REVIEW

Cobalt mediated cyclisations

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1   Introduction

The use of transition metal-centred reagents in organic synthesis is now commonplace. These reagents are used to perform highly regio- and stereo-selective bond forming reactions that would be much more difficult with conventional organic reagents alone. In addition, transition metal complexes and reagents can facilitate novel carbon–carbon bond forming reactions, and in favourable cases can perform several bond forming reactions in a single step. This review surveys the cycloaddition reactions of cobalt that fulfil the following criterion: multiple carbon–carbon bond forming reactions with high levels of regio- and stereo-selectivity. In addition, where appropriate, similar protocols in which alternative transition metals can be used are highlighted for comparison purposes.

2   The Pauson–Khand reaction

Perhaps the best known and most widely used cobalt mediated cycloaddition is the Pauson–Khand reaction (PKR). This was first discovered in 1971,[1] and in its simplest form represents a formal [2 + 2 + 1] cycloaddition between an alkyne, an alkene and a carbon monoxide ligand. A general reaction scheme is depicted in Scheme 1. The cobalt–alkyne complex is usually pre-formed by reaction of an alkyne with dicobalt octacarbonyl to produce the desired complex, normally in high yield. The cobalt–cobalt bond is below and at 90° to the two carbon atoms, and the bond order between these is reduced to around 2.5. Reaction of this complex with an alkene produces a cyclopentenone. The two alkenyl carbons in the product come from the alkyne, the two methylene carbons from the alkene and the carbonyl group from a carbon monoxide ligand present in the complex. A generally accepted mechanism is outlined in Scheme 2, and this will be referred to later in the review. The first step is loss of a carbon monoxide ligand from one of the prochiral cobalt atoms. This step is reversible, and is thought to be rate limiting. An alkene can then complex to the coordinatively unsaturated metal. The first carbon–carbon bond forming reaction then takes place between the less hindered end of the alkyne and the alkene, and it is this step
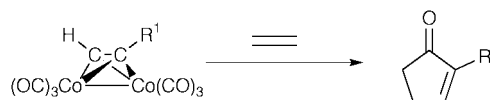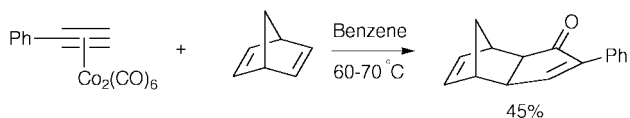

Scheme 1
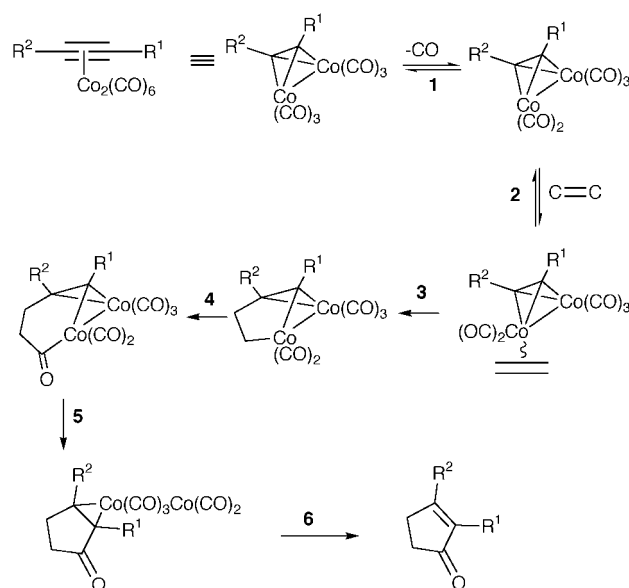
• **1** dissociative loss of CO,
• **2** addition of alkene
• **3** insertion of the alkene into the least hindered cobalt alkyne bond
• **4** CO insertion
• **5** reductive elimination
• **6** decomplexation

Scheme 2

that explains the regioselectivity with respect to the alkyne. Carbon monoxide insertion into the cobaltacycle takes place, followed by reductive elimination and decomplexation of the metal from the cyclopentenone.

Pauson and co-workers carried out the vast majority of the formative work on the reaction in the 1970s and this led to a general synthetic procedure and an understanding of the reaction regioselectivity, where the more bulky group on the alkyne is placed α to the carbonyl group (Scheme 3). With this in hand, other groups started to utilise the reaction, and more experimental evidence was gathered which allowed a mechanism to be postulated.[2] Several excellent reviews have already been published,[2] which highlight the work up until the late 1980s. The reader is directed to these for a fuller account of these studies. More recent advances in the Pauson–Khand reaction are highlighted below.

Scheme 3

## 2.1 Modified reaction conditions

Some of the most significant advances in the methodology for the PKR have been in the use of modified reaction conditions. These have allowed the reaction to become more accessible by providing simplified reaction conditions and improvements in yield. The first of these developments to be reported was the use of Dry State Absorption Conditions (DSAC).[3] In this procedure, the complex and alkene substrate are absorbed onto a solid support such as silica, alumina or zeolite. The reaction is then allowed to proceed, often under an air or oxygen atmosphere, until the characteristic deep red colour of the complex has disappeared and been replaced with the pink or grey colour of decomposed cobalt residues. The use of air can be important to avoid the reduction of ether linkages, presumably by cobalt hydride species. The organic products can then be simply washed off the solid support and purified in the usual way. An example is shown in Scheme 4, which illustrates the improvement in yield that can be obtained. This procedure is normally best used when the substrates have groups capable of hydrogen bonding to the surface of the silica, and is especially beneficial for intramolecular reactions. This has led to the hypothesis that hydrogen bonding to the surface may force the hydrophobic arms of the substrate together and thus facilitate the reaction. The silica may also aid in the promotion of ligand exchange from the complex *i.e.* by allowing carbon monoxide removal and coordination of the alkene. There has also been a report that the reaction is accelerated by molecular sieves[4] although a rationale for this is not yet clear.
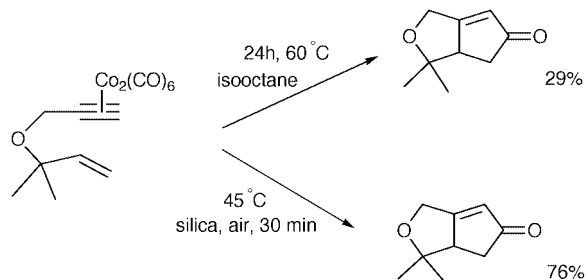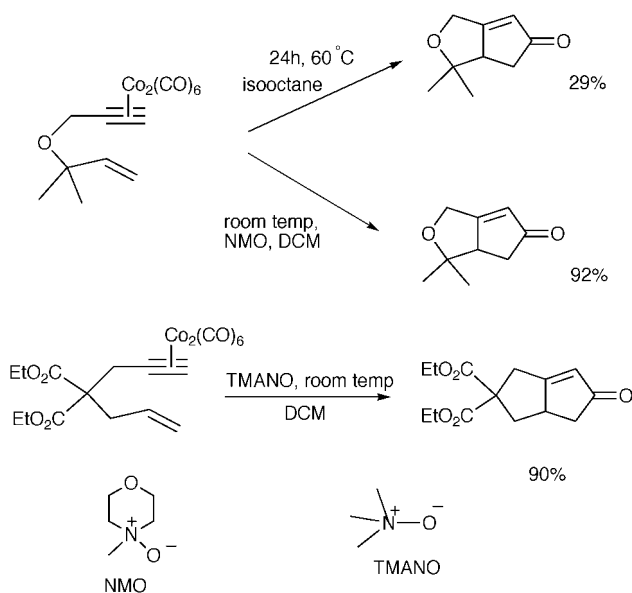

Scheme 4

Another solid support variant to have appeal is the polymer supported PKR. Bolton[5] first reported this in 1996. He utilised the PKR to provide entry to a series of cyclic amino acid derivatives through an intramolecular PKR where the substrate had been anchored to a Wang resin (Scheme 5). Schore and co-workers[6] then reported a detailed study on the effect of the solid support itself on intermolecular PKR. They found the amount of crosslinking in the polymer could effect the distribution of products. The best was found to be a 2% crosslinked Merrifield resin, as this reduced the amount of alkyne trimerization by-products that were produced. These studies have obvious connotations for combinatorial versions of the PKR to produce libraries of cyclopentenoid products.

In order to accelerate the solution phase reaction, methods for promotion of the rate and stabilisation of intermediates were sought. Since the first step of the reaction is loss of CO, and this is thought to be reversible, any means of promoting this will be beneficial. The use of *N*-oxides to oxidise transition metal carbonyls to carbon dioxide has seen significant use in the PKR. In this respect, the use of trimethylamine *N*-oxide or
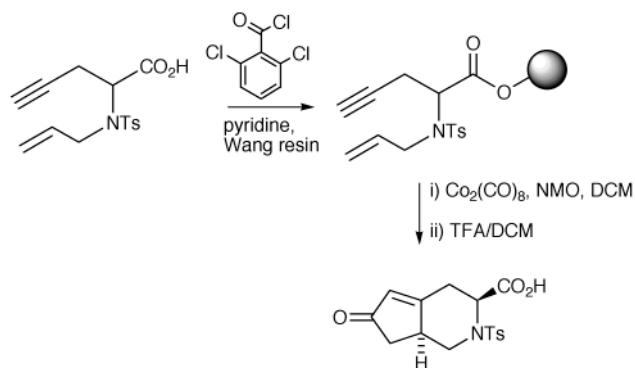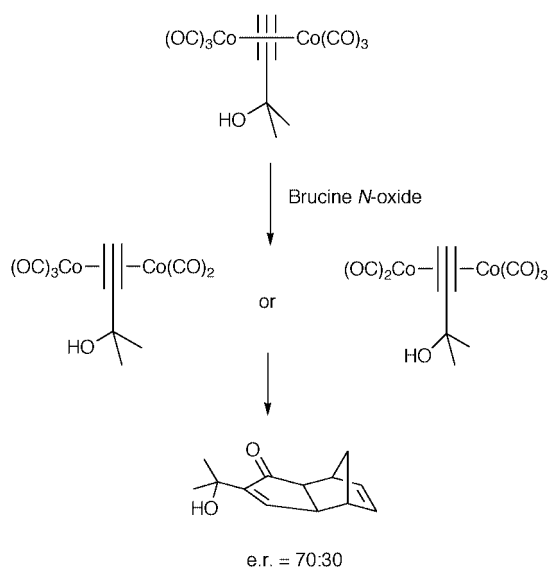

Scheme 5

N-methylmorpholine *N*-oxide has allowed the reaction to be run at room temperature or lower, as well as increasing the yields of reactions.[7] Comparative reactions from the classical thermal conditions and use of amine *N*-oxides are shown in Scheme 6. A major advance in this area is the use of chiral amine oxides.[8] Using these reagents as a source of chiral information, reasonable to good enantioselectivity can be achieved in an intermolecular Pauson–Khand reaction. Although the mechanism is not known, it seems likely that the chiral *N*-oxide discriminates between the prochiral cobalt atoms, either oxidising one carbon monoxide selectively to produce a vacant site for alkene insertion, or stabilising a vacant site on one of the cobalts preferentially, Scheme 7.
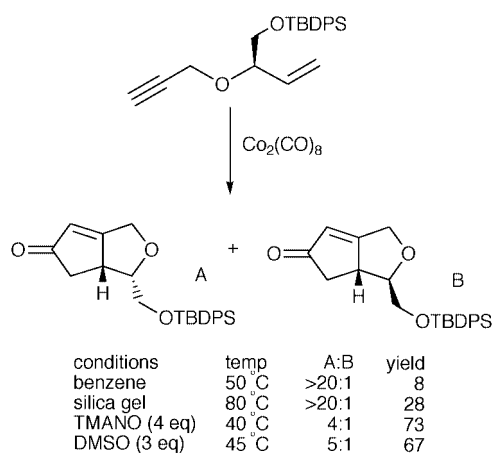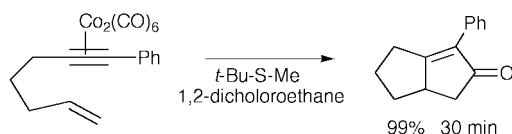

Scheme 6

In addition to *N*-oxide promoters, sulfoxide has also been noted to accelerate the PKR.[9] A comparison of *N*-oxide with DMSO promotion has shown that slightly higher reaction temperatures are required, but that similar yields are achieved (Scheme 8). It was felt that a sulfoxide would not be acting in the same way as an *N*-oxide, *i.e.* by oxidising the CO ligand to CO_2, but may rather have some sort of coordinating effect on the metal. To this end, other coordinating solvents such as acetonitrile were employed, but these showed no effect. However, studies using sulfides have shown a similar promotion in reaction rate and yield, presumably through just this sort of coordination effect.[10] Testing a range of ligands[10b] has shown that steric bulk of the sulfide has an effect on the reaction (Scheme 9), but that in general, reaction rates can be significantly increased using sulfides as coordinating groups. This has culminated in the trapping of an intermediate in the Pauson–Khand reaction, outlined in Fig. 1.[11] The ligating sulfur atom is
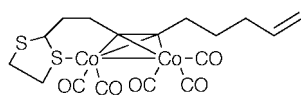
$(OC)_3Co$—|||—$Co(CO)_3$

HO

Brucine N-oxide

$(OC)_3Co$—|||—$Co(CO)_2$ or $(OC)_2Co$—|||—$Co(CO)_3$

HO   HO

O

HO

e.r. = 70:30

Scheme 7

OTBDPS

$Co_2(CO)_8$

O   A   +   O   B

H   H

OTBDPS   OTBDPS

conditions	temp	A:B	yield
benzene	50 °C	>20:1	8
silica gel	80 °C	>20:1	28
TMANO (4 eq)	40 °C	4:1	73
DMSO (3 eq)	45 °C	5:1	67

Scheme 8

$Co_2(CO)_6$

—Ph

t-Bu-S-Me
1,2-dichloroethane

Ph

O

99%   30 min

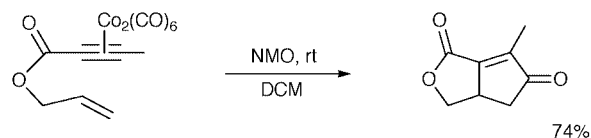**Scheme 9**

S

S—Co   Co—CO
OC CO OC   CO

Fig. 1

filling a vacant site on the coordinatively unsaturated cobalt. This represents one of the very few occasions where an intermediate in the PKR has been isolated, and is therefore an extremely important development in the methodology of the reaction. As well as sulfides, nitrogen donors have also been utilised.[12] An *in situ* preparation of bis-cobalt alkyne complexes with concomitant reaction with alkenes has been reported.[13] Reduction of cobalt bromide with zinc under an atmosphere of carbon monoxide, followed by reaction with the alkene and trifluoroacetic acid gave the organic product in reasonable yield.

2.2 New substrates

A number of interesting or new substrates have been reported. A major drawback of the PKR was the inability to have elec-
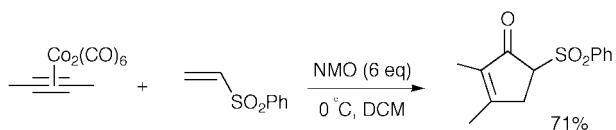
tron withdrawing substituents on the substrates. Krafft has noted that electron poor alkynes can be utilised if *N*-oxide conditions are employed.[14] This has allowed esters and amides to be used as linking groups in the intramolecular reaction (Scheme 10). Some interesting regiochemical issues are also explained by the polarity of the alkyne. Of related interest is the use of alkynyl sulfoxide complexes.[15] Activated alkenes have also been employed in the reaction (Scheme 11).[16,17] Both papers report the use of electron deficient alkenes in the reaction, and a second product that arises from a Michael reaction on the newly formed cyclopentenone. This can be minimised by the use of *N*-oxides,[17] and as such provides a route to the required substituted cyclopentenones which was not available through the classical thermal activation method. Kerr has used vinyl esters as substrates in an intermolecular PKR.[18] Of note here is the fact that the ester functionality is reduced to a methylene unit during the reaction, making this an ethylene equivalent, without the use of ethylene gas, Scheme 12. Aromatic enynes have been used as substrates for the intramolecular PKR.[19] This reaction gave rise to tricyclic cyclopentenones with some isomerisation of the double bond being noted. de Meijere[20] and Motherwell[21] have both used methylenecyclopropanes as the olefin portion of an intramolecular PKR, Scheme 13. The former reports reasonable yields of cyclopentenones with an α-cyclopropyl group whilst Motherwell notes moving the alkene to the terminus of the enyne allows either the expected product, or a rearranged hydroindenone to form. Cazes has used allenes in both inter- and intra-molecular cyclisations to produce cyclopentenones.[22] The regioselectivity with respect to the allene is dependent on the type of substitution, Scheme 14. An intramolecular version gave rise to a mixture of 5,6 and 5,5-fused bicyclic ring systems, with the remaining alkene either *exo* or *endo* cyclic, Scheme 15. Brown and Pauson have used the intramolecular PKR to produce routes to pyrrolone and pyridinones, Scheme 16.[23] Unusually, when terminal acetylenes were used, the main products were cyclopentanones. In a related reaction, Alcaide's group have used cobalt alkyne complexes to form fused tricyclic β-lactam and azetidines, Scheme 17.[24] The Pauson–Khand reaction has proven one of the most popular ways to gain access to tri- and tetra-cyclic molecules. Schore and Knudsen first used an intramolecular PKR with one pre-formed ring to produce a route to the triquinane series of compounds (Scheme 18).[25] Clive used a similar approach, but formed the third ring *via* a radical ring closing reaction.[26] Most recently, Hoshino has provided an effective synthesis of angularly fused triquinanes having two contiguous quaternary centres (Scheme 19).[27] Moving from three to four fused rings, Smit and Caple have used an intramolecular PKR followed by a [2 + 2] cycloaddition of the resultant alkene to provide a route to the fenestrane skeleton.[28] Linear tetracycles have been formed by Cook and co-workers.[29] In a remarkable double intramolecular Pauson–Khand reaction, all four rings and six carbon–carbon bonds are formed in a single synthetic step. The procedure provides the products in up to 50% yield, requiring each bond to be formed in at least 89%, Scheme 20.

O $Co_2(CO)_6$ O
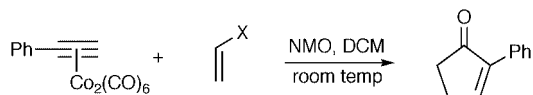=|=

O   NMO, rt   O
DCM

O   O

74%

Scheme 10

2.3 Natural product synthesis

The Pauson–Khand reaction has been used as the key step in a number of natural product syntheses. Of these, notable recent additions include: Magnus's stereospecific enyne cyclisation for the synthesis of methyl deoxynorpentalenolactone H[30] and
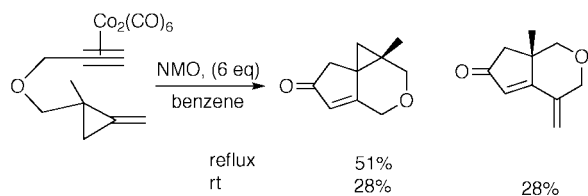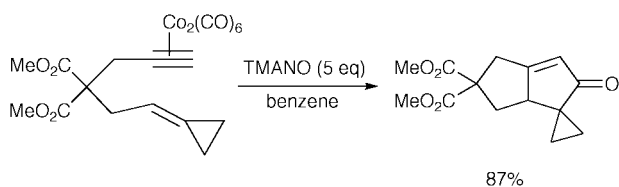
Scheme 11

X = OAc	52%
CO$_2$CF$_3$	50%
BzO	58%
^{t}BuCO$_2$	31%
Br	54%

Scheme 12

Scheme 13

74%   95:5

47%   70/30

Scheme 14

45%   80:20

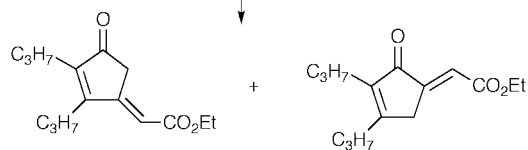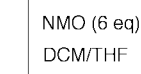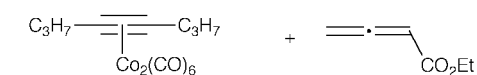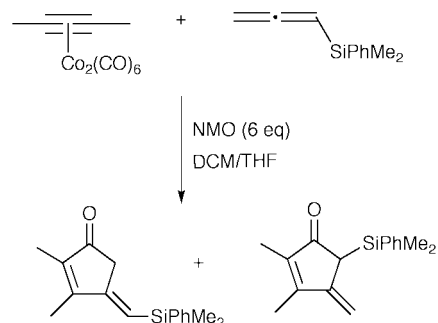**Scheme 15**

57%

Scheme 16

63%

Scheme 17

Takano's chiral approach to the dendrobine skeleton.[31] Kainic acid has attracted the attention of two different groups who have employed a similar intramolecular PKR.[32,33] Jeong and co-workers have also reported the preparation of bicyclic lactols and the application of these to a racemic synthesis of loganine.[34] Pericàs and co-workers have synthesised (+)-β-cuparenone using an intramolecular PKR.[35] This scheme uses a phenylcyclohexanol chiral auxiliary to induce selectivity in the PKR. For other syntheses, see Section 4, the intramolecular Nicholas reaction.
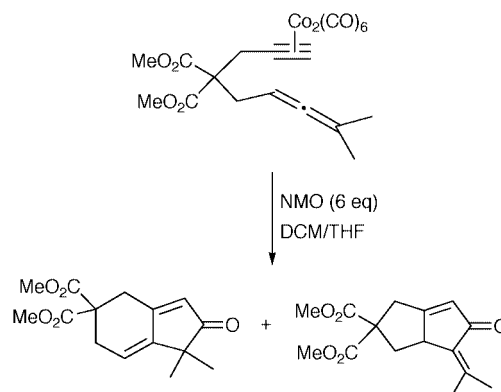
2.4   Stereoselective Pauson–Khand reaction

Various methods for making the PKR stereoselective have been introduced; however two main categories have become evident: use of a chiral auxiliary and desymmetrisation of the bimetallic core. The former has found more extensive use since it is easier to employ an external means of chirality. Chiral substrates have been used to probe both the mechanism and selectivity of the Pauson–Khand reaction. Again, much of the early work is presented in earlier reviews, and only more recent examples will be highlighted here. Schore has reported the first example of reversal of the normal stereoselectivity on the intramolecular PKR.[36] Normally, substituents show a preference for the *exo* face of the new bicyclic system, and this has been explained by the steric interactions between the *endo* allylic and propargylic positions and the alkyne terminus. However, by using a dienyne as a steric probe, the bicyclic cyclopentenoid showed a preference for the *endo* product (Scheme 21). de Meijere has used a chiral ketal to promote stereoinduction in an intramolecular PKR,[37] and a highly stereoselective Pauson–Khand reaction has been employed in the synthesis of a highly functionalised proline.[38] A substantial body of work has been produced by Pericàs and co-workers over the last five years.[39] This group started with a series of terpenoid chiral auxiliaries and tested
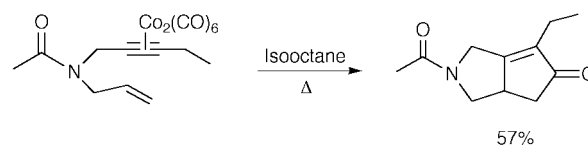
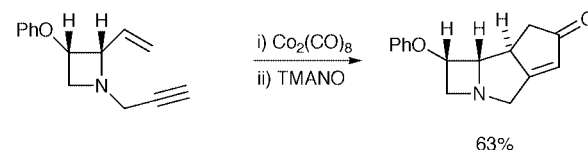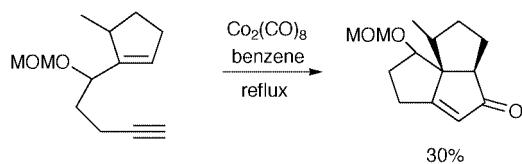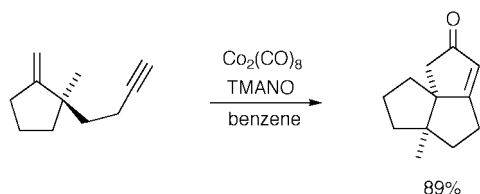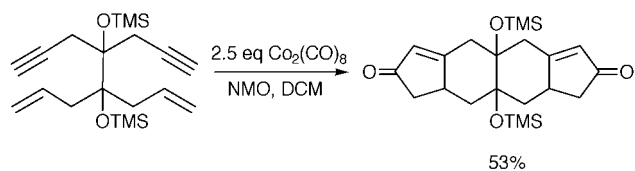them for enantioinduction in the intermolecular Pauson–Khand reaction of alkynoates. The product cyclopentenones were produced in good yield, with high regiocontrol, but the stereocontrol was variable at best.[39a] By using similar chiral
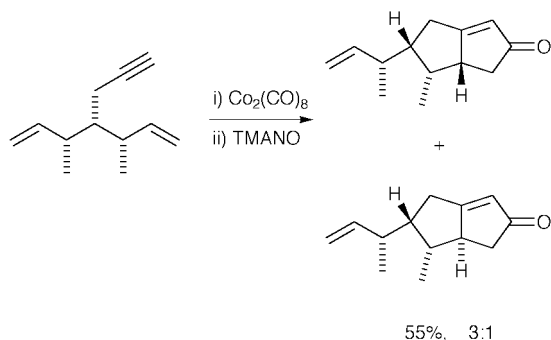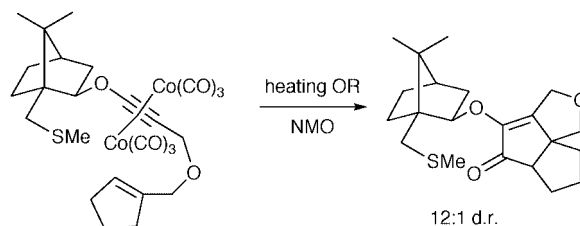
Scheme 18

MOMO → (30%) [Co₂(CO)₈, benzene, reflux]

Scheme 19

Co₂(CO)₈, TMANO, benzene → (89%)

Scheme 20

2.5 eq Co₂(CO)₈, NMO, DCM → (53%)

Scheme 21

i) Co₂(CO)₈
ii) TMANO

55%, 3:1

Scheme 22

heating OR NMO

12:1 d.r.

Scheme 23

trimethyl phosphite analogue through displacement of a CO. Separation of the isomers was followed by Pauson–Khand cyclisation to give the product cyclopentenones in 100% diastereomeric excess (Scheme 24).[40] A similar approach was adopted by Kerr and co-workers who employed the chiral phosphine glyphos, and separated the isomeric cobalt complexes.[41] Under classical cyclisation conditions of simply heating, the enantiomeric excess of the products was compromised, presumably by scrambling of the phosphine prior to reaction with the alkene. However, by promoting the reaction with an *N*-oxide, the temperature could be lowered significantly, controlling this scrambling, and the enantiomeric excesses were good to excellent (Scheme 25). These two methods differentiate the cobalts electronically. Another method of doing this is to replace one of the cobalts by a completely different metal. This has been achieved recently by making the mixed cobalt–molybdenum alkyne complexes.[42] The complexes are formed by reaction of the CpMo(CO)₃ anion on the parent cobalt alkyne complex. Having a menthyl group present on the alkyne allowed separation of the diastereoisomers, and reaction of each of these individually gave rise to a distinct cyclopentenoid products, each of which was diastereoisomerically pure (Scheme 26). All of these methods effectively differentiate the two metals of the complex, and produce high levels of stereocontrol in the product. The key will be to ascertain around which of the metal centres the cyclisation reaction is occurring. This will then allow prediction of the chirality of the cyclopentenone for a given enantiomer of metal–alkyne complex.
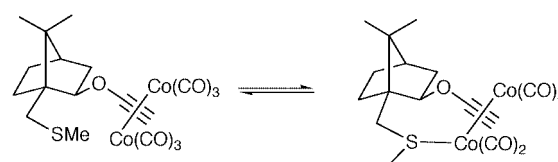
controlling elements in the intramolecular reaction, routes to fused ring compounds were produced with diastereoselectivities up to 12:1 for the formation of an angularly fused triquinane (Scheme 22).[39b] This paper also showed that a chelating sulfur group was responsible for the chiral induction by coordinating one of the diastereotopic cobalt atoms. Development of this principle led to the characterisation of what may be an intermediate in the Pauson–Khand mechanism. By reacting the hexacarbonyldicobalt alkyne complex with an *N*-oxide in the absence of any alkene, a new complex is formed, presumed to be the pentacarbonyldicobalt complex with intramolecular stabilisation through coordination of the sulfur. This complex could be converted back to the parent complex by reaction with carbon monoxide, or reacting with an alkene to give the expected cyclopentenone (Scheme 23). The more appealing method for invoking stereocontrol is to desymmetrise the metal alkyne core. The two cobalt atoms in the starting dicobalt alkyne complex are enantiotopic (or diastereotopic if there are chiral centres in the alkyne). Reaction at one of the cobalt atoms preferentially will give rise to an enantiomerically (diastereomerically) enriched product. The trick, therefore, is to render the two cobalts electronically different. The approach by Pericàs outlined above achieves this by complexing one of the cobalt atoms with a pendant sulfur prior to reaction with the alkene, and as such uses both a chiral auxiliary and a desymmetrisation approach. An alternative means is to substitute one of the carbon monoxide ligands for a phosphine, and separate the diastereoisomeric complexes. Chung and co-workers used menthyl protected propargyl alcohol complex and formed the
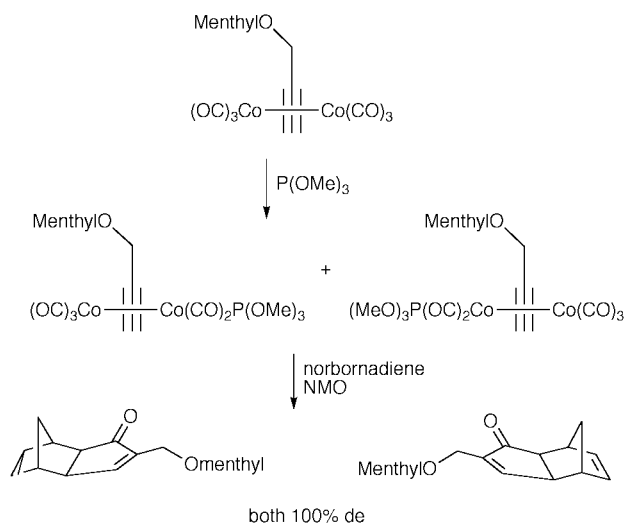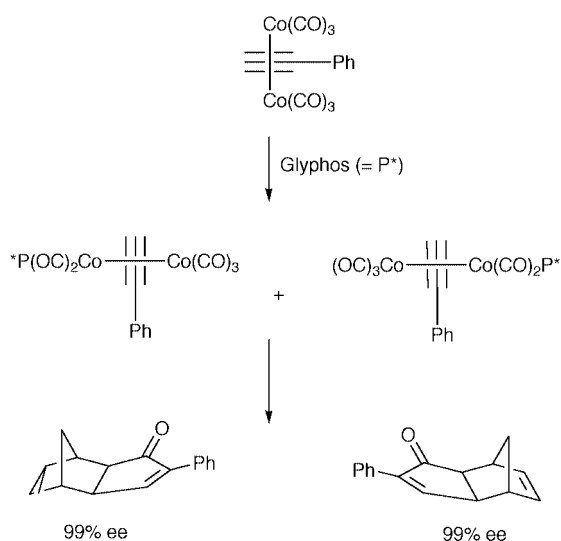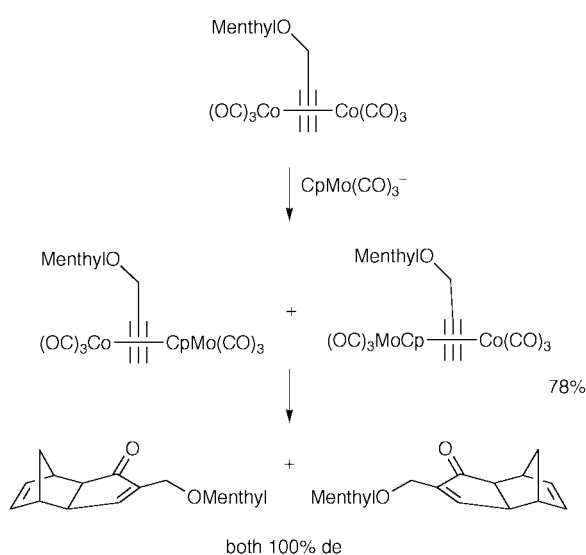
Scheme 24

MenthylO
(OC)₃Co——Co(CO)₃

↓ P(OMe)₃

MenthylO   MenthylO
(OC)₃Co——Co(CO)₂P(OMe)₃   +   (MeO)₃P(OC)₂Co——Co(CO)₃

↓ norbornadiene NMO

Omenthyl   MenthylO

both 100% de

Co(CO)$_3$
=||=—Ph
Co(CO)$_3$

Glyphos (= P*)

P(OC)$_2$Co—|||—Co(CO)$_3$ (OC)$_3$Co—|||—Co(CO)$_2$P
        | |
        Ph   +   Ph

99% ee   99% ee

Scheme 25

MenthylO

(OC)$_3$Co—|||—Co(CO)$_3$

CpMo(CO)$_3^-$

MenthylO   MenthylO

(OC)$_3$Co—|||—CpMo(CO)$_3$ +   (OC)$_3$MoCp—|||—Co(CO)$_3$

                                              78%

O   O
...—OMenthyl   +   MenthylO—...
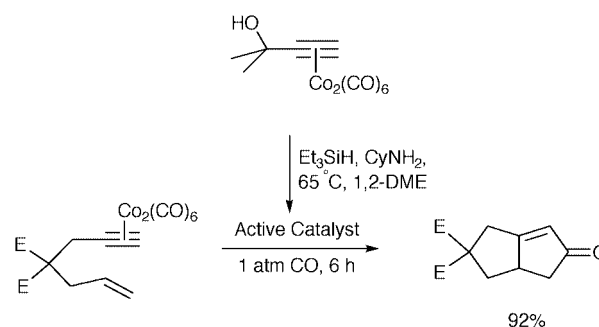
both 100% de

Scheme 26

2.5 Alternative pathways

Recently, Krafft has noticed some interesting products from Pauson–Khand reactions. In the interrupted PKR, the final product is an acyclic α,β-unsaturated ketone.[43] It appears that the normal pathway proceeds to give reaction between the alkene and alkyne. However, before carbon monoxide insertion can take place, oxidation (presumably by adventitious oxygen) releases the organic product. Further evidence for this was gained when the ratio of the new product was increased by running the reaction under an oxygenated atmosphere. Krafft has also reported the cycloisomerisation of enyne substrates to conjugated dienes through their cobalt alkyne complexes.[44] Thermolysis of 1,6- or 1,7-enynes gave monocyclic 1,3-dienes. However, deuterium labelling studies have shown that the products come from an α-elimination pathway, as opposed to the expected β-elimination. For related examples, see Section 6.

2.6 Catalytic versions

Perhaps the greatest challenge has been to make the PKR catalytic in transition metal. Most of the procedures outlined in this review have utilised a pre-formed cobalt hexacarbonyl alkyne complex and reacted this with an alkene to produce the cyclopentenone. Although this does allow preparation of three new carbon–carbon bonds, it is wasteful with respect to the metal. The key is to regenerate the metal complex and allow a
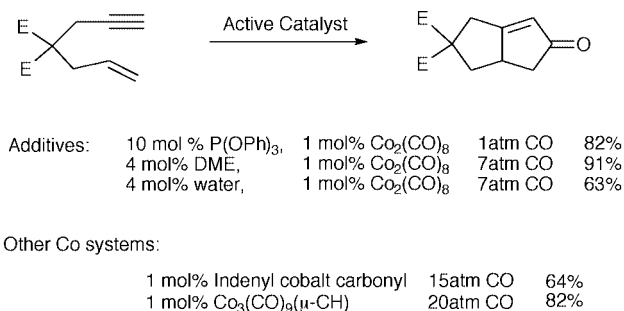
catalytic cycle to begin. This has been attempted using carbon monoxide atmosphere, and some turnover has been realised. Livinghouse has shown that dicobalt octacarbonyl on its own can catalyse the PKR.[45] The reagent must be extremely pure, and there is a small temperature window at which the reaction proceeds (60–70 °C). Using an alkyne complex surrogate circumvents the drawback of the need for ultrahigh purity cobalt carbonyl.[46] *In situ* decomplexation of a stable cobalt alkyne complex with a silane gives a catalytically active cobalt carbonyl species that can facilitate cycloaddition reaction when used at only 5 mol% (Scheme 27). Livinghouse has also reported the use of visible light as a means of promoting a catalytic PKR.[47] Using a commercially available high powered torch, and by careful control of reaction temperature, as little as 5 mol% of cobalt octacarbonyl was required to facilitate an intramolecular PKR in yields from 67–95%. Jeong and co-workers have found that addition of phospite ligands to a PKR reaction can allow the use of catalytic Co$_2$(CO)$_8$.[48] The "secondary ligands" are presumed to stop the formation of inactive metal clusters such as tetracobalt dodecacarbonyl. Yields of up to 90% are reported in an intramolecular PKR using only 3% Co$_2$(CO)$_8$. Of note in this context, Sugihara and Yamaguchi[49] have demonstrated a catalytic PKR that is mediated by a higher order metal cluster. Although the tetrameric cobalt cluster is known to be inactive, as noted above, these authors replaced one of the cobalts with a carbon to give a methylidynetricobalt cluster. This was found to be an excellent catalyst for the PKR. Yields of up to 98% were recorded with as little as 1 mol% of the catalyst, although slightly higher pressures of CO were required compared to the previous two procedures. The same authors also note the use of small amounts of 1,2-dimethoxyethane and, remarkably, water to promote the PKR.[50] Addition of these Lewis bases often gave different results in the stoichiometric and catalytic versions of the same cyclisation. Jeong and co-workers have achieved the reaction in supercritical fluids,[51] and also report[52] the use of indenyl cobalt dicarbonyl as a catalyst. This latter report, although moving away from the dimeric cobalt species, is probably related and indeed may lie halfway between the classical PKR and that mediated by other transition metals reported in Section 2.7. An overview of these methods is given in Scheme 28. One of the most notable catalytic variants involves the use of an inorganic source of cobalt, which is reduced *in situ* to an active catalyst which then reacts with the alkyne, alkene and carbon monoxide. Lee and Chung have used Co(acac)$_2$ and sodium borohydride for their protocol and achieve good yields for a number of cyclisations.[53] Rajesh and Periasamy start with cobalt bromide and use zinc as the reducing agent.[54]

HO
...=||=
Co$_2$(CO)$_6$

Et$_3$SiH, CyNH$_2$,
65 °C, 1,2-DME

E
...Co$_2$(CO)$_6$
E

Active Catalyst
1 atm CO, 6 h

E
...=O
E

92%

Scheme 27

2.7 Other transition metals

The use of other transition metals has seen significant advances in the catalytic preparation of cyclopentenones. Buchwald has shown that titanocene complexes can be used for coupling of alkenes and alkynes in the presence of carbon monoxide or an isocyanide.[55] Initial studies used titanocene dichloride as a

Scheme 28

Active Catalyst

Additives:
10 mol % P(OPh)₃,	1 mol% Co₂(CO)₈	1atm CO	82%
4 mol% DME,	1 mol% Co₂(CO)₈	7atm CO	91%
4 mol% water,	1 mol% Co₂(CO)₈	7atm CO	63%

Other Co systems:

1 mol% Indenyl cobalt carbonyl	15atm CO	64%
1 mol% Co₃(CO)₉(μ-CH)	20atm CO	82%

Scheme 28

Scheme 29

Active Metal

|		
R = Me, R' = H,	5 mol% Cp₂Ti(PMe₃)₂, Et₃SiCN,	71%
R = Me, R' = H	5 mol% Cp₂Ti(CO)₂	94%
R = H, R' = H,	(CpMo(CO)₃)₂	50%
R = H, R' = H,	Mo(CO)₆	76%
R = H, R' = H,	W(CO)₆	60%
R = H, R' = H,	Fe(CO)₄(acetone), CO pressure	55%
R = H, R' = H,	cat. Ru₃(CO)₁₂, CO pressure	47%

Scheme 29

pre-catalyst with a Grignard reagent for activation to the unsaturated titanocene intermediate. This then complexes the enyne, and provides a template for the reductive cyclisation to a titanocycle. Reaction of this with an isocyanide is followed by reductive elimination to give the iminocyclopentenes, which are hydrolysed to the cyclopentenones. Since then, Buchwald and co-workers have developed the reaction. Recent advances include an enantioselective version[55e] using a derivative of Britzinger's catalyst. This proceeds in the same general manner as the previous example, except that the dicarbonyl catalyst is used, and the reaction is carried out under CO pressure. Both chemical yield and enantiomeric excess of the products are good to excellent. Closely related to this work is Negishi's zirconium mediated bicyclisation of enynes.[56] This proceeds *via* much the same mechanism as the titanium version, but is perhaps more demanding with respect to functional group compatibility. The cyclopentenone forming reaction most closely related to the PKR was reported in 1992 by Hanaoka and co-workers.[57] Here, a dimolybdenum alkyne complex was reacted with alkenes to give the corresponding cyclopentenones. The starting complex is isoelectronic with the biscobalt species, and has a very similar geometry. The only difference in the two reactions is the regiochemical control with respect to the alkyne. Monomeric molybdenum has also been shown to effect the same cycloaddition.[58] Molybdenum hexacarbonyl, in the presence of dimethyl sulfoxide and under an atmosphere of CO, produces the same overall cyclisation of alkene, alkyne and carbon monoxide. Brummond and co-workers have reported the use of allene substrates in the intramolecular PKR using molybdenum hexacarbonyl as the transition metal reagent.[59] This gives rise directly to α-methylenecyclopentenones, a strutural feature which is important in a number of antibiotics. Similarly, tungsten hexacarbonyl has been employed by Hoye and Suriano.[60] This was termed a semi-batch process since the stoichiometric tungsten could be recovered and recycled in subsequent batches. Continuing along the transition metal series, both iron[61] and ruthenium[62] carbonyls have been reported to catalyse cycloadditions, as has a rhodium(I) species.[63] The last major series of studies has been done on nickel mediated cyclisations.[64] These reports use either nickel (cyclooctadiene) or nickel tetracarbonyl as the starting catalyst. Buchwald also reports the use of chiral ligands in an attempt to induce to asymmetric control in the cyclisation.[64d] Again, an overview of these is presented in Scheme 29. Most of the above reactions involve the use of catalytic amounts of transition metal complex with either carbon monoxide or an isocyanide. Each has pros and cons as to the utility in the lab, as well as functional group compatibility. To date, none has challenged the traditional Pauson–Khand protocol of a bis-cobalt alkyne complex in overall ease of use, but each may be a viable option in a given set of circumstances. However the underlying message seems to be that different transition metals can facilitate similar cyclisation reactions. This allows the chemist to design a protocol using the known chemistry of a given metal and apply it to different substrates, thus allowing new reactions, or at least procedures, to be realised.
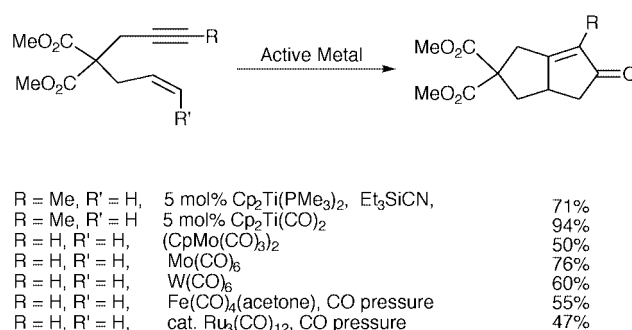
3 Cobalt mediated [2 + 2 + 2] cycloadditions

A number of different transition metal systems have been used for alkyne oligomerization[65] and trimerization[66] in particular. Trimerization of alkynes is the most common cyclooligomerization process catalysed by cobalt, the product being an arene. Although entropically the reactions should proceed very slowly if at all, the metal acts as a template to bring the alkynes together and around which cyclisation can take place. A generally accepted mechanism is given in Scheme 30. Binding of two alkyne units is probably followed by a redox process that renders the metal coordinatively unsaturated again. A third alkyne can be complexed, and this can insert into the metallacycle to give a metallacycloheptatriene. An intermediate of this type has been isolated by Vollhardt and co-workers.[67] Reductive elimination produces a π-coordinated arene. The metal can then pick up further alkyne units to complete the catalytic cycle. Alternative mechanisms invoke a Diels–Alder type reaction of the metallacyclopentadiene with the third alkyne.[68] Albright and co-workers have recently published a theoretical study of the trimerization process with CpCo,[69] which suggests that formation of the metal bound arene may arise from a cobalt mediated intramolecular Diels–Alder reaction. Most of the pioneering chemistry in this area was done in the 1970's and 1980's and the reader is directed to the reviews indicated above for this work. This review will principally deal with developments since 1990.
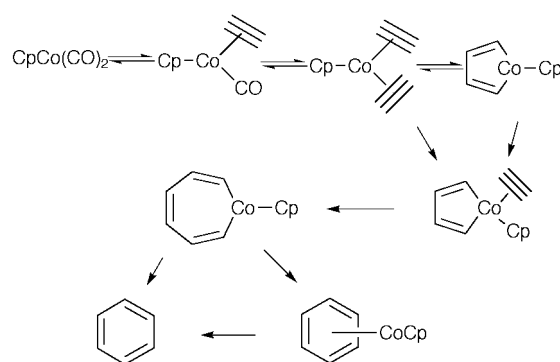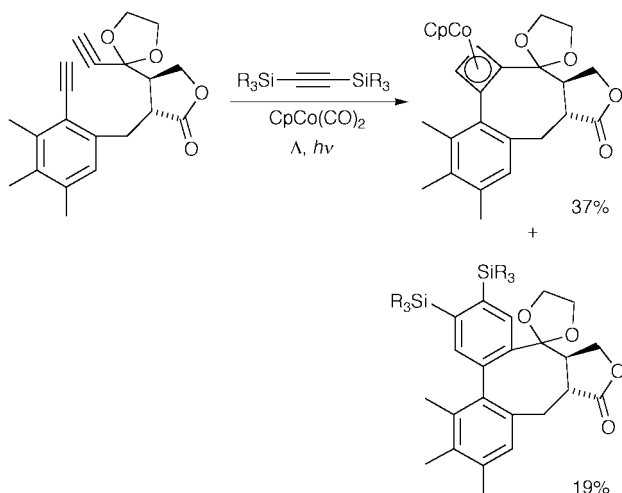
Scheme 30

Recent work on this cycloaddition reaction has focussed on the use of different starting materials to produce novel organic products. Vollhardt has used the reaction in an iterative fashion to build up angular [4] and [5] phenylenes.[70] As outlined in Scheme 31, this clever synthesis uses the cobalt cyclisation to build up one aromatic ring at a time, before inserting more acetylene units to continue the framework. This cyclisation is also of use in natural product synthesis. In the synthesis of steganone,[71] Motherwell used a diyne and an external alkyne to produce one of the two aromatic rings. Interestingly, the main product of the reaction was a cyclobutadiene cobalt complex, shown in Scheme 32, which must arise from cyclisation of the
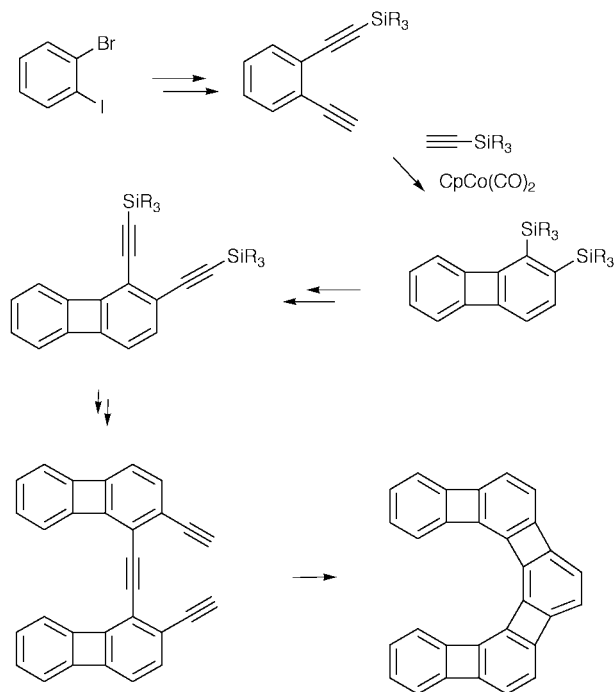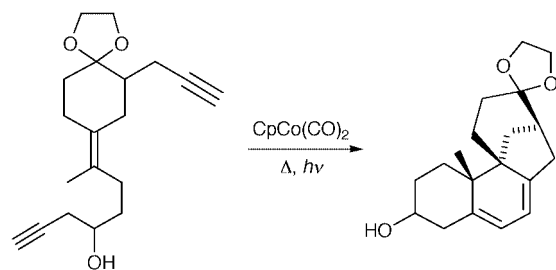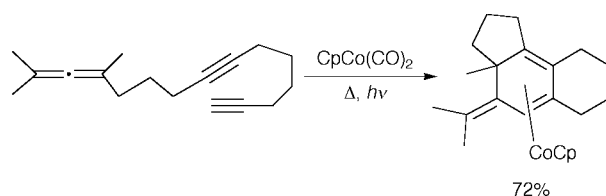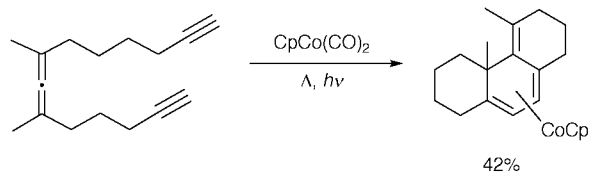
Scheme 31

Scheme 32

Scheme 33

Scheme 34

two alkyne units, but not incorporation of the third. Malacria and co-workers have found a similar problem during their route to the taxane skeleton.[72] Here, the reaction was completely intramolecular, but the main product was again a cyclo-butadienecobalt complex. By using an alkene as one of the coupling partners, cyclohexadienes can be formed.[73] This has been used in the production of natural products, such as stemodane,[74] which utilised an enediyne precursor for cyclisation by cobalt in a reasonable 55% as a mixture of isomers (Scheme 33). The use of an alkene as a coupling partner has been extended to more diverse functionality to provide routes to interesting types of skeletons. Furan[75] and indole[76] have both been used in this respect, the latter being used in the synthesis of natural products such as γ-lycorane. Malacria and co-workers have also shown that allenes can be used to provide tricyclic frameworks from acyclic precursors (Scheme 34).[77] Further extension of the protocol to the synthesis of pyridines has been achieved by incorporating a nitrile into the cyclisation process. Using this procedure, a route to lysergene has been published.[78] Saá and co-workers have incorporated the use of nitriles to great effect in their synthesis of 2,2′-bipyridines.[79] In a remarkable one-pot procedure, this group has made sym-

metrical substituted bipyridines from acyclic precursors using the cobalt mediated [2 + 2 + 2] cycloaddition to form six carbon–carbon bonds in up to 63% yield (Scheme 35). The stereoselectivity of the cyclisation has been addressed by using chiral phosphine oxides substituted onto linear enediynes.[80] Moderate diastereoselectivities (up to 77%) were realised using this procedure. Finally, Eaton and co-workers have found that by modifying the catalyst, the cyclisation can be performed in water.[81] Suitable substitution on the cyclopentadienyl ring facilitates the solubility of the catalyst, and yields of up to 85% have been recorded (Scheme 36).

R = CH₂OMe   63%   2.7:1
R = CH₂OSiEt₃ 45%   4:1
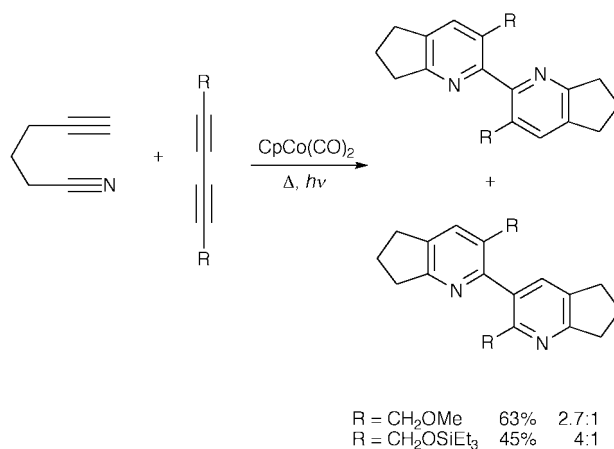
Scheme 35

4   Intramolecular Nicholas reactions

The use of dicobalt hexacarbonyl alkyne units to stabilise prop-argylic cations has been noted for almost twenty years, and these are commonly referred to as Nicholas carbocations.[82] These have found extensive use in synthesis and have been the subject of mechanistic and physical studies. In keeping with the theme of the rest of this review, here we will look at only intramolecular cyclisations onto a Nicholas carbocation.

Scheme 36

cod = cyclooctadiene
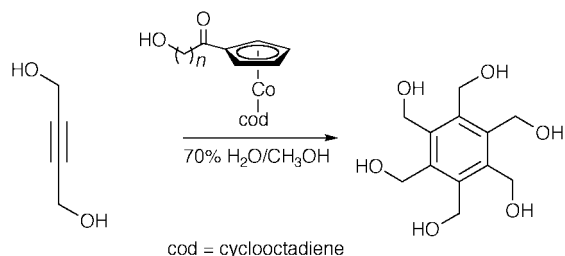
The use of heteroatoms to close onto a Nicholas carbocation has found use for the formation of heterocycles. In this vein, Mukai, Hanaoka and co-workers have produced a definitive method for the preparation of tetrahydrofuran and tetrahydropyran systems containing ethynyl substituents.[83] Using alkynyl epoxides with suitable pendant hydroxy groups, the cobalt complex forces the alcohol to cyclise onto the propargylic position (Scheme 37). Proof that the metal was the controlling influence was gained by running the reaction without the cobalt being complexed to the alkyne.[84] In this case, a mixture of compounds was formed, with the regioselectivity being determined by the substituent on the alkyne. The reaction was also found to be highly stereoselective since *trans* epoxides gave predominately the *cis* product, and *cis* epoxides gave rise to the *trans* substituted pyran. Isobe and co-workers have used the stabilising effect of cobalt complexed propargylic cations to great effect in sugar-acetylene chemistry.[85] Of particular note is the recent publication of a one step recyclisation of sugar acetylenes to form medium ether rings.[86] The C-1 alkynylated glucals were recyclised to give seven to ten membered rings (Scheme 38). Also of note here is the stability of the strained cyclic acetylene, which is stabilised by complexation to the cobalt fragment. It is interesting that this stabilisation was cited as the reason for the difficult deprotection of these complexes. Palazón and Martín have shown that medium sized cyclic ethers can also be produced by a Nicholas mediated synthesis.[87] Extension of the basic principle has allowed access to the skeleton of polycyclic ethers such as brevetoxin.


trans epoxide: 96%, 99:1
*cis* epoxide : 93%, 1:99

Scheme 37

40%
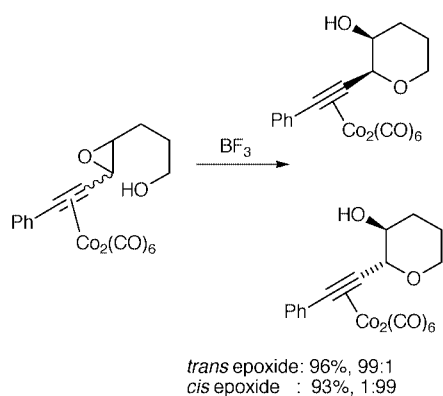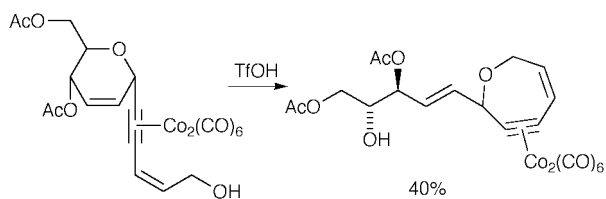
Scheme 38

The use of carbon nucleophiles to effect ring closure onto a Nicholas carbocation has also received a good deal of attention. Grove and co-workers have employed a Friedel–Crafts

type reaction to synthesise octahydrophenanthrenes (Scheme 39).[88] Boron trifluoride mediated formation of the Nicholas carbocation resulted in cyclisation onto the electron rich aromatic ring. The stereoselectivity of the reaction was increased to synthetically acceptable levels by cooling the reaction to low temperature. Muehldorf and co-workers have noted a similar reaction.[89] These authors also found that the stereochemical integrity of the reaction was closely related to reaction temperature. Thus conducting the reaction below $-50 \, ^{\circ}C$ led to high selectivity, but above this extensive racemisation occurred, presumably in the Nicholas carbocation itself, prior to cyclisation. Another stereoselective use of cobalt stabilised propargylic cations has allowed access to enantiomerically pure α-hydroxy acid derivatives.[90] Elaboration of camphoric acid provided separable alkynyl alcohol complexes that could be further manipulated to provide optically enriched organic end products. Of interest here is the observation that use of methanol as the nucleophile gave a kinetic mixture of substituted alkyne complexes, but when acetic acid was employed and the reaction left for a period of time, the thermodynamic product was produced in excess (Scheme 40). This presumably arose due to the acetate being able to act both as a nucleophile and an effective leaving group under the reaction conditions. Synthesis of β-alkynyl ketones has been achieved by the intramolecular attack of a silyl enol ether onto a pendant Nicholas carbocation.[91] This route has produced a range of cyclic products from four to eight membered rings. A similar approach has also been used to provide access to fused carbocycles.[92] Even mild nucleophiles such as alkenes can be used as effective partners in an intramolecular Nicholas reaction. Tyrell and co-workers have shown that trisubstituted alkenes can cyclise onto a pendant Nicholas carbocation to give rise to benzopyrans in a diastereoselective manner.[93] Finally, Green has effected an intramolecular cyclisation to produce a cycloheptyne cobalt complex.[94] In a remarkable procedure, an allylsilane on one end of a complexed alkyne is forced to cyclise onto a carbocation formed at the other terminus (Scheme 41). The resultant complex is formed in high yield and is thermally stable, unlike the parent alkyne.

Scheme 39

NuH = MeOH: 51%, 12:88
AcOH: 80%, 88:12
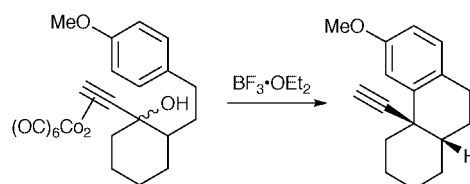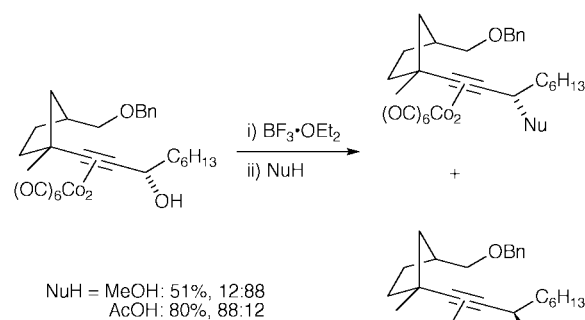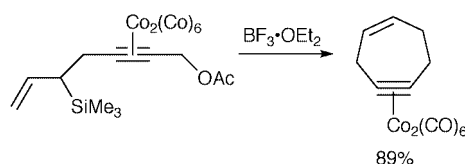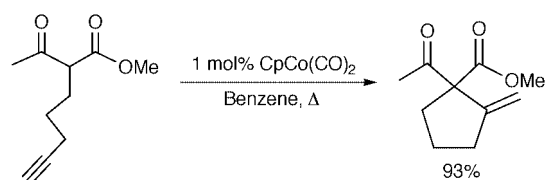
Scheme 40

The power of the intramolecular Nicholas reaction is perhaps best illustrated when it is used in natural product synthesis. The ability to effect this type of cyclisation in high yield and under relatively mild reaction conditions has made it of great synthetic value. Nicholas himself has used the reaction during the synthesis of a pseudoguaianolide intermediate.[95] Magnus
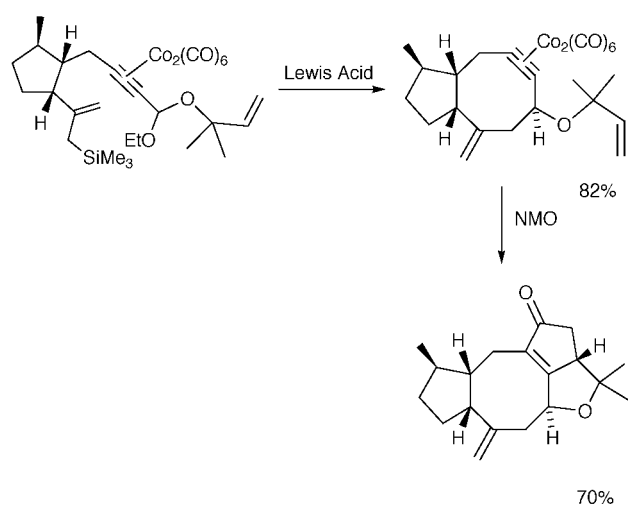
Scheme 41

Scheme 43

has published routes to related neocarinostatin and dynemicin cores using propargylic cation cyclisations.[96] The route was very appealing since the desired molecule has the sensitive enediyne functionality present. The cobalt not only facilitates the cyclisation to stitch the molecule together, but also helps to stabilise the molecule during the synthesis. The total synthesis of (+)-secosyrin also used a cobalt mediated cyclisation as the key step.[97] Schreiber has made extensive use of cobalt mediated reactions in his synthesis of (+)-epoxydictymene (Scheme 42).[98] Firstly, the cobalt alkyne complex is used in a Nicholas cyclisation to provide the requisite eight membered ring. With the cobalt still present in the product, this was then used to form two more rings. An intramolecular Pauson–Khand reaction furnished the two fused five membered rings in high yield with a high degree of stereocontrol. This use of two cobalt mediated reactions in tandem, provides a remarkably quick and efficient entry to a highly complex structure containing four fused rings. It illustrates how organometallic chemistry can be used to great effect to solve problems in the synthesis of organic molecules.
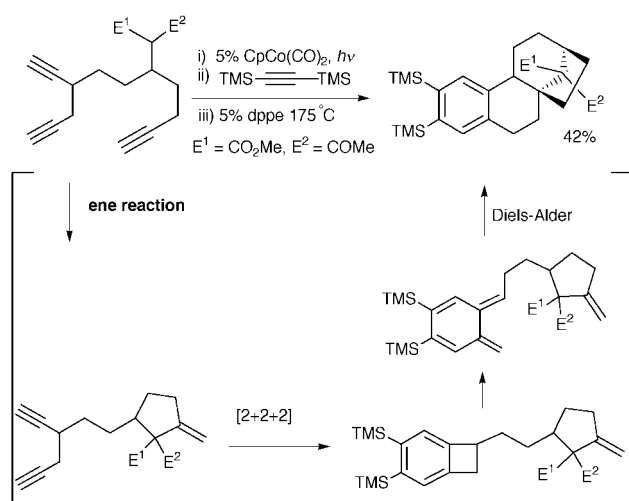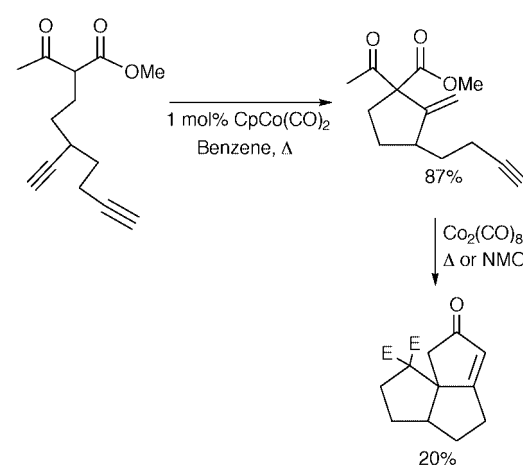

Scheme 42

5 Other cyclisations and tandem reactions

As outlined in the previous sections, there are a number of distinct cyclisations that cobalt facilitates, and these have found great use in organic synthesis. An interesting protocol has been developed by Malacria over the last five years:[99] an activated methylene unit with a suitably placed alkyne group can, in the presence of a $CpCo(CO)_2$, undergo a cycloisomerisation to produce the corresponding exocyclic methylene (Scheme 43). Using a β-keto ester, a study on the diastereoselectivity of the reaction has shown that reasonable levels of stereocontrol can be achieved.[100] However, the most impressive use of this strategy is when it is coupled with another cobalt mediated cyclisation. Malacria noticed that the exocyclic methylene produced in this reaction could be used in a subsequent reaction to provide further elaboration of the carbon framework. Setting up an acyclic triyne skeleton allowed a series of tandem reactions to proceed: a cycloisomerisation reaction to produce an exocyclic methylene, then a [2 + 2 + 2] cycloaddition with an external alkyne; the benzocyclobutene produced in this opens to provide a Diels–Alder substrate which cyclises onto the

pendant exocyclic methylene (Scheme 44). This remarkable sequence, involving three separate cycloaddition reactions, produces four new carbon–carbon bonds, and five rings from an acyclic precursor in an overall yield of 42%. Not content with this, Malacria has also coupled up his cycloisomerisation with an intramolecular Pauson–Khand reaction.[101] Again, the exocyclic methylene unit acts as a substrate for a second cobalt mediated process (Scheme 45). The Pauson–Khand reaction only proceeds in 20% yield, but this procedure still provides a remarkably quick route to angularly fused triquinanes.

Scheme 44

Scheme 45

A few other miscellaneous cobalt mediated cyclisations deserve comment. Malacria has published an enyne cyclisation,[102] and a related Alder-ene reaction on alleneynes[103] both mediated by $CpCo(CO)_2$. In a procedure related to the Pauson–Khand reaction, Soai has shown that two alkynes can be coupled to give a cyclopentadienone (Scheme 46).[104] This highly reactive species can then act as a substrate for a [2 + 2 + 2] cycloaddition to yield the tetracyclic product. Finally, cobalt has also been shown to mediate a [3 + 2 + 2][105] and a [4+2+2] cyclisation.[106]
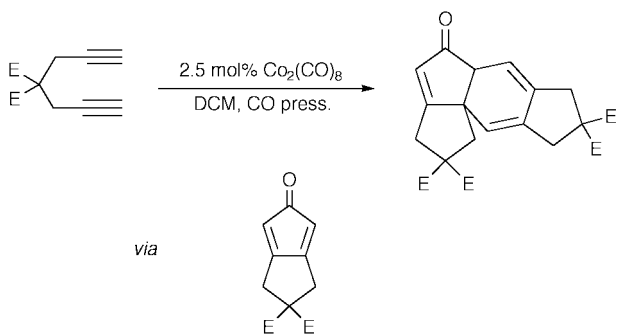
Scheme 46

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