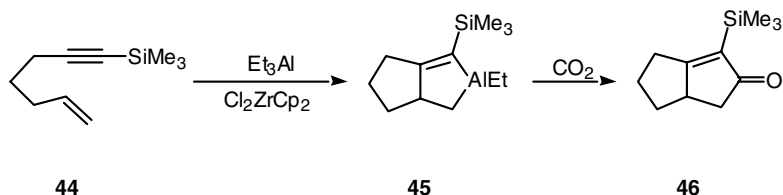


zirconacycloprenes **39**, which then undergo intramolecular zirconium–carbon bond addition to the alkene moiety to produce **40**. These zirconabicycles are discrete products, which can be converted into a range of derivatives. Treatment of **40** with carbon monoxide (1.1 atm), for example, yields bicyclisation products **41** in good yields [39]. A number of methods have been devised for the generation of “ZrCp₂”, which is a convenient species for obtaining the intermediate zirconacycles [40].

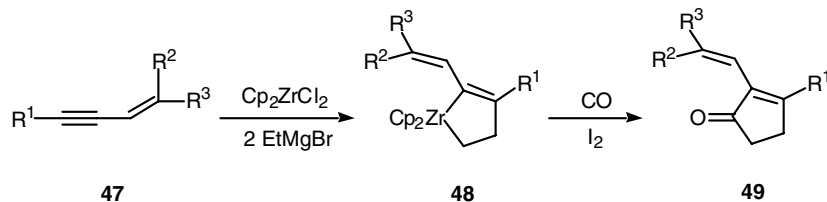
Zirconocene-promoted bicyclisation–carbonylations have been applied to the synthesis of several natural products [41]. Cycloadduct **43** provides ready access to a family of tigliane and daphnane analogues. An attempted PKR of **42** using octacarbonyldicobalt(0) was unsuccessful, but zirconocene-promoted carbonylation provided **43** in modest yield as a single diastereoisomer [42].



A more recent report described the preparation of cyclopentenones via zirconium-catalysed (12.5 mol%) carboalumination of enynes, such as **44**. The intermediate aluminacyclopentene **45** was converted into cyclopentenone **46** using carbon dioxide (1 atm), since with carbon monoxide no migratory insertion was observed. Although these transformations are stoichiometric in aluminium, an asymmetric route could be devised by attaching chiral ligands to the catalytic “ZrCp₂” complex [43].

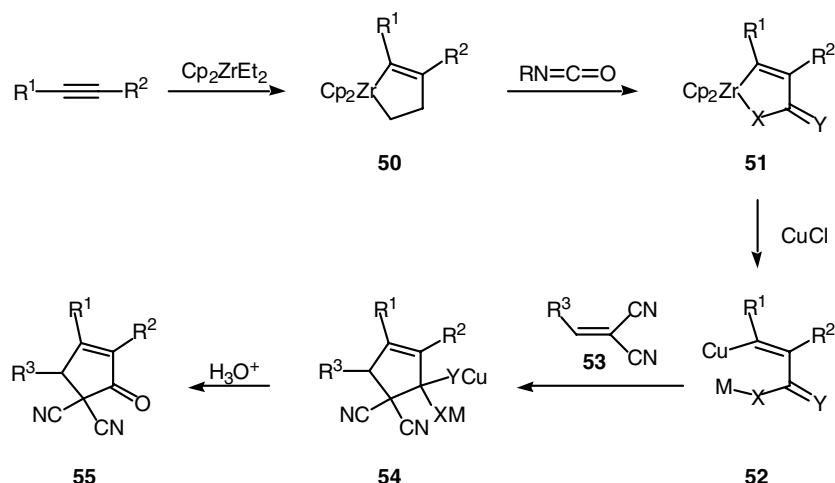


Several intermolecular routes have been devised to prepare substituted cyclopentenones. α,β -Disubstituted cyclopentenones can be obtained from alkynes, ethylmagnesium bromide (as the alkene source), and carbon monoxide (1 atm) via “ZrCp₂” complexes.

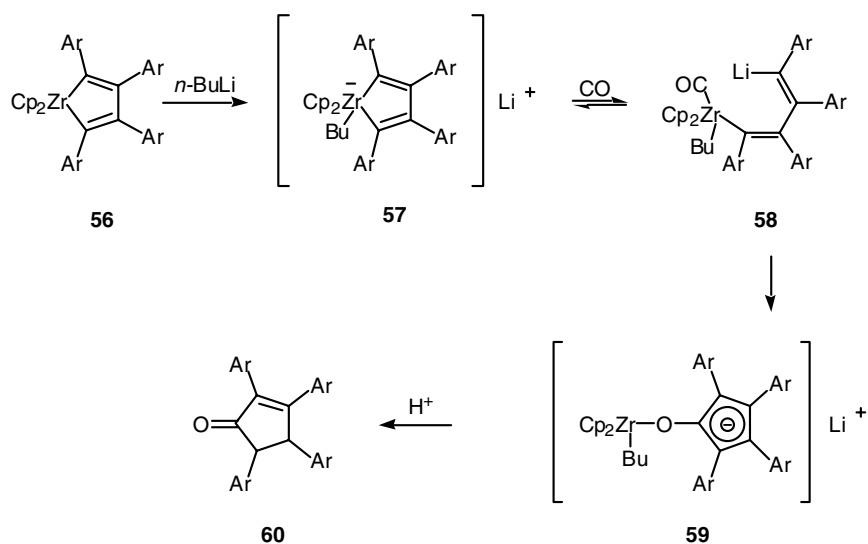


For example, conjugated enynes **47** have been used as alkyne components to obtain α -alkenyl-substituted zirconacyclopentenones **48**, before being treated with carbon monoxide/iodine to release the corresponding cyclopentenones **49**. α -Alkyl, aryl, silyl, alkynyl and α,α' -bridged cyclopentenones have been prepared by this route [44].

Use of trisubstituted alkenes in three component intermolecular coupling reactions represents a substantial challenge because they display low reactivity, and control of their regioselectivity is problematic. It is thus significant that a strategy for preparing polysubstituted cyclopentenones **55** has been reported, using a trisubstituted non-strained alkene, an alkyne and an isocyanate. Incorporation of the isocyanate into the zirconacyclopentene **50** results in the formation of **51** (X=O, Y=NR or X=NR, Y=O). Ring opening of **51** with copper(I) chloride generates a bimetallic species **52** (where M=zirconium or copper), which reacts with ylidene malonitriles **53** to give **55**, via **54**. Thus alkenes conjugated with electron-withdrawing groups, which are generally not suitable for the intermolecular PKR, are successfully introduced onto the cyclopentenone ring [45].



Synthesis of substituted cyclopentenones has been achieved, using two (different) alkynes and carbon monoxide, via a zirconacyclopentadiene complex. Alkyl-substituted zirconacyclopentadienes react with carbon monoxide at room temperature to give the corresponding cyclopentenones. Aryl-substituted zirconacyclopentadienes are inert towards carbon monoxide insertion reactions, but in the presence of *n*-butyllithium, insertion of carbon monoxide (1 atm) takes place to produce substituted cyclopentenones in moderate to good yields [46]. Although the mechanism for this reaction has not yet been established, it has been suggested that the reaction proceeds via a zirconium-ate complex **57**.



n-Butyllithium coordinates to the zirconium metal centre of **56** to produce a zirconium-ate complex **57**. Reaction of **57** with carbon monoxide gives **58** and the alkenyl lithium moiety attacks the carbon monoxide on the zirconium metal centre, followed by cyclisation to produce **59**. Hydrolysis of **59** releases cyclopentenone **60**, with effective reduction of one of the double bonds.

An enyne cyclocarbonylation, complementary to the zirconium-promoted systems described above, has been demonstrated using a number of titanocene complexes in the presence of carbon monoxide (1 atm) or an isocyanide. It proceeds via a similar mechanism to that of the zirconocene complexes **39** [47]. The process displays a high functional group tolerance (including terminal alkynes), and a wide range of bicyclic cyclopentenones have been prepared. A chiral titanocene complex, (*S,S*)(EBTHI)Ti(CO)₂, (EBTHI=ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)) has been used to effect catalytic, asymmetric PKRs of enynes, producing bicyclic cyclopentenones with good yields and high enantioselectivities [48].

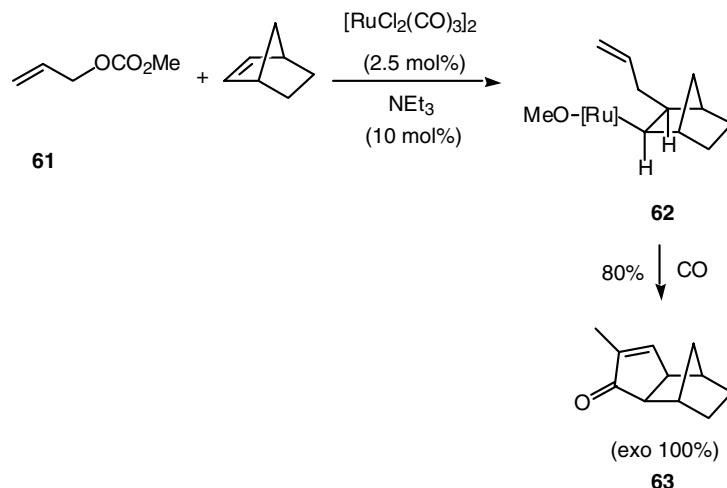
4.1.5. The iron- and ruthenium-mediated PKR

Iron carbonyls have been found to promote the cyclocarbonylation of alkynes and allenes, producing β -methylene-cyclopentenones in modest yield [49]. The preparation of bicyclopentenones from 1,6-enynes has also been reported

[50]. The intramolecular cyclocarbonylation was carried out in a sealed tube and a high pressure of carbon monoxide was necessary to effect the reaction. The reaction proceeds in an analogous way to the PKR.

Ruthenium carbonyls have been reported to effect a catalytic PKR of enynes and carbon monoxide (10–20 atm), generating the corresponding cycloadducts in very good yield [51].

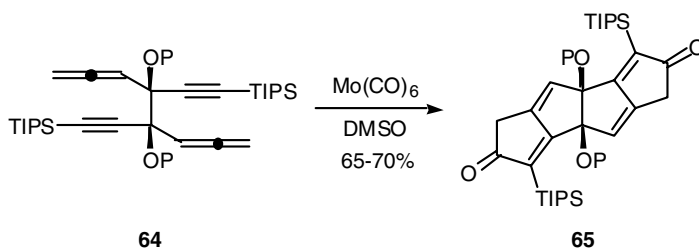
A ruthenium-catalysed route to prepare cyclopentenones has been described using allylic carbonate **61**, norbornene and carbon monoxide (3 atm). The reaction is believed to proceed via the ruthenium intermediate **62**, followed by insertion of carbon monoxide and subsequent intramolecular insertion of a C=C bond into an acyl ruthenium bond. β -Hydride elimination/isomerisation gives the corresponding cyclopentenone **63** [52].



4.1.6. The chromium-, molybdenum- and tungsten-mediated PKR

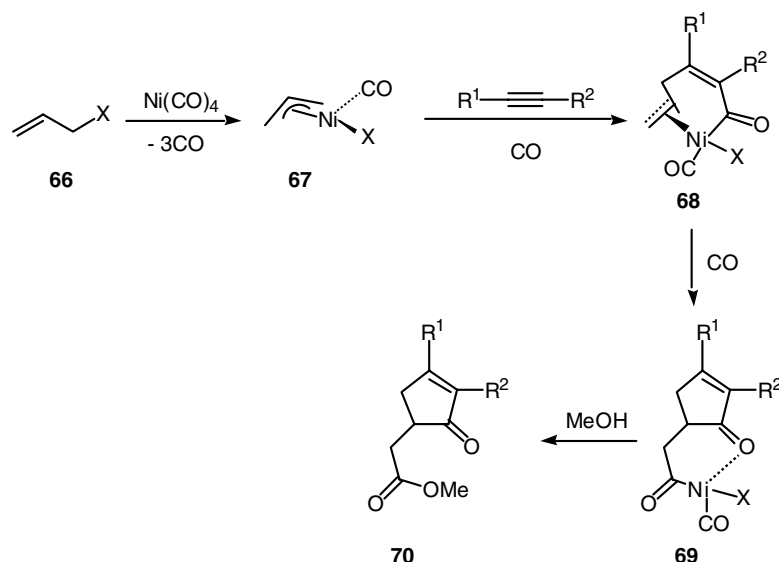
A pentacarbonyl chromium–tetrahydrofuran complex has been used to promote carbonylative cyclodimerisation of allenes, to prepare substituted 4-methylene-cyclopentenones [53]. Furthermore, the tungsten carbonyl analogue of the above complex was applied successfully to the cyclocarbonylation of enynes [54]. Anionic $[(\text{CO})_5\text{MF}]^-$ systems (where M=chromium or tungsten) can also effect the carbonylative cycloaddition of enynes [55].

Molybdenum carbonyls have been used to promote the intra- and intermolecular PKR of a variety of substrates [56]. This system has been further developed to perform PKR on alkynyl-allenes [57]. For example, a molybdenum-promoted tandem PKR of the diyne–di-allyne system **64** (TIPS=triisopropylsilyl) has been accomplished, producing the tetracycle **65** in good yield [58]. This reaction involves the formation of six carbon–carbon bonds in a one-pot process.



4.1.7. Nickel(0)- and palladium(0)-promoted carbonylative cycloaddition

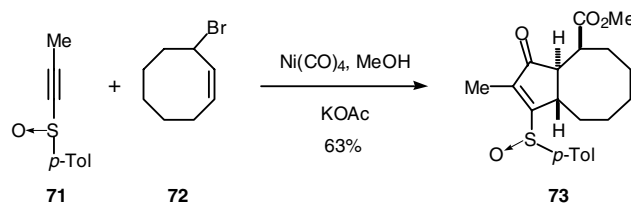
A process superficially similar to, but mechanistically distinct from the PKR, is the nickel(0)-mediated carbonylative reaction of allyl halides and alkynes to form substituted cyclopentenones. In this process, $\text{Ni}(\text{CO})_4$ is the transition metal promoter and the double bond of an allyl halide serves as the alkene component of a formal [2+2+1] cycloaddition. Several nickel-promoted carbocyclisations have been reported under mild reaction conditions; however, it has attracted much less interest than the PKR because most of the cyclisations demand the use of stoichiometric amounts of the hazardous $\text{Ni}(\text{CO})_4$ complex [59]. Despite the complexity of this reaction, careful selection of reagents and reaction conditions (to minimise side reactions) has led to an optimised synthesis of cyclopentenone derivatives [60].



The reaction proceeds via a well-defined sequence of steps, which have been supported by mechanistic studies [61]. Usually, the initially formed allylnickel complexes **67** (generated by oxidative addition of allyl halides **66** to zerovalent nickel) undergo alkyne insertion and concurrent carbonylation to give **68**. A 5-*exo-trig* cyclisation, followed by a second carbonylation, yields the complex **69**, which is cleaved by methanol to give the product **70**.

It has been shown that the high regioselectivity of this reaction is a result of triple-bond polarisation. The π -allylnickel complex behaves as an electrophile and adds to the most negative end of the alkyne; steric factors do not seem to affect the mode of addition. Most functional groups are tolerated in the alkyne, and indeed they may be used to improve the yield and regioselectivity of the resulting cycloadduct. An intramolecular version of this reaction has been exploited in the synthesis of bicyclo[3.3.0]octenone derivatives [62], and the monocyclic antibiotic methylenomycin B has been prepared in just four steps via a nickel(0)-promoted cyclisation of allyl bromide and 2-butynol [63].

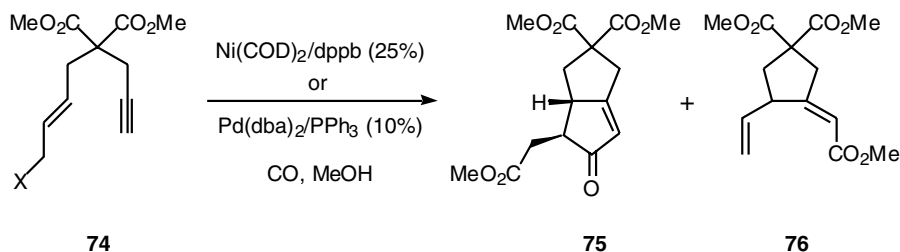
Nickel(0)-mediated carbonylative cycloaddition of cyclic allylic systems and alkynes have provided a one-step synthesis of various ring-fused systems and spiro cyclopentenones, giving good yields and total stereocontrol [64]. For example, the homochiral acetylenic sulfoxide **71** reacted with cyclic allyl halide **72**, to form the fused cyclopentenone **73** in moderate yield and diastereoselectivity [65].



dr 82:18

A variation on the nickel(0)-promoted cyclisation of enynes has been reported using isocyanides (as isoelectronic counterparts to carbon monoxide) to form 1-imino-2-cyclopentenones, which may be hydrolysed to the corresponding cyclopentenones [66]. Recently, Mackenzie's π -allylnickel complexes (generated from Ni(COD)_2 , enals, and trimethylsilylchloride), have been exploited in the synthesis of cyclopentenones [67]. In this variant, the siloxy-substituted nickel π -allyl complex reacts with an alkyne under a carbon monoxide atmosphere and then methanol to produce an acetal-substituted cyclopentenone.

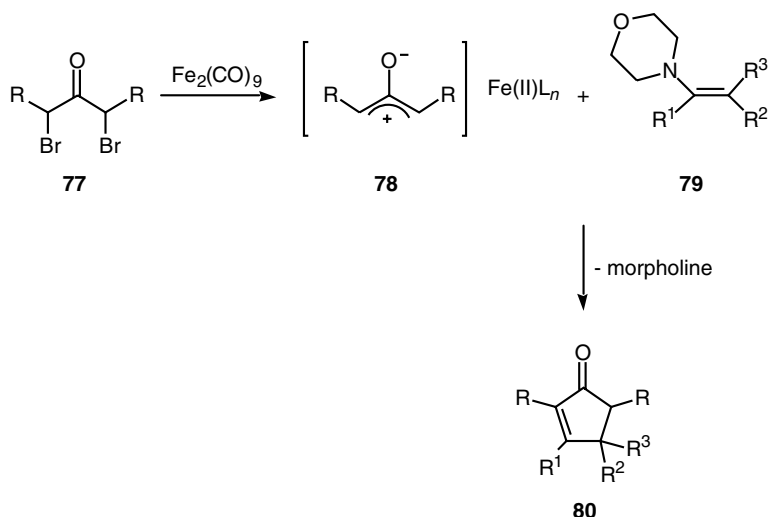
An intramolecular palladium and nickel-catalysed metallo-ene-type cyclisation/carbonylation, using an atmospheric pressure of carbon monoxide, has been exploited for the synthesis of annulated cyclopentenones. Use of $[\text{Ni(CO)}_3\text{PPh}_3]$ or $[\text{Ni(COD)}_2/1,4\text{-bis(diphenylphosphino)butane}]$ (25 mol%), or $[\text{Pd(dibenzylidene-acetone)}_2/\text{PPh}_3]$ (10 mol%) with enynes bearing an allylic acetate or a halide moiety **74**, afforded either mono- or bicyclisation products. The outcome of the reaction was dependent not only on the choice of metal and ligands, but also on the substitution pattern of the substrate. The reaction proceeds by a similar mechanism to the one described above, leading to the formation of cyclopentenone derivatives **75** or dienes **76**, respectively [68]. This methodology has further been exploited in the preparation of a number of natural products, including (\pm)-hirsutene (**9**) [69].



α -Methylenecyclopentenones, fused to five-membered rings, have also been prepared via a palladium-catalysed (10 mol%) carbonylative cyclisation (40–100 atm carbon monoxide) of enynes [70].

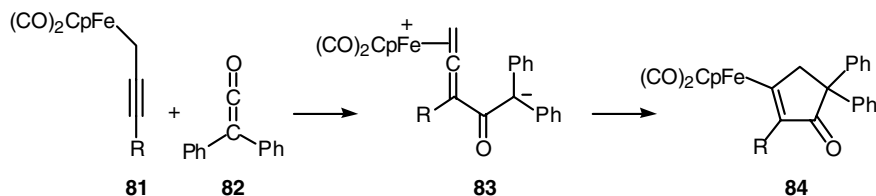
4.2. [3+2] strategies

The iron carbonyl promoted cyclocoupling between a secondary dibromoketone **77** and an enamine **79** provides a route to α,α' -dialkylated cyclopentenones **80**. Iron carbonyl converts the ketone **77** to the iron enolate **78**, which undergoes cycloaddition to nucleophilic alkenes such as **79**, yielding five-membered ring carbocycles. Use of enamines such as **79** leads to products that rapidly eliminate morpholine, providing cyclopentenones in a single-pot procedure [71].



Enamines of both ketones and aldehydes have been used; with cyclic ketone enamines, bicyclic cyclopentenones have been prepared, where the second ring size can be changed arbitrarily. This procedure cannot be used for the preparation of α -unsubstituted cyclopentenones.

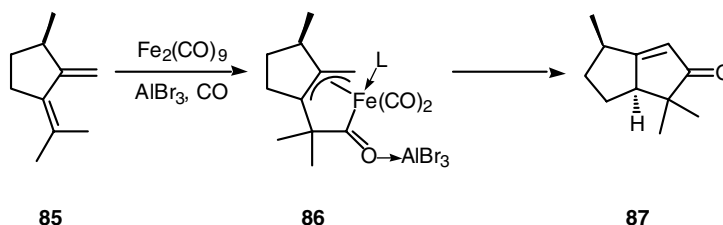
[3+2] Cycloaddition reactions of 2-alkynyl iron complexes **81** with diphenyl ketene **82** proceed via iron complexes **83** [72]. The iron complex of **84** can subsequently be cleaved under a variety of oxidative and non-oxidative conditions. A limited range of alkynyl iron complexes has been tested.



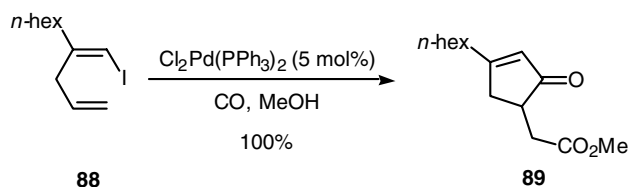
4.3. [4+1] strategies

A novel iron carbonyl-mediated synthesis of cyclopentenones has been described, starting from 1,3-butadienes [73]. Substituted iron tricarbonyl 1,3-diene complexes are decomposed by aluminium halides to produce the corresponding cyclopentenones in good to excellent yield. The reactions were carried out at atmospheric pressure and room temperature, and were complete within a few minutes. For example, a chiral diquinane **87** has been prepared

from diene **85**. The cycloadduct **87** was obtained as a 9:1 mixture of two enantiomerically pure diastereomers, demonstrating that the cyclocarbonylation is a stereoselective process. The reaction is thought to proceed via an acyl π -allyl complex **86**, whose formation is promoted by the coordination of aluminium tribromide with a carbon monoxide ligand [74].

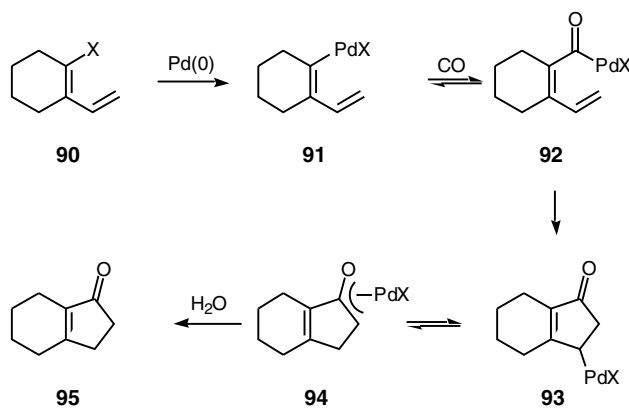


A palladium-catalysed carbonylative cyclisation (40–100 atm of carbon monoxide) of 1-iodo-1,4-alkadienes **88**, has been carried out in the presence of alcohols, leading to the formation of monocyclic cyclopentenones **89** [75]. In contrast carrying out the reaction under an atmospheric pressure of carbon monoxide, and in the absence of alcohol, 1-iodo-1,4-alkadienes were carbonylated to α -methylene-cyclopentenones.



A recent procedure has described the preparation of cyclopentenones from dienyl triflates, bromides and iodides, using a palladium catalyst under an atmospheric pressure of carbon monoxide [76]. Following mechanistic studies, the reaction is proposed to proceed as outlined below. The dienyl halide **90** oxidatively adds to the active palladium(0) catalyst, generated in situ, to form **91**. Coordination and insertion of carbon monoxide produces the acylpalladium intermediate **92**, which undergoes acylpalladation of the neighbouring carbon–carbon double bond **93**.

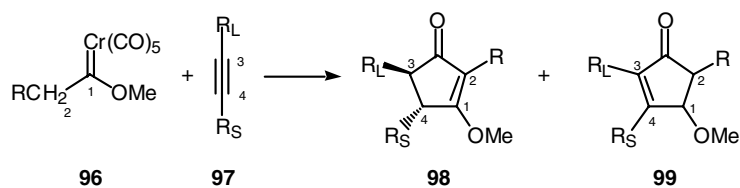
Reversible β -hydride elimination and re-addition leads to the formation of the palladium enolate **94**, which after protonation releases the product **95**.



4.4. Metal–carbene strategies

4.4.1. Alkylcarbene chromium complexes

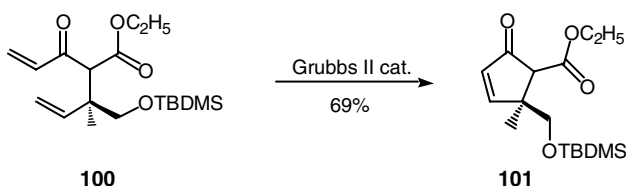
The reactions of alkyl-substituted group VI transition metal–carbene complexes with alkynes have been investigated; for example alkylchromium carbene complexes **96** have been developed for the synthesis of cyclopentenones **98** and **99** [77]. The thermodynamically more stable cyclopentenone **98** is usually the major product and the original alkyne substituents have the *trans* stereochemistry in the product. The products are believed to be formed via a cyclopentendione that is subsequently reduced to the cyclopentenone derivatives under the reaction conditions [77c].



When the alkyne is tethered to the carbene via the alkoxy substituent, the intramolecular reaction between cyclopropylcarbene–chromium complexes and alkynes provides cyclopentenone-fused oxygen heterocycles [78]. The coupling of propargyl alcohol derivatives with cyclopropylcarbene chromium complexes produces alkylidene–cyclopentenones [79].

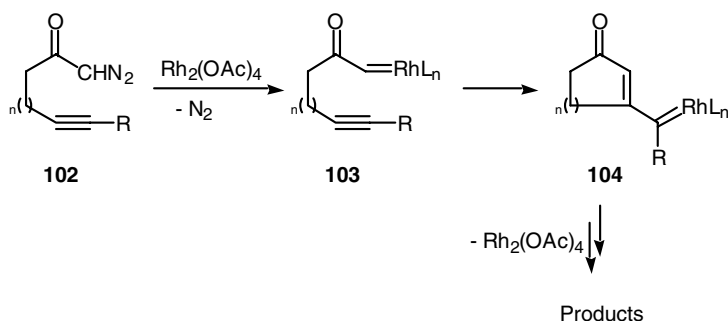
4.4.2. Grubbs catalyst

An intramolecular ring-closing metathesis reaction using the second generation Grubbs catalyst has been used to prepare cyclopentenones in good yield [80]. The diene **100** was converted to cyclopentenone **101**, which was further manipulated to form the cyclopentane ring of viridenomycin [81].



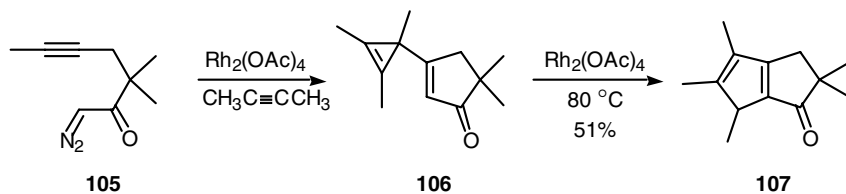
4.4.3. Rhodium(II)-catalysed cyclisations

The rhodium(II)-catalysed intramolecular cyclisation of α -diazo ketones bearing tethered alkyne units represents a useful route to the construction of a variety of substituted cyclopentenones [82].

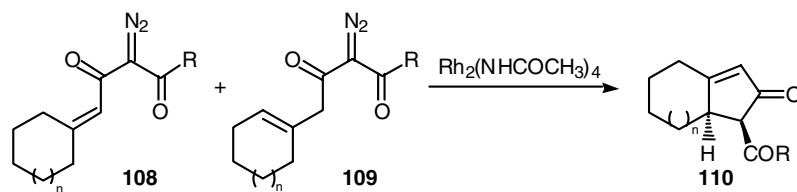


The reaction is believed to proceed via decomposition of the α -diazo ketone **102** to generate a rhodium carbenoid intermediate **103**. Addition of the rhodium-stabilised carbenoid onto the alkyne π -bond generates a vinyl carbenoid intermediate **104**, in which carbene-like character has been transferred to the more remote carbon of the alkyne. The intermediate vinyl carbenoid may then react further in either an intra- or intermolecular fashion to give novel products.

In a typical example, α -diazo ketone **105** underwent internal alkyne insertion, followed by external alkyne insertion to produce cyclopropene **106**, along with several byproducts. Subsequent treatment of **106** with catalytic amounts of rhodium(II) complex led to a clean isomerisation, to give **107** as a single product [83].



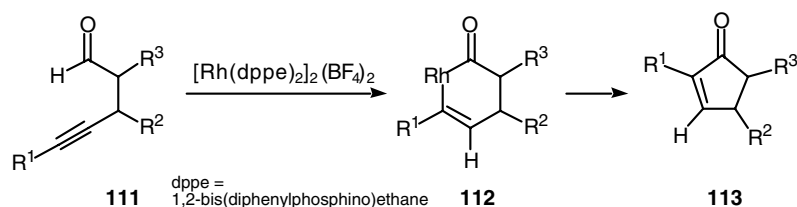
Recently, fused cyclopentenone derivatives, **110**, have been synthesised via a rhodium(II)-catalysed diazo decomposition of a mixture of α,β -unsaturated carbonyl compounds **108** and **109** [84].



4.5. Miscellaneous strategies

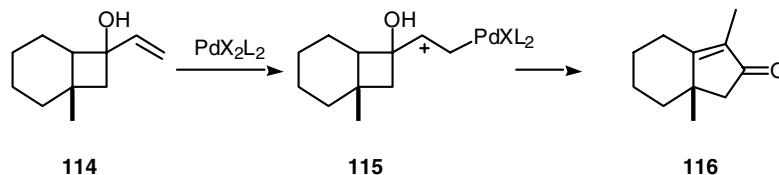
4.5.1. Hydroacylation reactions

Rhodium(I) complexes (10 mol%) have been reported to catalyse the intramolecular hydroacylation of a range of 4-alkynals **111** to generate cyclopentenones **113** [85]. The postulated reaction mechanism indicates a *trans* addition of rhodium hydride to the coordinated alkyne to generate a six-membered rhodium metallacyclohexene **112**. Reductive elimination of **112** produces cyclopentenone **113** and regenerates the rhodium(I) catalyst.



4.5.2. Ring expansion reactions

Vinylcyclobutanols **114** have been reported to undergo ring expansion to give cyclopentenones **116**, in the presence of a palladium catalyst and benzoquinone (two equivalents) [86]. The mechanism has been postulated to pass through intermediate **115**. Fused 5,5-, 5,6- and 5,7-ring systems have been readily synthesised by this method.



5. Conclusions

The main part of this review has focused on the synthesis of cyclopentenones using transition metals and their complexes. The Pauson–Khand family of reactions has established a prominent position in the repertoire of synthetic organic chemists. Recent advances in the number of catalytic and asymmetric protocols available illustrate the versatility and flexibility of this method. The number of applications to natural product synthesis has further exemplified the wide applicability of this reaction. Its use enables the construction of complex molecules in a convergent and atom economic way, starting from structurally simple precursors. Although high levels of enantioselectivity can be achieved in the intramolecular catalytic PKR, the scope of the reaction needs to be expanded to more demanding substrates with greater functionalities. Furthermore the catalytic, asymmetric intermolecular PKR remains very limited.

The results for the catalytic asymmetric PKR obtained with rhodium and iridium complexes are very impressive, however these transition metals are significantly more difficult to handle than the cobalt carbonyl complexes and also a lot more expensive. Although iron carbonyl is substantially cheaper, the range of cyclocarbonylations that can be carried out with this metal carbonyl is limited. The molybdenum carbonyl systems also show potential, particularly in the tandem PKR reactions, however catalytic and enantioselective systems have yet to be developed with this metal complex.

Alternative methods using zirconocene- and titanocene-complexes display a wide range of substrate applicability, for both inter- and intramolecular carbocyclisations, and a very elegant chiral titanocene-complex has been developed as an effective catalyst. However a distinct disadvantage of this method is the highly air-sensitive nature of the transition metal species used.

The nickel-mediated cyclocarbonylation is a very attractive method, as the intermolecular version offers a greater degree of regioselectivity than the intermolecular PKR, and concurrently it introduces a methyl ester functionality at the β -position of the cyclopentenone ring. Unlike the other PKR systems, nickel-mediated cyclocarbonylation does not require any external activation. Unfortunately nickel tetracarbonyl is very hazardous to handle and as it is required in stoichiometric amounts for the reaction to occur, the scope of this reaction remains very limited. More recent developments that avoid the handling of toxic nickel tetracarbonyl offer interesting prospects for the future. However a nickel-catalysed system has yet to be developed.

Finally, it is of note that recent reports have been described using aldehydes as a source of carbon monoxide or isocyanides as carbon monoxide surrogates. Carbon dioxide has also been used to mediate carbonylation of zircona-cycles. These methods are very attractive, as they circumvent the use of the highly toxic carbon monoxide and developments in this area are very promising.

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