Developing Novel Synthetic Methods for the Pauson-Khand Reaction

A Thesis submitted in part fulfillment of the requirements of the degree of Doctor of Philosophy

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Dedicated to my family

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Contents

Abbreviations

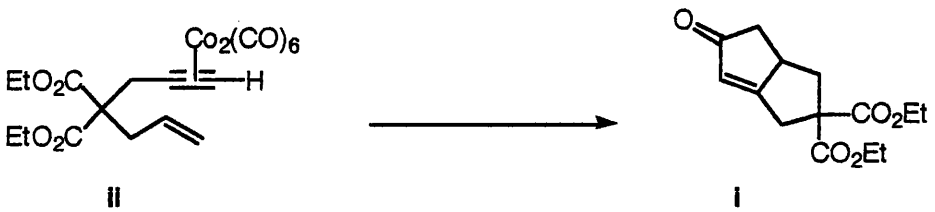
Ac	acetyl
aq.	aqueous
APCI	atmospheric pressure chemical ionisation
Ar	aromatic
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
br	broad
BuLi	butyl lithium
°C	degrees centigrade
CI	chemical ionisation
cod	cyclooctadiene
d	doublet (NMR spectroscopy)
d	day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DCM	1,2-dichloromethane
de	*diastereomeric excess*
DEPT	distortionless enhancement through polarisation transfer
DIBAL–H	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
DVB	divinyl benzene
EBTHI	ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)
ee	*enantiomeric excess*
EI	electron ionisation
FT	Fourier Transform

h	hour(s)
GLC	gas liquid chromatography
HL	high loading
Hz	Hertz
HRMS	high resolution mass spectrum
IR	infra red
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
m	multiplet (NMR spectroscopy)
Me	methyl
min	minute(s)
mol	mole(s)
NMM	*N*–methyl morpholine
NMO	*N*–methyl morpholine *N*–oxide
NMO.H_2O	*N*–methyl morpholine *N*–oxide monohydrate
NMR	nuclear magnetic resonance
PKR	Pauson-Khand reaction(s)
q	quartet (NMR spectroscopy)
RT	room temperature
s	singlet (NMR spectroscopy)
t	triplet (NMR spectroscopy)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMANO	trimethylamine *N*–oxide
TMANO.$2H_2O$	trimethylamine *N*–oxide dihydrate
TMEDA	*N,N,N',N'*–tetramethylenediamine
Ts	tosyl

Summary

The Pauson-Khand cyclisation is one of the most useful reactions for the formation of cyclopentenone ring systems. It is a [2 + 2 + 1] cycloaddition between an alkyne, alkene and one molecule of carbon monoxide. The reaction is mediated by dicobalt octacarbonyl. The aim was to develop a general and simple route to generating cyclopentenone ring systems utilising the Pauson-Khand cyclisation.

We chose to use amines as promoters as opposed to the more commonly used amine *N*-oxides. An efficient route to cyclopentenone **i** was developed. Substrate **ii** was heated to 50 °C for 24 hours in 5:1 toluene/isopropanol with 3 equivalents of NMM under air (*Scheme A*).

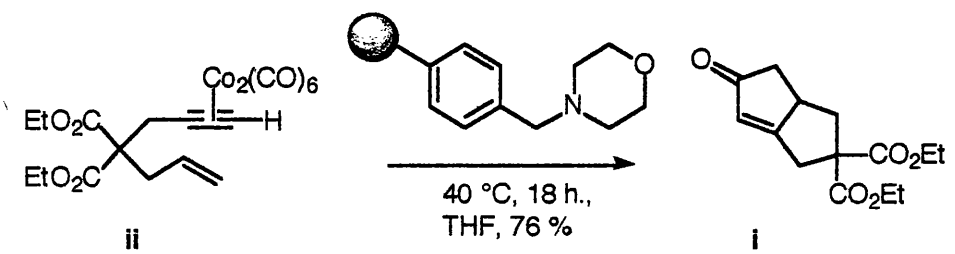


ii **i**

Scheme A

A yield of 84 % of **i** was obtained. The route was shown to be effective for other substrates that are commonly used in the Pauson-Khand reaction.

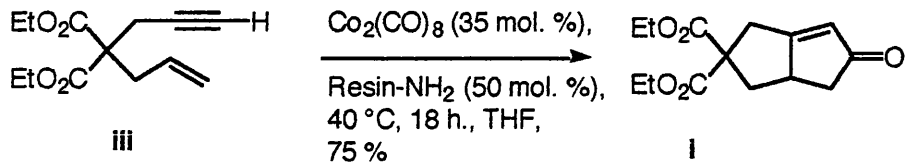
The next strategy was to use solid supported amines as promoters. The advantage was that the solid supported amines could be recycled. Several promoters were tested and the results were promising (an example is shown in *Scheme B*).



ii **i**

Scheme B

In our previous Pauson-Khand reactions, we used three equivalents of the amine promoter. We proceeded to successfully develop an efficient route to the cyclopentenone products **i** using a substoichiometric amount of dicobalt octacarbonyl (*Scheme C*).



Scheme C

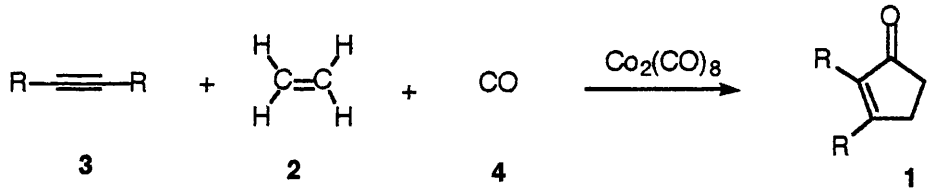
We demonstrated that the above conditions worked on a variety of substrates and the resin was recycled 5 times with no detrimental loss of yield of **i**.

The references included in this text are current until the end of November 2001. This was when I left Glasgow University and no longer had access to a library or the electronic journals for personal use.

Chapter 1

1.1 Introduction

The Pauson-Khand cycloaddition is one of the most synthetically useful and powerful reactions for the generation of cyclopentenone systems **1**.[1-5] Whilst researching the formation of alkene **2** and alkyne complexes **3** with cobalt, Ihsan Khand, working within the research group of Peter Pauson, discovered the presence of metal free cyclopentenone-containing compounds **1**. In 1973, the reaction between the π-bond of the alkyne **3**, the π-bond of the alkene **2** and one molecule of carbon monoxide **4** was first described as a [2 + 2 + 1] cycloaddition.[2] It is important to note that the annulation is mediated by a stoichiometric amount of dicobalt octacarbonyl (*Scheme 1*).[2]

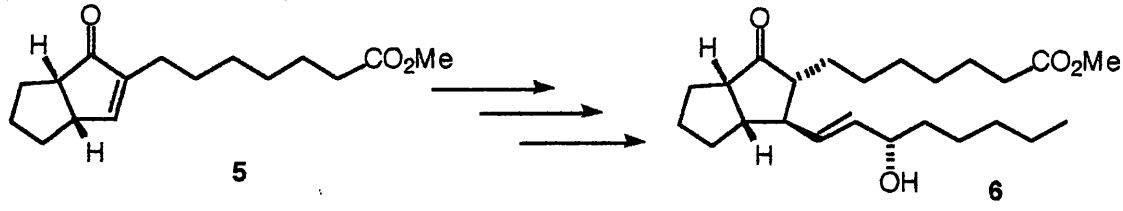


3 **2** **4** **1**

Scheme 1

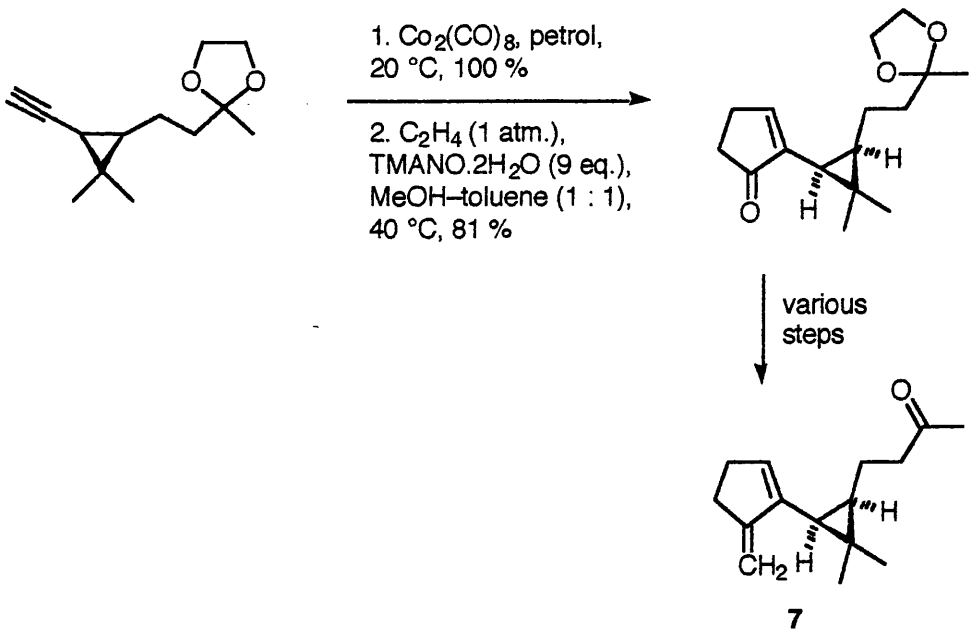
1.2 Applications in Synthesis

The Pauson-Khand reaction (PKR) has been widely used in organic synthesis. For example, Pauson and co-workers synthesised the prostaglandin precursor **5** before conversion into the prostaglandin analogue (±)-11-deoxy-10α,11α-trimethylene-prostaglandin E_1 methyl ester **6** (*Scheme 2*).[6]



Scheme 2

Kerr and co-workers have also applied the PKR to synthesise the natural product (+)-taylorine **7** utilising the conditions that they had developed to incorporate gaseous ethylene as the alkene component in the process (*Scheme 3*).[7]

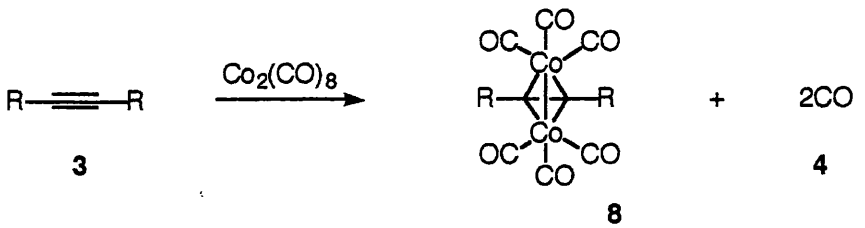


Scheme 3

Other examples of the PKR include the synthesis of Japanese hop ether by Pauson and co-workers[8] and a simple synthesis of (±)-α-cuparenone by Chavan *et al.*[9]

1.3 Mechanism of the Pauson–Khand Cyclisation

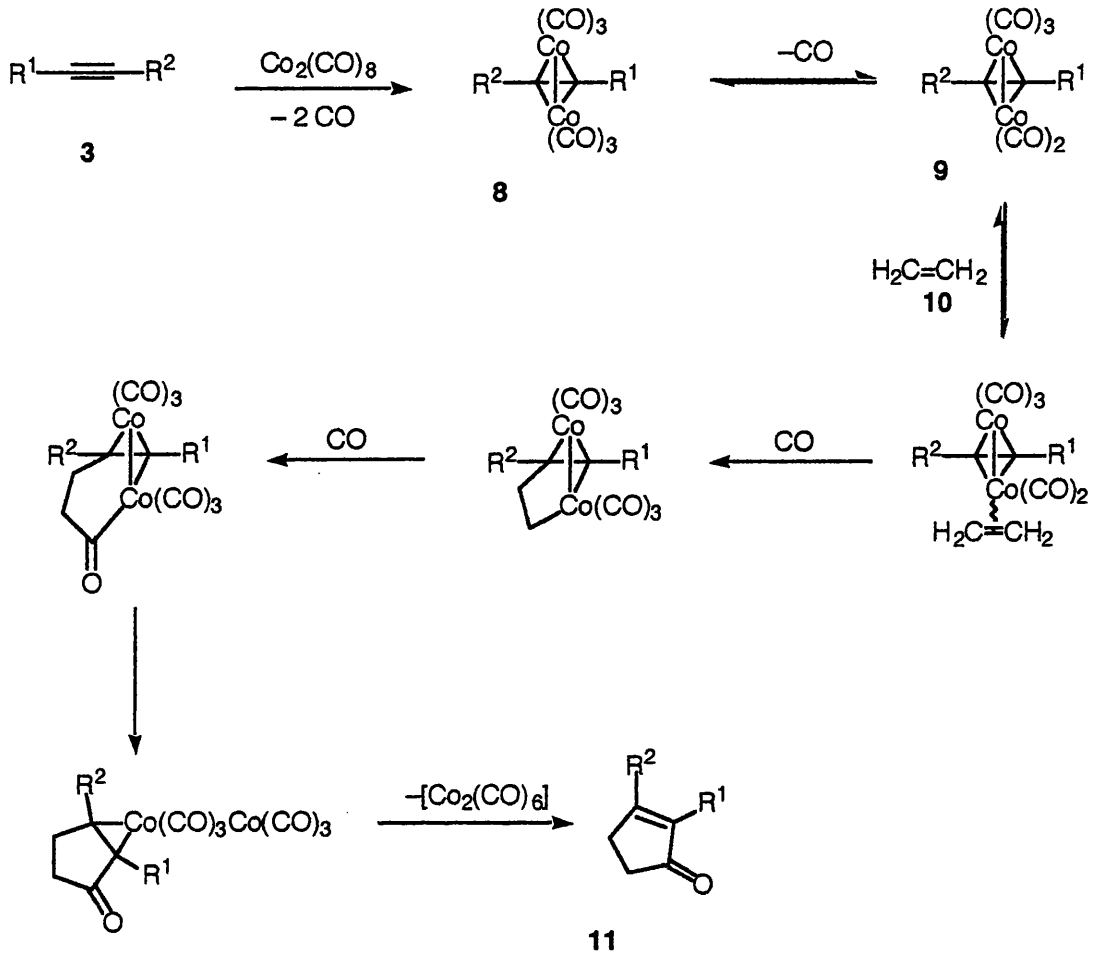
Until very recently, the mechanistic details of the PKR were unclear. It was thought that alkyne **3** underwent complexation with dicobalt octacarbonyl replacing two of the bridging carbonyls in a direct reaction, generating a hexacarbonyl dicobalt complex **8** (*Schemes 4 and 5*).[1]



Scheme 4

Loss of one carbon monoxide group created a vacant site around the cobalt atom **9**. The hexacarbonyl complex **9** was then believed to react with the alkene component **10**. Following reduction and elimination processes at one cobalt atom and complex breakdown at the other, there was subsequent insertion of a carbonyl group producing the cyclopentenone ring **11** (*Scheme 5*). Very recently Nakamura and co-

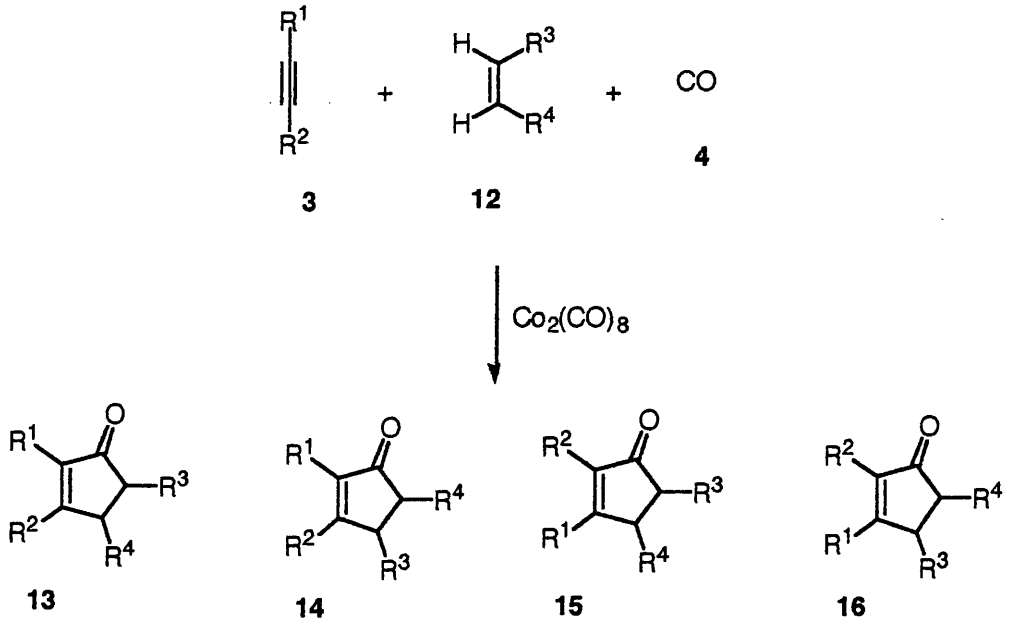
workers have conducted density functional studies on the PKR.[10] They have concluded that the currently accepted mechanism is indeed the correct one with the alkene insertion step being the critical step for determining stereo- and regio-chemistry.



Scheme 5

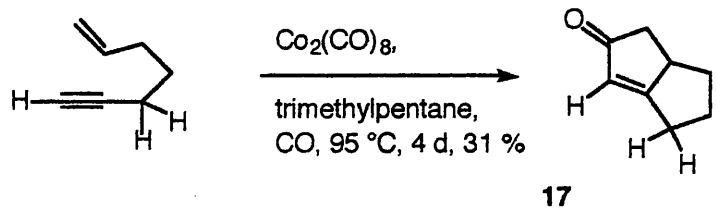
1.4 Intramolecular Pauson–Khand Cyclisations

In the intermolecular PKR, there is no element of control over the orientation of the alkyne **3** and alkene **12**, although Pauson noted that the bulkiest substituent on the alkyne **3** tended to align itself next to the carbonyl group[2,11] but any of the four possible structural isomers **13**, **14**, **15** or **16** could form (*Scheme 6*). Poor reactivity of some alkenes and alkynes coupled with a lack of control of stereoselectivity have limited the potential of this reaction and its use in synthesis has been hindered considerably.



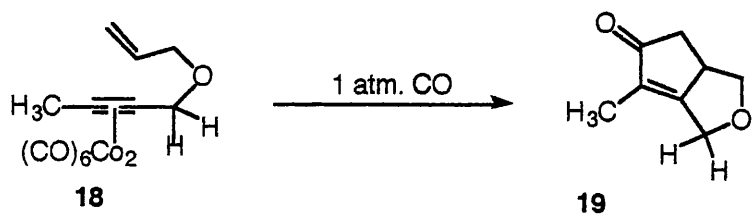
Scheme 6

Schore and Croudace developed the intramolecular reaction to overcome the problems of regioselectivity associated with the intermolecular reaction.[12] Only one of the four possible structural isomers **17** was formed (*Scheme 7*).



Scheme 7

Billington and Willison found milder conditions for the PKR and conducted the first synthesis of heterobicyclic compounds *via* the intramolecular reaction in reasonable yield (*Scheme 8*).[13] When cobalt complex **18** was reacted in isooctane at 60 °C for 24 hours under an atmosphere of carbon monoxide, product **19** was isolated in a yield of 41 %.

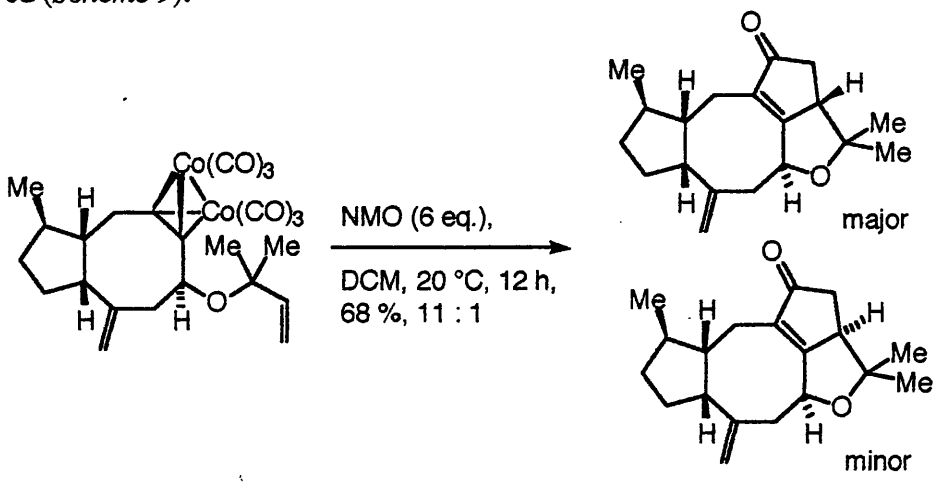


Scheme 8

1.5 Development of Amine *N*-Oxide Promoters

The development of promoters in the late 1980s has increased the yields, ease and use of the PKR. Originally Pauson and co-workers tested a range of amine *N*-oxides.[14] Tertiary amine *N*-oxides were efficient promoters but in the Pauson group found the results were found to be erratic. Despite these findings, amine *N*-oxides are still the most popular promoters. *N*-Methylmorpholine *N*-oxide (NMO) (*Scheme 9*), and trimethylamine *N*-oxide (TMANO) are two of the most commonly employed. It was believed that these compounds oxidised metal-bound carbonyl ligands to carbon dioxide and provided free coordination sites for the alkene. The reaction conditions were milder and thus reactions could be conducted at room temperaure and a wider range of functionality could be tolerated. The prospect of inducing stereoselectivity in the PKR was also within reach.

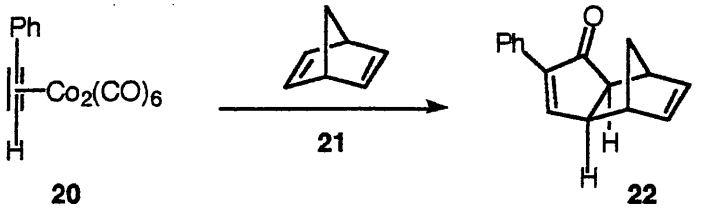
Although Magnus and co-workers originally used NMO in the work-up procedure of the PKR[15] it took Schreiber and co-workers to develop it effectively as a promoter of the cyclisations.[16] They found that, since lower temperatures could be used, more functionality could be tolerated and higher levels of stereoselectivity were observed (*Scheme 9*).



Scheme 9

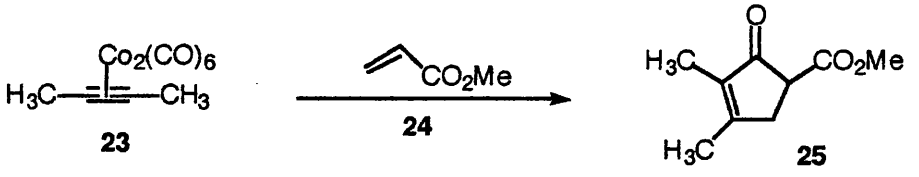
Jeong and co-workers had also been working with amine *N*-oxide promoters and developed a set of conditions using TMANO.[17] Again, lower temperatures and shorter reaction times meant that this process had many advantages over the thermally promoted PKR. When cobalt complexed phenylacetylene **20** was reacted with norbornadiene **21** in the presence of 3 equivalents of TMANO in dichloromethane

(DCM) at 0 °C for 2 hours, **22** was isolated in 80 % yield with a diastereomeric ratio of 83 *exo* : 17 *endo* (*Scheme 10*).[18]



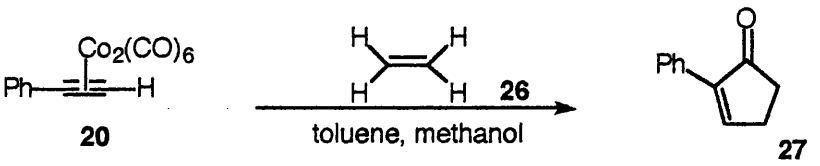
Scheme 10

Cazes and co-workers examined the use of amine *N*-oxides in conjunction with alkenes having an electron withdrawing group, such as an ester or cyano group. These alkenes are very unreactive in the thermally promoted PKR, often leading to the formation of conjugated dienes *via* a β-hydrogen elimination process. However, in the hands of the Cazes group, the alkenes reacted in the manner anticipated and formed cyclopentenone products in reasonable yields.[19] When cobalt complex **23** was reacted with 2 equivalents of methyl acrylate **24** in the presence of 6 equivalents of NMO in DCM / tetrahydrofuran (THF) (2 : 1) at 20 °C for 4 hours, **25** was isolated in 59 % yield (*Scheme 11*).



Scheme 11

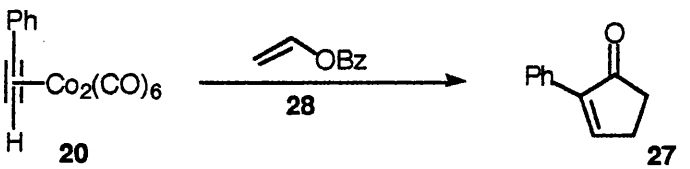
Kerr and co-workers also investigated the use of amine *N*-oxides as promoters in the PKR. One of their most significant achievements was to induce mild and efficient cyclisation of ethylene with various substrates.[20] In order to achieve cyclisation of gaseous or volatile alkenes, elevated temperatures and pressures must be used, yielding only moderate amounts of products. However, when the Kerr group added TMANO.2H_2O to the reaction mixture the need for such high pressures and temperatures was eliminated. The reaction between cobalt complexed phenylacetylene **20** and ethylene **26** (30 atm.) yielded **27** in 71 % yield when the substrates were heated in an autoclave at 40 °C for 7 hours with 9 equivalents of TMANO.2H_2O (*Scheme 12*).



Scheme 12

When the same reaction was conducted under an atmospheric pressure of ethylene and the mixture was stirred at room temperature, 46 % of **27** was obtained.

Continuing in this approach, the same group developed an even simpler method of introducing an ethylene equivalent in the Pauson-Khand reaction.[21] When cobalt complex **20** was reacted with excess vinyl benzoate **28** (as solvent), slow addition of 10 equivalents of $NMO.H_2O$ in DCM at 20 °C for 3 hours yielded the desired product **27** in 80 % yield (*Scheme 13*).[21]



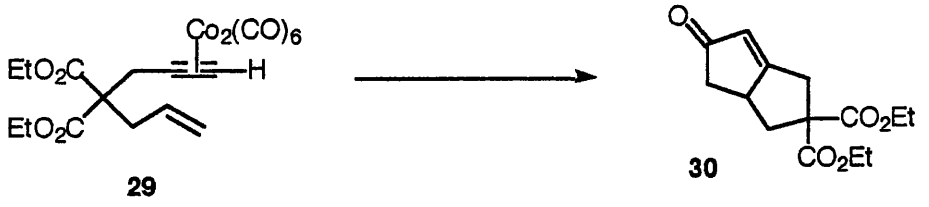
Scheme 13

The isolated cyclopentenones were thought to be the products of reduction by low oxidation state cobalt species. The C–O cleavage and subsequent replacement of the ester oxygen with a hydrogen atom must be the product of reduction and they believe that the required hydrogen atom comes from the water molecule obtained from the hydrated *N*-oxide.

1.6 Sulfoxides as Promoters of the Pauson-Khand Reaction

Following his work using amine *N*-oxides, the Pauson group went on to investigate a range of other promoters. Phosphine oxides were used because they are poor oxidants and do not act in the same way as amine *N*-oxides.[13] There was the possibility that they might substitute carbon monoxide by a weaker, more easily replaceable ligand. However, results were disappointing. Even irradition with low powered ultrasound could not entice the reactions to generate higher yields but did decrease the reaction times.

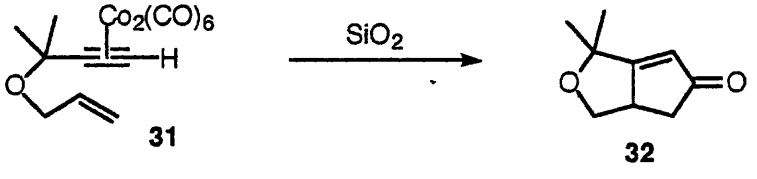
Dimethyl sulfoxide (DMSO) was used in the hope that it would be more efficient than the phosphine oxides.[17] Another potential advantage of using DMSO was the expectation that oxidative destruction of the cobalt complexes would not occur. Oxidation of cobalt complexes was commonly observed using amine *N*-oxide species. This might be useful for developing catalytic systems and use of optically active sulfoxides might lead to enantioselectivity. DMSO was found to promote the reaction well. Other highly polar compounds were examined but DMSO was the most efficient promoter tested. Optimum conditions for the reaction were found to be reacting complex **29** with 1 equivalent of DMSO in DCM at 40 °C for 4 hours under air and a yield of 85 % of **30** was obtained (*Scheme 14*).



Scheme 14

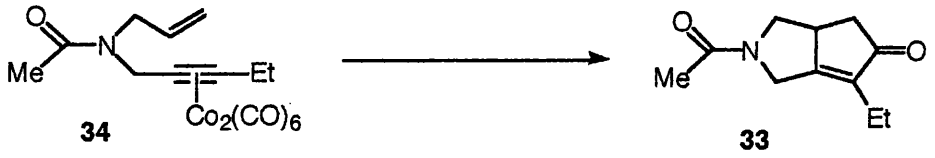
1.7 Dry State Adsorbtion Conditions for the Pauson-Khand Reaction

Smit and co-workers developed novel conditions for promoting the PKR.[22] The cobalt complex **31** was adsorbed onto silica and warmed under an oxygen stream at 45 °C for 30 minutes to yield **32** in 75 % (*Scheme 15*).



Scheme 15

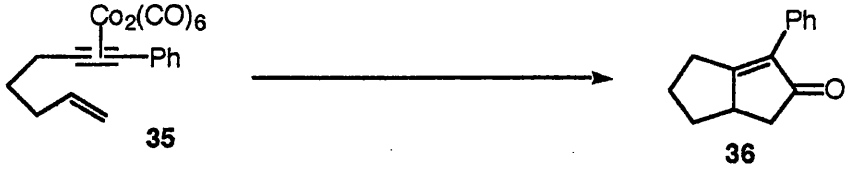
Utilising these conditions, Brown and Pauson isolated the first nitrogen heterocycle **33** to be synthesised using the PKR in a yield of 75 % by combining **34** with silica gel at 70 °C for 4 hours under air (*Scheme 16*).[23]



Scheme 16

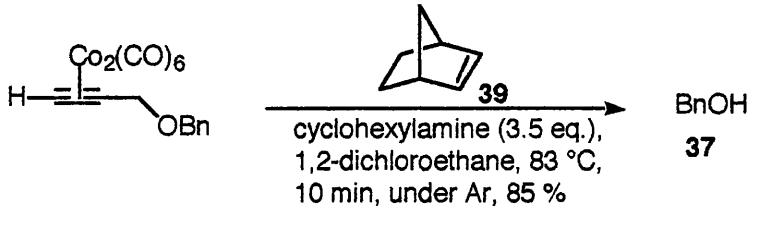
1.8 Amines as Promoters in the Pauson-Khand Cyclisation

Within the last two years, Sugihara's group, adopting a similar approach to Pauson, have begun to investigate the use of amines as promoters.[24] It has been well documented that hard ligands, containing a nitrogen or oxygen atom labilise the carbon monoxide (CO) ligands attached to a metal atom and therefore facilitate the ligand substitution reaction.[25] If the hard ligands react with $Co_2(CO)_6$(alkyne) complexes in the presence of alkenes, the substitution of CO ligands by alkenes may be facilitated.[24] Since the coordinated alkyne is also made reactive by the labilising effect of the hard ligands, the PKR might be promoted. It was found that primary amines promoted the reactions well but that tertiary amines retarded the reaction. When complex **35** was reacted with 3.5 equivalents of the primary amine cyclohexylamine in dichloroethane (DCE) at 83 °C for 5 minutes under argon, a yield of 99 % of **36** was isolated (*Scheme 17*).



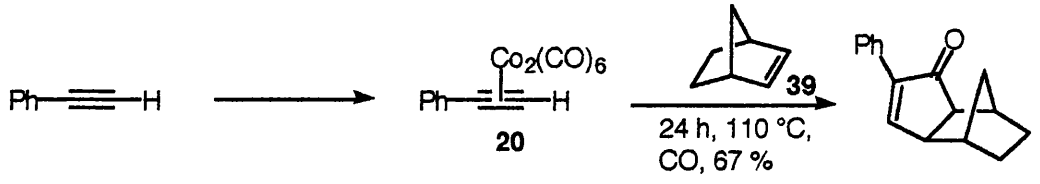
Scheme 17

However, one problem with primary amine promoters was that reactions with simple alkenes did not proceed. The other drawback was that, in some cases, formation of highly reducible cobalt complexes cleaved the carbon-hetero atom bond at the α-position of the complex to yield products like **37** (*Scheme 18*).



Scheme 18

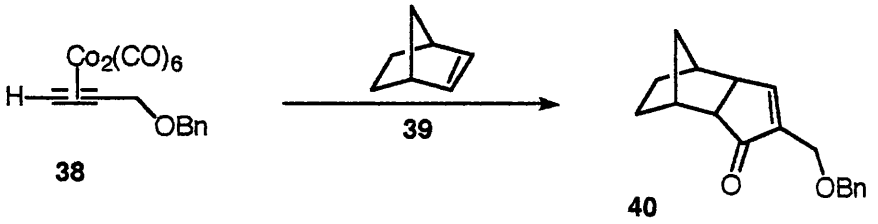
Rajesh and Periasamy have also used the tertiary amine *N,N,N',N'*,-tetramethylethylenediamine (TMEDA) as a promoter in their substoichiometric reactions.[26] The Pauson-Khand reaction could be easily conducted by generating an alkyne-$Co_2(CO)_6$ complex **20** *in situ* using 0.40 equivalents of $CoBr_2$ and 0.43 equivalents of zinc in toluene / TMEDA (50 : 1.5) at 25 °C for 5 hours under an atmospheric presssure of CO (*Scheme 19*).



Scheme 19

1.9 Sulfides as Promoters in the Pauson-Khand Reaction

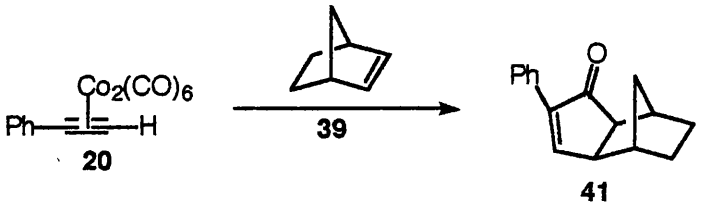
In order to overcome the problem of cleavage of the carbon-hetero bond that was encountered in the amine promoted PKR, Sugihara's group tested a variety of promoters. They found that sulfides, particularly alkyl methyl sulfides,[27] were the most efficient. Krafft and co-workers found that alkyne-dicobalt hexacarbonyls having sulfides in the side chain gave the corresponding alkyne-dicobalt pentacarbonyl sulfide by treatment with NMO.[28] Subsequent cyclisation yielded the desired cyclopentenones. Sugihara *et al* thought that externally added sulfides might act as promoters for the PKR.[27] Since sulfides are better π-acceptors and slightly poorer σ-donors than amines, then the cobalt complexes produced in the reaction might not exhibit reducibility and hence the undesired product **37** would not form (*Scheme 18*). When complex **38** was reacted with norbornene **39** in the presence of 3.5 equivalents of *n*–BuSMe in DCE at 83 °C for 30 minutes under argon, 99 % of **40** was isolated (*Scheme 20*).



Scheme 20

1.10 High Intensity Ultrasound as a Promoter in the Pauson-Khand Cyclisation

Recently Kerr and co-workers have adopted a different strategy for the promotion of the PKR. An external source of promotion would be very beneficial and would simplify the purification procedure. They used high intensity ultrasound.[29] Low powered ultrasound had been previously used by the groups of both Pauson[14] and Crowe,[16] to promote the intermolecular PKR. When cobalt complexed phenylacetylene **20** was reacted with norbornene **39** in the presence of high intensity ultrasound and toluene at 20 °C for 10 minutes, 84 % of **41** was obtained (*Scheme 21*).[29]



Scheme 21

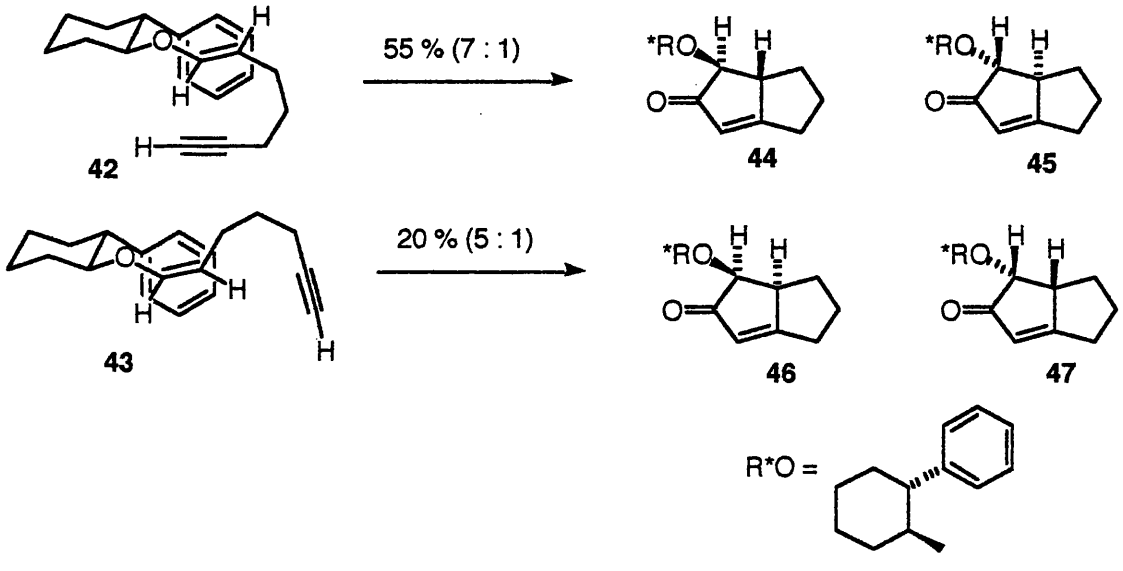
However, addition of 6 equivalents of TMANO.$2H_2O$ decreased the reaction time to 6 minutes and boosted the yield to 95 %. Alternatively, addition of 6 equivalents of triethylamine increased the reaction time to 15 minutes but an increased yield of 99 % was obtained.

1.11 Enantioselectivity in the Pauson-Khand Reaction

One of the major drawbacks of the PKR was the lack of control of stereoselectivity in the reaction.[30] Pauson had noted that in the intermolecular reaction the bulkiest group on the alkyne tended to align itself next to the carbonyl group but there was no element of control over the approach of the alkene.[11] In the intramolecular reaction, the problem of regiochemistry had been solved but the control of stereochemistry was still elusive. There have been many different approaches to solve this problem, such as the use of chiral auxiliaries,[31] chiral groups attached to the cobalt complex[32] and desymmetrisation of the cobalt complex by replacement of a cobalt atom for a molybdenum atom.[33] However, a general procedure for a range of substrates has still to be developed.

1.12 Chiral Auxiliary Approach

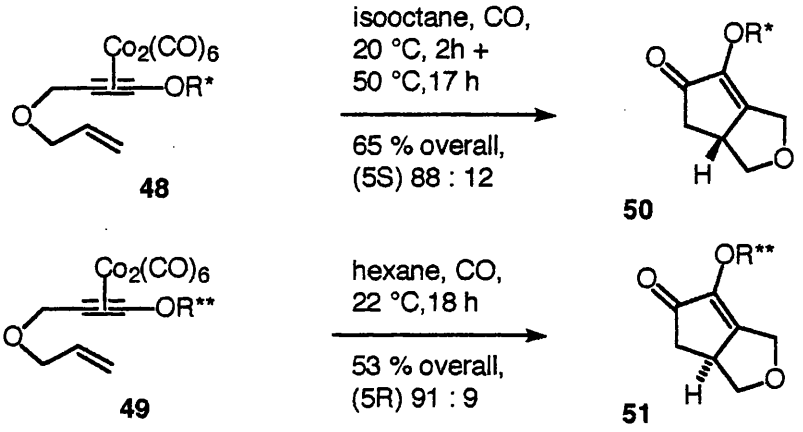
Pericás and co-workers have utilised chiral auxiliary π-face discrimination in acetylenic O-alkyl enol ether-dicobalt hexacarbonyl complexes.[34] The *E* and *Z* enol ethers **42** and **43** were stirred in isooctane with 1.1 equivalents of $Co_2(CO)_8$ at 20 °C for 1.5 hours. The mixture was then heated at 95 °C for 1.5 hours to yield products **44** and **45** and **46** and **47** (*Scheme 22*).



Scheme 22

Both isomers underwent diastereoselective bicyclisation, although the *E* isomer gave better yields of the bicyclo[3.3.0]octenones **44** and **45** with an induction level of 7 : 1. The chiral auxiliary could be easily removed and recovered in 92 % yield using samarium diiodide.

The same group then prepared camphor-derived neopentyl ethers (*Figures 1 and 2*) as chiral auxiliaries for asymmetric PKRs.[31] The auxiliaries (*Figures 1 and 2*) were attached to substrates **48** and **49** and underwent cyclisation to yield diastereoisomers **50** and **51** in varying yields but with high stereoselectivity (*Scheme 23*).



Scheme 23

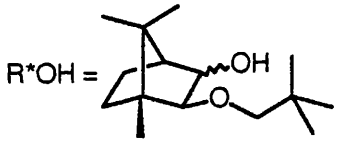


Figure 1

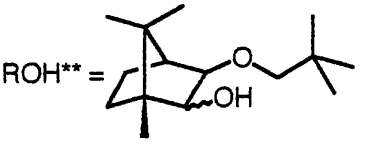
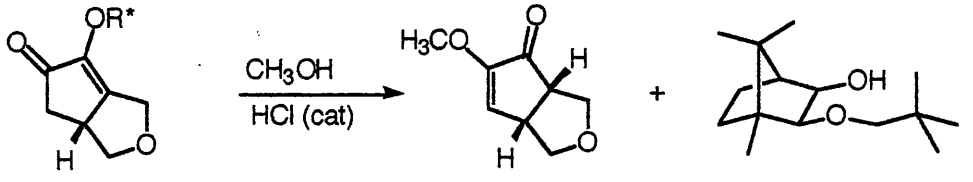


Figure 2

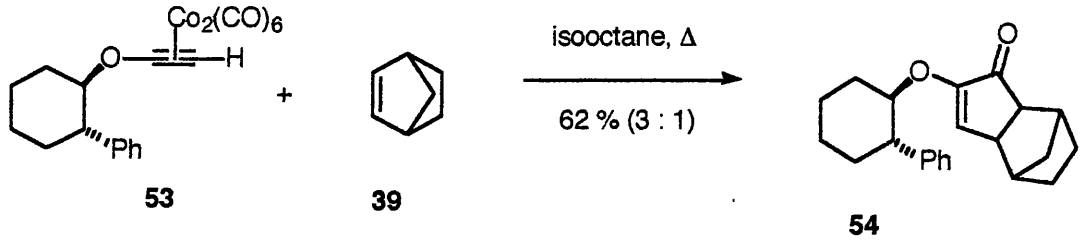
Again the chiral auxiliaries (*Figures 1 and 2*) could be removed in excellent yield using methanol and a catalytic amount of hydrochloric acid to yield α-methoxyenones **52** with almost complete recovery of the auxiliaries (*Scheme 24*).



Scheme 24

Two years later, the same group developed a range of chiral O-alkyl acetylenic ethers **53** as substrates.[35] The main advantage was that the reactions were not limited to

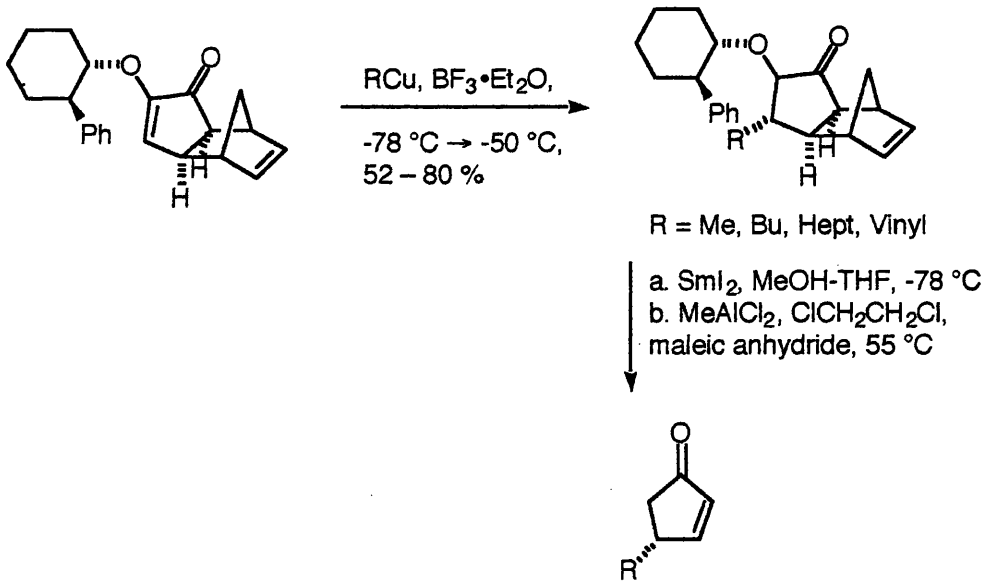
intramolecular reactions but could also be applied to intermolecular cyclisations. The propargylic cobalt complex **53** was reacted with norbornene **39** and yielded **54** in 62 % with a diastereomeric ratio of 3 : 1 (*Scheme 25*).



53 **39** **54**

Scheme 25

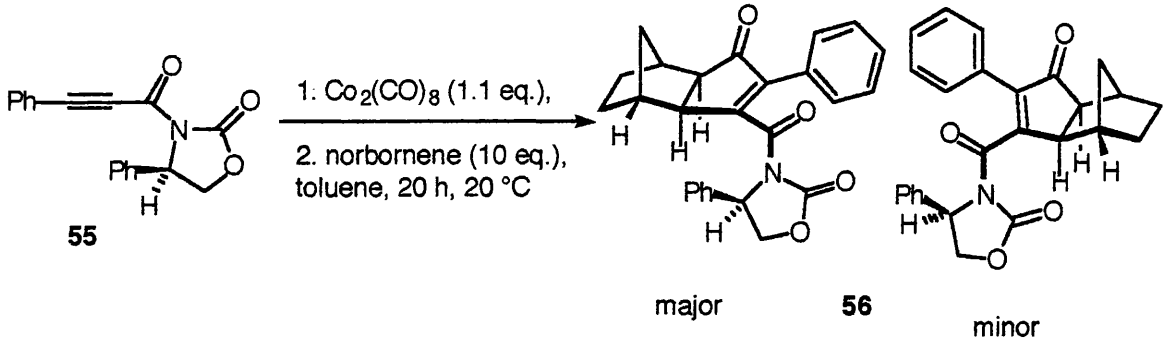
In keeping with findings from other PKR, the bulkiest substituent on the alkyne **53** tended to align itself next to the carbonyl group.[11] Also, where *endo-exo* annulation was possible, the *exo* diasteroisomers were the only isomers isolated.[35] Boron trifluoride etherate-promoted conjugate addition reactions of methyl, butyl, heptyl and vinyl copper reagents provided only the *exo* adducts in 52 – 80 % yields (*Scheme 26*).



Scheme 26

Again, the auxiliary could be easily removed using samarium diiodide and the intact chiral auxiliary was readily recovered for reuse.

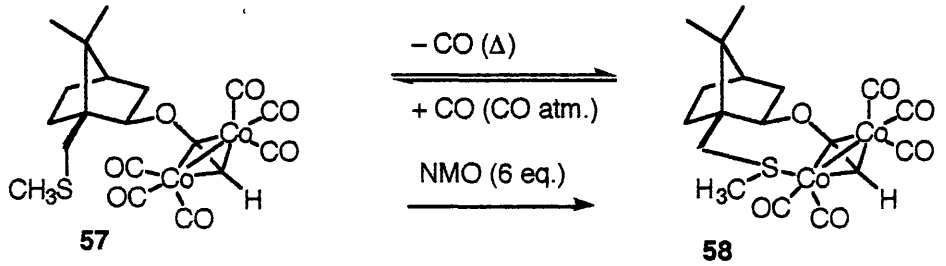
The next step was to use chiral oxazolidin-2-ones to induce diastereoselectivity in the PKR.[36] Upon reaction of **55** with norbornene **39**, product **56** was obtained in 91 % yield with a diastereoisomeric ratio of 4.3 : 1 (*Scheme 27*).



Scheme 27

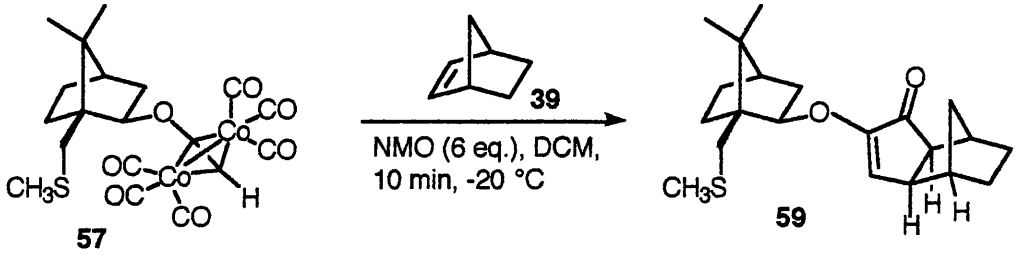
The chiral oxazolidinones could be easily removed using hydrogen peroxide and lithium hydroxide in THF/H_2O.

Chiral oxazolidinones are expensive, so based on their previous work, Pericás and co-workers modified camphor and found this to be an excellent auxiliary in intermolecular PKR.[37] Their new approach involved developing an auxiliary with a chelating capacity that could allow efficient transfer of chirality to the C_2Co_2 cluster and could secure the diastereoselectivity of the process by directing the reaction towards one of the two diastereotopic cobalt atoms. They chose sulfur as the chelating atom since the ability of sulfur to stabilize coordinatively unsaturated cobalt species has been well established by Krafft and co-workers.[28] Also, the labile nature of the Co-S dative bond should greatly facilitate the dissociative equilibrium thus contributing to a rate enhancement in the overall reaction process.[37] The chiral auxiliary, (2*R*)-10-mercaptoisoborneol was synthesised by reduction of camphorsulfonyl chloride with lithium aluminium hydride, followed by regioselective alkylation with methyl iodide. They found that reaction with dicobalt octacarbonyl yielded the desired cobalt complex **57** but that an equilibrium was formed between the sulfur atom being chelated to the cobalt atom **57** and the unchelated form **58** (*Scheme 28*).



Scheme 28

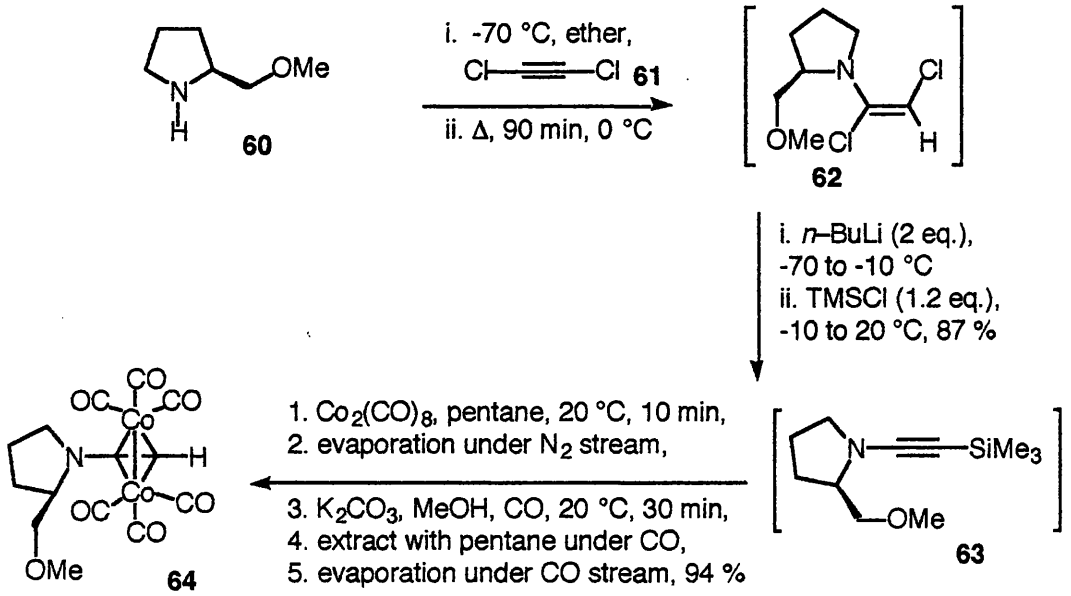
The first step of the mechanism of the amine *N*-oxide promoted PKR is oxidation of a carbon monoxide ligand to carbon dioxide which leaves irreversibly and creates a vacant coordination site around the cobalt.[1] When 6 equivalents of NMO were added, the equilibrium displayed in *Scheme 28* lay entirely to the side of the chelated complex **58**.[37] Upon reaction of **57** with 10 equivalents of norbornene **39**, product **59** was obtained in 77 % yield with a diastereoisomeric excess of 84 % (*Scheme 29*).



Scheme 29

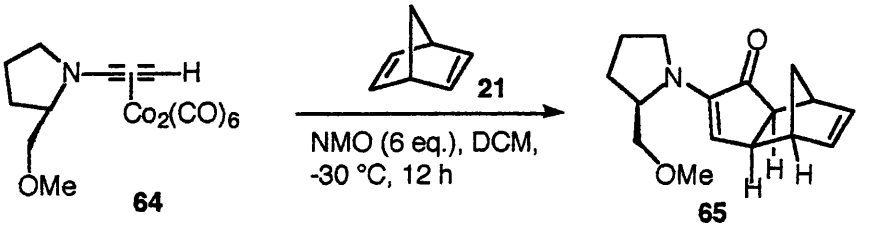
The chiral auxiliary can be easily recovered in almost quantitative yield using samarium diiodide in THF / MeOH at 0 °C for 10 minutes.

The use of chiral amines with respect to inducing diastereoselectivity in the Pauson-Khand reaction was examined.[38] Chiral secondary amine **60** was reacted with dichloroacetylene **61** to form the alkene intermediate **62** followed by reaction with *n*-butyl lithium and trimethylsilyl chloride to form silylynamine **63**. Addition of dicobalt octacarbonyl gave cobalt complex **64** in good yield (*Scheme 30*).



Scheme 30

Surprisingly the Pauson-Khand reactions could be conducted at low temperatures with or without a promoter. Upon reaction of **64** with 10 equivalents of norbornadiene **21**, product **65** was obtained in 68 % yield with a diastereoisomeric ratio of 2.3 : 1 (*Scheme 31*).

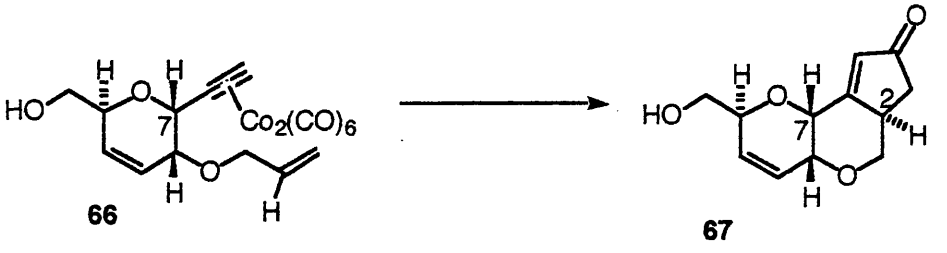


Scheme 31

The chiral auxiliary could be easily removed or compound **65** could be further manipulated to form enantiomerically pure α-aminocyclopentanones and α-aminocyclopentanols.

1.13 Asymmetry Derived From the Chiral Pool

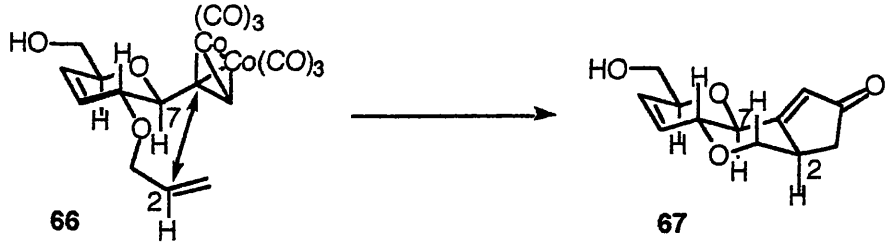
Isobe and Takai have utilised the chirality present in a sugar acetylene to give high stereoselecitivity in the PKR and to yield tricyclic compounds that are potentially useful for natural product synthesis.[39] Substrate **66** was reacted with 6 equivalents of NMO in DCM at 20 °C under nitrogen and a yield of 90 % of **67** was obtained (*Scheme 32*).



Scheme 32

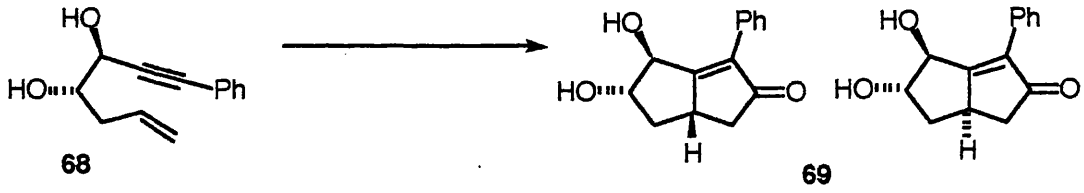
The major diastereoisomer was obtained with the stereochemistry of 2-H being assigned primarily α in orientation with respect to 7-H. Isobe and Takai believed that the stereocontrol of 2-H arose from the tetrahydropyran ring taking an inverted conformation ; therefore the terminal alkene was predestined to approach the cobalt complex such that the subsequent [2 + 2] cycloaddition took place through a minimum-energy intermediate. *Scheme 33* illustrates the intermediate from the 1,2-*cis*

alkene explaining the stereochemical course so that 2-H is directed to the α orientation, where only one of the two *apical* carbonyl groups can exchange with the alkene.



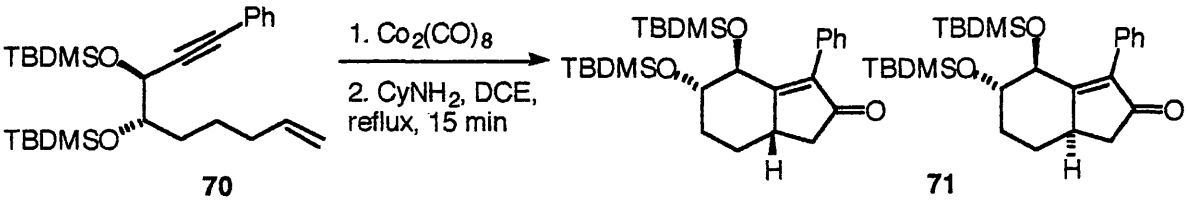
Scheme 33

Mukai *et al.* have reported stereoselective synthesis of bicyclo[3.3.0]octenone derivatives using the PKR.[40] Their strategy involved the synthesis of (4*S*, 5*S*)-4,5-dihydroxy-hept-1-en-6-yne derivatives from L-ascorbic acid using standard procedures. Compound **68** was reacted with dicobalt octacarbonyl and the crude mixture was dissolved in THF. Subsequent addition of 6 equivalents of $TMANO.2H_2O$ at 20 °C for 1 – 5 hours yielded product **69** in 84 % with a diastereomeric ratio of 92 : 8 (*Scheme 34*).



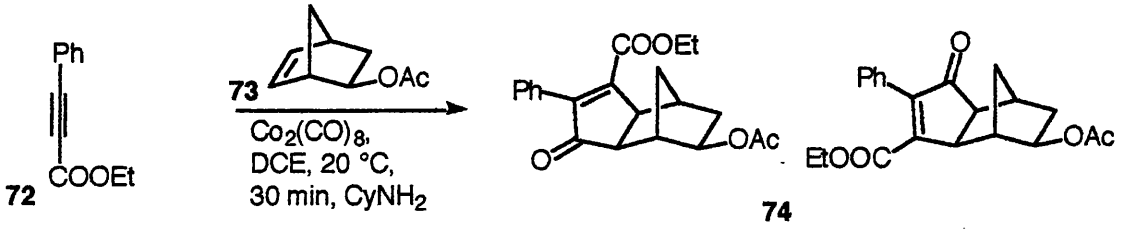
Scheme 34

They continued this work and have subsequently developed a route to optically active 6,7-bis(*tert*-butyldimethylsiloxy)non-1-en-8-ynes. The starting enynes were generated from diethyl L-tartrate following standard procedures. Compound **70** was reacted with dicobalt octacarbonyl and the crude mixture was dissolved in DCE before addition of 4 equivalents of cyclohexylamine gave product **71** in 74 % yield with a diastereomeric ratio of 85 : 15 (*Scheme 35*).



Scheme 35

Schore and co-workers have studied remote substituent effects with respect to stereoselectivity in the Pauson-Khand reaction and found that only moderate regioselectivities were observed.[41] Mayo and Tam have studied remote substituent effects in the PKR using 2-substituted norbornenes.[42] The reaction between alkyne **72** and *exo*-2-substituted norbornene **73** gave product **74** in a yield of 77 % with a diastereomeric ratio of 66 : 34 (*Scheme 36*).



Scheme 36

When no promoter was added, the regioselectivity was only 52 : 48 but when either TMANO.$2H_2O$, cyclohexylamine or dimethyl sulfide were added, the enantiomeric excess increased from 4 % to over 24 %. They also found that *exo* substituents on 2-norbornene had a stronger remote effect than the corresponding *endo* substituents.

1.14 Optical Activity Induced By A Chiral Ligand Attached to Cobalt

Pauson and co-workers also attempted to induce enantioselectivity in the PKR. He replaced one of the carbon monoxide ligands with a phosphine ligand in the hope of inducing asymmetry in the cobalt core,[43] providing $R^1 \neq R^2$ and L ≠ CO (*Figures 3 and 4*). Ligand L was substituted with triphenylphosphine and trimethyl phosphite but these proved to be unsuccessful. (*R*)-(+)-Glyphos (*Figure 5*) was used as the ligand and when R^1 = Ph and R^2 = H upon reaction with norbornene **39**, excellent enantioselectivity was exhibited but the yields were poor. Separation of the diastereoisomeric cobalt complexes (*Figures 3 and 4*) was not trivial and the high temperatures required for the reaction meant that both diastereoisomers (*Figures 3 and 4*) were present prior to reaction.

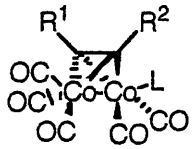


Figure 3
L = PPh_3,
L = PMe_3,
L = (*R*)-(+)-Glyphos

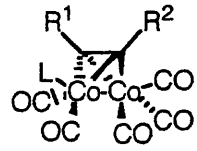


Figure 4
L = PPh_3,
L = PMe_3,
L = (*R*)-(+)-Glyphos

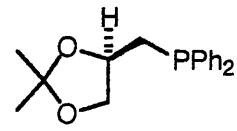
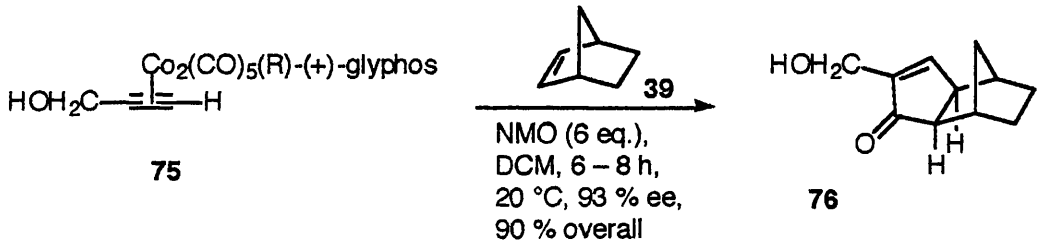


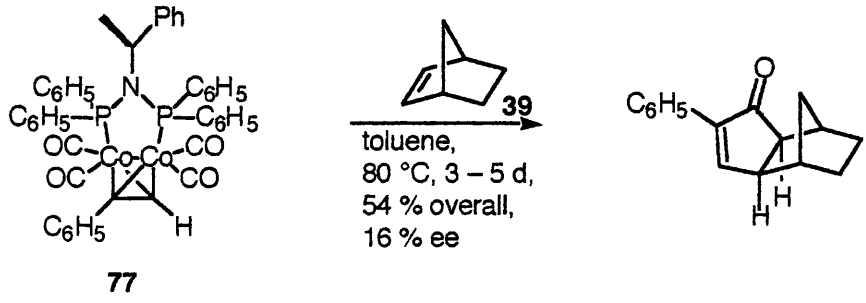
Figure 5
(*R*)-(+)-Glyphos

Kerr's group developed a more reliable synthesis of the (*R*)-(+)-glyphos cobalt complexes **75**. [32] They found that preparative HPLC separated the diastereoisomers (*Figures 3 and 4*) easily. Conditions were found, utilising the promoting ability of anhydrous *N*-methylmorpholine *N*-oxide, to give high yields with high enantioselectivity (*Scheme 37*). Kerr believed that the enantioselectivity did not arise from the (*R*)-(+)-glyphos ligand (*Figure 5*) but from the chirality induced in the cobalt core and therefore this method could be used to produce cyclopentenone products, like **76**, enriched with the enantiomer of choice.



Scheme 37

Greene and co-workers recently reported the development of new bidentate ligands to attach to the cobalt atoms.[44] Diphosphorus compounds, having an amino group or a single methylene group between the two phosphorus atoms **77**, have been commonly used as chelating and bridging ligands to transition-metal centres[30] but never in the PKR. Changing the bridging group to a chiral ligand induces stereoselectivity. The effect is small but it has potential and further work is underway to optimise the conditions (*Scheme 38*).[44]



Scheme 38

It was well known that trialkyl- and triaryl-phosphines could readily displace a carbon monoxide ligand from alkyne-dicobalt hexacarbonyls when they occupied an axial coordination position in the tetrahedral Co_2C_2 core *trans* to the cobalt-cobalt bond (*Figure 6*).[45,46] This substitution was also known to be accompanied by an appreciable shortening of the cobalt-carbonyl distances, a fact that was usually ascribed to the poorer π-acceptor character of phosphines relative to that of carbonyl ligands. In the case of bidentate phosphines, both chelated and bridged complexes, in which the ligand occupies equatorial coordination positions about the metal atoms, have been obtained.

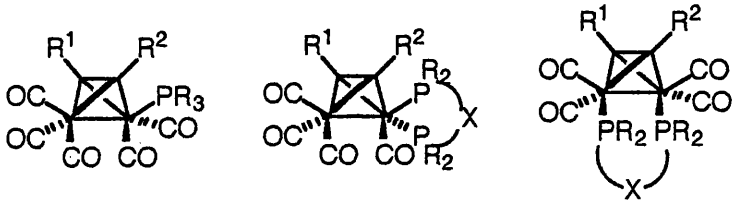
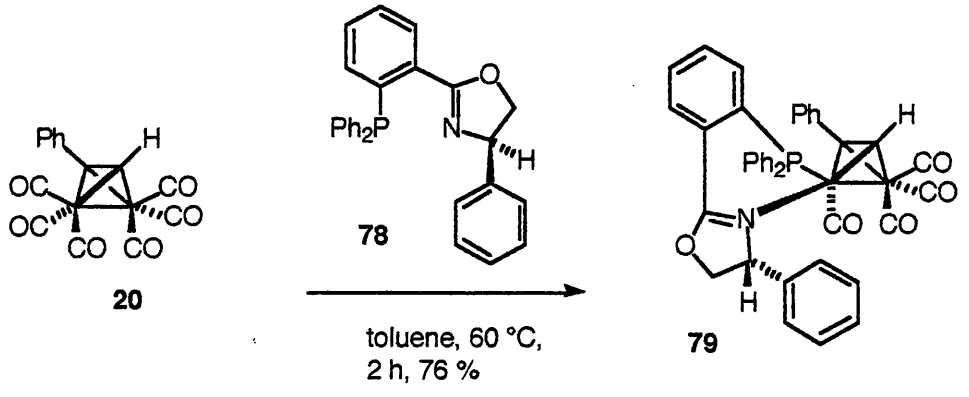


Figure 6

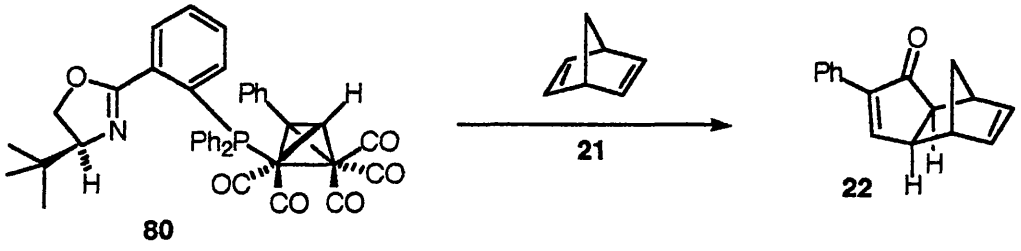
Pericás and co-workers found that when they attached (*R*)-2-(2-diphenylphosphinophenyl)-4-phenyloxazoline **78** to cobalt-complexed phenylacetylene **20**, an 85 : 15 mixture of diastereosiomeric complexes was formed (*Scheme 39*).[47] The structure of the major one **79**, elucidated by X-ray diffraction analysis, revealed an unprecedented P–N chelation of the ligand with one cobalt atom.



Scheme 39

These complexes were very stable towards isomerization but showed only moderate enantioselectivities (up to 51 % enantiomeric excess) in the intermolecular PKR. However, when the complexes were reacted with a ligand with a bulky *tert*-butyl substituent in the oxazoline moiety the formation of a chelated complex was strongly

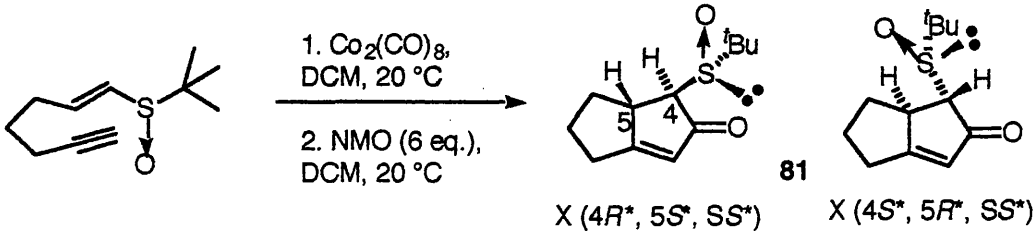
hindered and ligand **78** acted as a monodentate chiral phosphine. An additional bonus was that the two diastereoisomers could be easily separated using standard column chromatography and were obtained in high diastereoisomeric purity. In the case of the nonchelated complexes **80**, high yields and high enantioselectivities were obtained. When **80** was reacted with norbornadiene **21** in the presence of NMO at 0 °C for 24 hours in DCM, compound **22** was isolated in 85 % yield with an enantiomeric excess of 94 % (*Scheme 40*).



Scheme 40

The phosphine oxide derived from ligand **78** was recovered in 87 % yield.

Not only was phosphorus found to be an effective chiral auxiliary and bridging ligand but sulfur was also found to be just as an effective chiral auxiliary.[48] Carretero and Adrio found that when the *trans* alkene was reacted with the *tert*-butylsulfinyl group to form compound **81**, the intramolecular PKR occurred in a yield of 46 % with a diastereomeric ratio of > 98 : 2 (*Scheme 41*).[49]

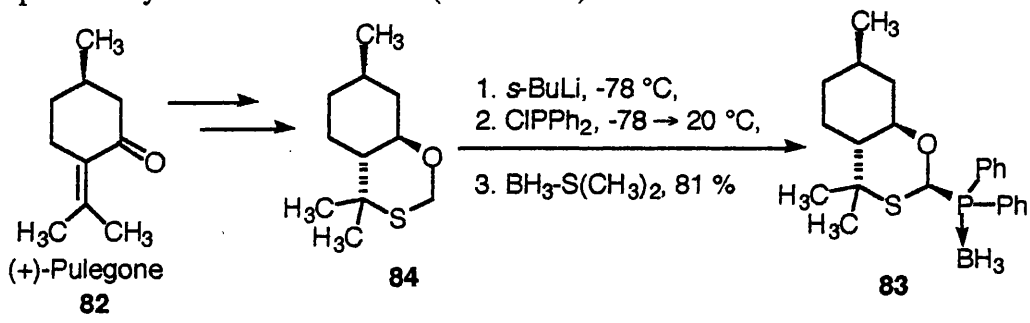


Scheme 41

They found that *cis* and *trans* alkenes led to formation of the same enantiomer. This shows that the reaction occurs on the opposite face from the *tert*-butylsulfinyl group. Epimerization at C-4 led to the same product **81**. Therefore *trans* + *cis* mixtures of 1-sulfinyl-1,6-enynes can be used directly since both isomers display the same stereoselectivity in the PKR. The *tert*-butylsulfinyl group could be easily removed using activated zinc in THF at room temperature leading to very high yields of the

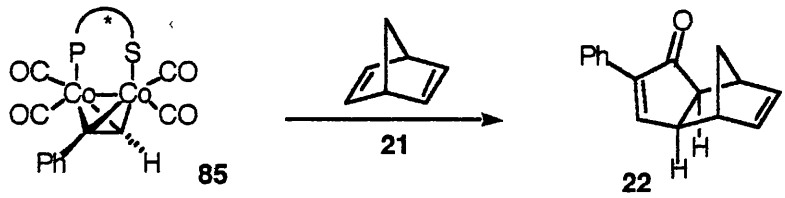
corresponding optically active bicyclo[3.3.0]oct-1-en-3-ones. However, the general procedure is limited since substituted alkynes do not react.

Pericás and co-workers continued their search for a chiral bidentate ligand that would control diastereoselectivity in the Pauson-Khand reaction. They found that when a phosphorus atom and a sulfur atom were combined in a chiral bidentate ligand, their aim could be realised.[50] The chiral ligand was synthesised from naturally occurring (+)-pulegone **82** and through a series of steps yielded compound **83**. Chlorodiphenylphosphine was alkylated with the lithium anion of **84**, generated at low temperature by reaction with *s*-BuLi (*Scheme 42*).



Scheme 42

The reaction was totally selective, affording the chiral ligand as a single diastereoisomer. It was isolated as its borane-protected form **83** and was found to be a stable crystalline solid. It is well known that mono- and di-phosphino dicobalt complexes of phenylacetylene tend to display lower reactivity in the PKR.[44] However, when deprotected chiral ligand **83** was reacted with hexacarbonyl phenylacetylene dicobalt **20** and the resulting complex used in the PKR, excellent yields and enantioselectivities were obtained.[50] When compound **85** was reacted with norbornadiene **21** at 50 °C for 30 minutes, product **22** was isolated in 99 % yield with an enantiomeric excess of 99 % (*Scheme 43*).



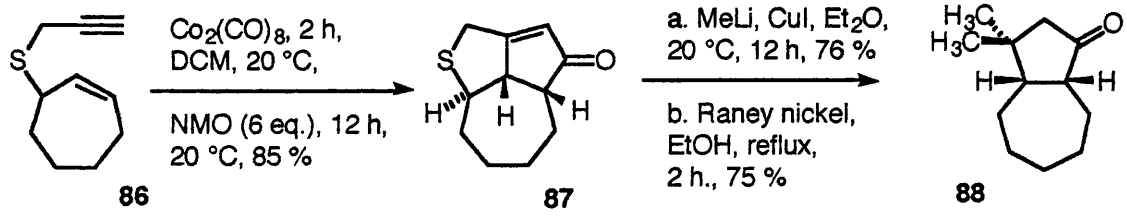
Scheme 43

The thioether was the more labile of the two coordinative bonds (Co–S / Co–P) and its dissociation controlled the stereochemistry of the reaction while leaving, on one cobalt

atom, a free coordination site for the incoming alkene. Dissociation of a hemilabile sulfide moiety was much easier than the loss of any CO ligand in the complex. Therefore, the normally difficult dissociative step in the PKR was facilitated and the overall rate was increased.

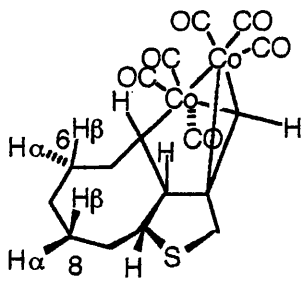
1.15 Stereoselectivity Induced By Temporary Bridges

The enantioselective synthesis of cyclopentanones fused to 7 or 8 membered rings was not trivial but Pericás and co-workers found that use of a temporary sulfur bridge gave ready access to bicyclo[5.3.0]decan-1-ones.[51] The starting material was easily prepared and reaction with dicobalt octacarbonyl formed the Pauson-Khand precursor **86**. Treatment with NMO in DCM overnight at 20 °C yielded **87** in 85 % yield as a single diastereoisomer (*Scheme 44*). Conjugate addition with lithium dimethyl cuprate yielded the cyclopentanone and removal of sulfur using Raney nickel yielded the octahydroazulenone **88** in 57 % yield over two steps.

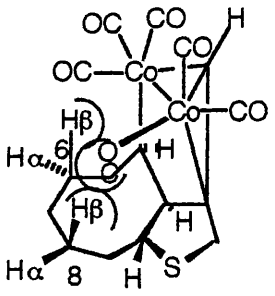


Scheme 44

The stereochemical outcome of the PKR can be easily rationalized in the framework of the currently accepted mechanistic model, if it is assumed that the intermediate cobaltacycles adopt conformations similar to those depicted for *Figures 7 and 8*. While the cobaltacycle, arising from the attack of the complex at the β-face of the olefin (*Figure 8*), would be strongly destabilized by the steric repulsion of the CO ligands of one cobalt with H-6β and H-8β, the cobaltacycle obtained through attack at the α-face is free of these repulsive interactions thus leading to the observed adduct (*Figure 7*).

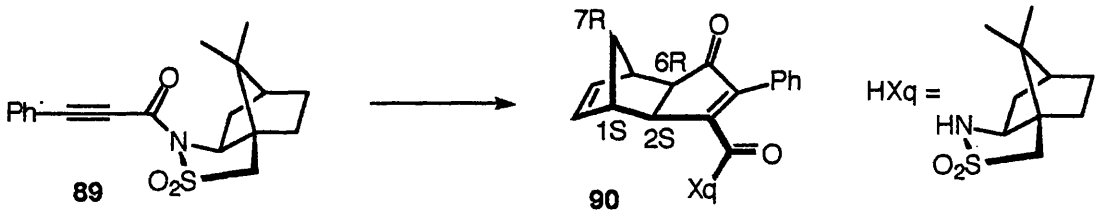


α–attack
(preferred)
Figure 7



β–attack
(disfavoured)
Figure 8

The same group were then prompted to use borane-2,10-sultam as a highly efficient asymmetric controller.[52] Reacting the alkyne with the borane-2,10-sultam before subjecting complex **89** to dicobalt octacarbonyl formed the crude cobalt-complexed intermediate. Subsequent reaction with 5 equivalents of norbornadiene **21** in the presence of NMO.H_2O in DCM at 20 °C for 1 hour yielded **90** in 93 % with a diastereomeric ratio of > 800 : 1 (*Scheme 45*).



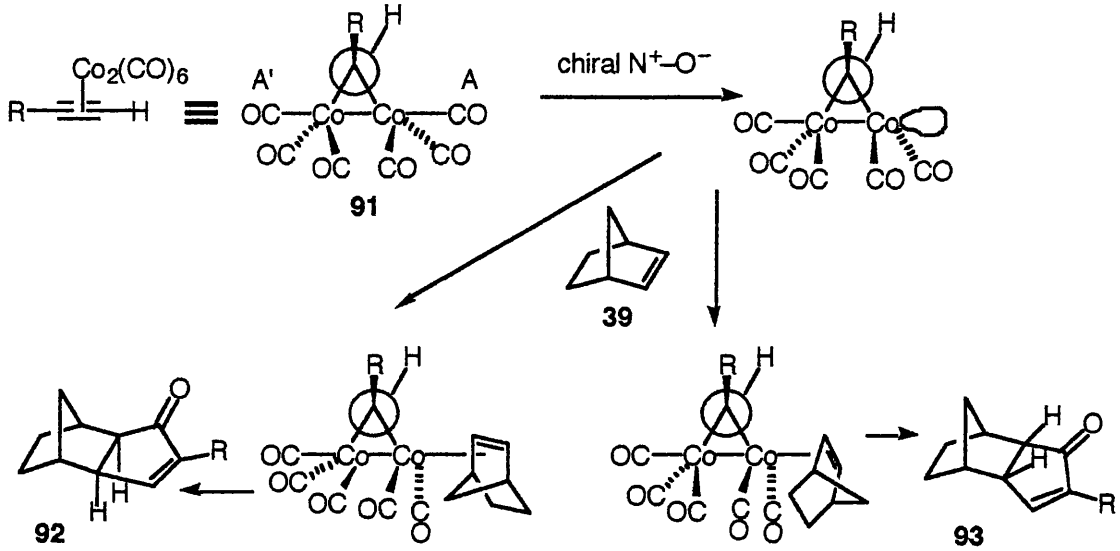
Scheme 45

The stereoselectivity relies on the fact that if the starting alkyne is chiral non-racemic, upon reaction with dicobalt octacarbonyl, the two cobalt atoms become diastereotopic. They assume that the sultam auxiliary can selectively chelate one of the cobalt atoms of the initially formed alkyne-dicobaltpentacarbonyl complex, thus directing the coordination of the alkene to this internally activated complex.

1.16 Enantioselectivity With Chiral Non-racemic Amine *N*-Oxides

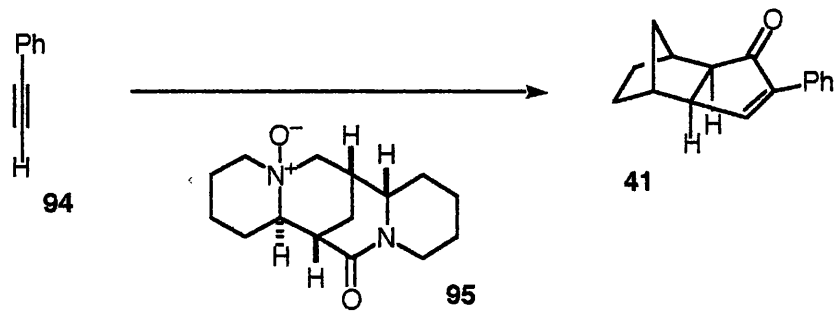
Laschat and co-workers hoped that enantioselectivity in the PKR might arise from a chiral amine *N*-oxide being able to differentiate between the two enantiotopic CO ligands A and A'.[53] The resulting coordinatively unsaturated chiral complex **91** could attack norbornene **39** either from the *exo* face or from the *endo* face. *Exo* attack

would lead to the enantiomerically pure *exo* product **92** whereas *endo* attack would give the enantiomerically pure *endo* product **93**. However, *endo* attack should be disfavoured due to steric interactions between the methylene bridge of **93** and the remaining CO ligands (*Scheme 46*).



Scheme 46

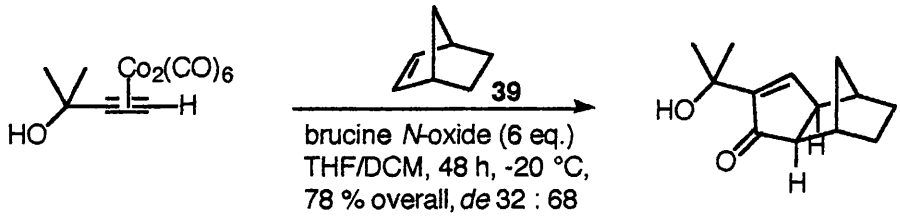
Amine *N*-oxides derived from alkaloids were tested as chiral promoters in enantioselective Pauson-Khand reactions.[53] When phenylacetylene **94** was reacted with dicobalt octacarbonyl in THF followed by treatment with norbornene **39** and 6 equivalents of (-)-17-oxosparteine *N*-oxide **95** in THF at -78 °C → 20 °C for 8 hours, product **41** was obtained in 73 % yield with an enantiomeric excess of 16 % (*Scheme 47*).



Scheme 47

Kerr *et al.* also used a chiral amine *N*-oxide in an attempt to induce asymmetry.[54] Brucine *N*-oxide (*Figure 9*) was tested. The advantage was that it did not

depend on chiral auxiliaries or optically pure starting materials. Optimal results, both in yields and stereoselectivity were obtained when THF was used as a solvent or as a co-solvent with DCM (*Scheme 48*).



Scheme 48

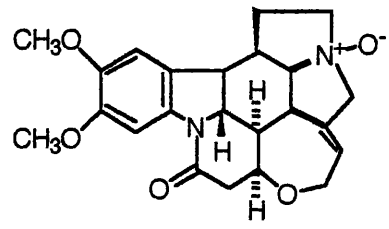
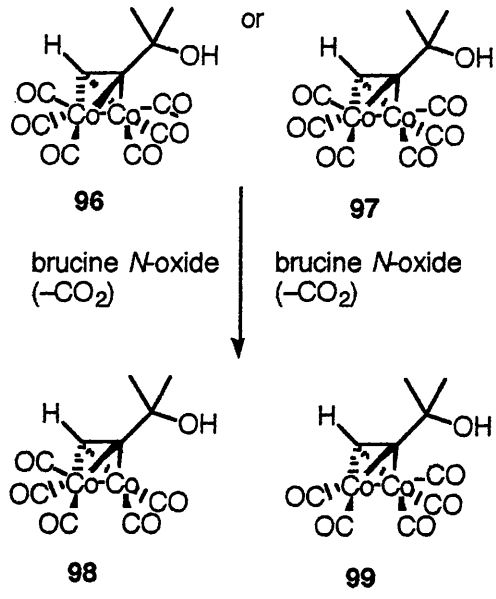


Figure 9
Brucine *N*-oxide

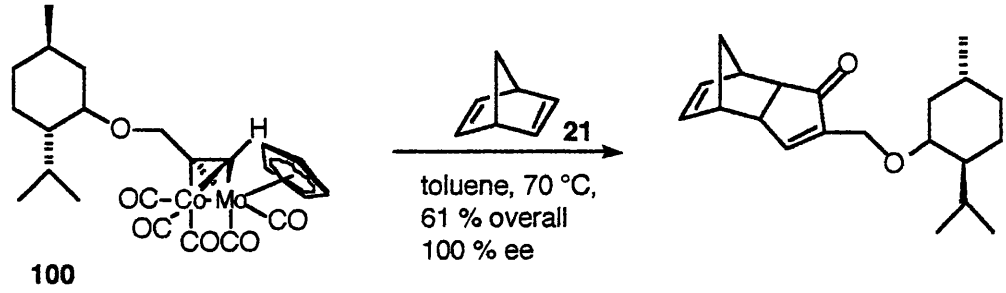
As mentioned earlier,[1] it has been shown that amine *N*-oxides mildly decarbonylate metal carbonyl species by oxidation of CO ligands to CO_2. Kerr proposed that the observed asymmetric control in the PKR was due to the selective decarbonylation of the prochiral starting hexacarbonyl alkyne-cobalt complexes **96** or **97** and one CO ligand was selectively removed from one of the two Co atoms in the complex **98** or **99**.[54] Alternatively or additionally, brucine, an amine, resulting from *N*-oxide attack on a CO ligand, could selectively stabilize one of the two possible coordinatively unsaturated Co sites of an intermediate in the PKR process, again inducing asymmetric cyclisation (*Scheme 49*).



Scheme 49

1.17 Asymmtery Induced by Using Two Metals

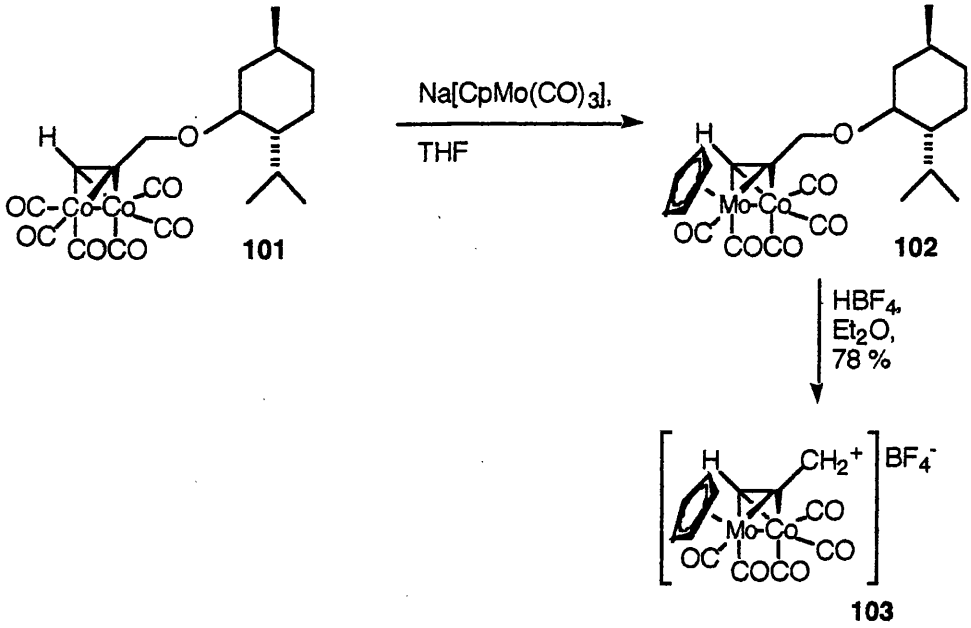
A completely different approach was adopted by Christie and co-workers. In order to induce asymmetry, they developed heterobimetallic alkyne complexes **100**.[33,55] By replacing one of the cobalt atoms with molybdenum, new complexes, such as complex **100** were created and the yields were comparable to those of the exisiting systems.[55] When unsymmetrical alkenes were used, the four corners of the metal-alkyne core were differentiated and the complex was chiral. It was thought that the electronic differences between the metals might induce chirality in the cyclisation. So far, this approach has exhibited one of the highest selectivities observed (*Scheme 50*).



Scheme 50

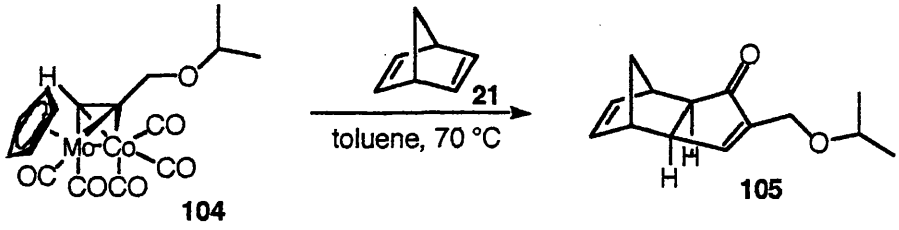
Christie and co-workers decided that since many chiral auxiliaries had been previously used to induce enantioselectivity, removal of the chiral auxiliary prior to the PKR would demonstrate that the chirality did indeed originate from the metal-alkyne core and not

from the chiral auxiliary. The bimetallic complex was synthesised by reaction of compound **101** with a molybdenum complex before the diastereoisomers **102** were easily separated. The chiral auxiliary was removed using hydrofluoroboric acid to yield the essentially air stable tetrafluoroborate salt of the metal stabilised propargylic cation **103** (*Scheme 51*).



Scheme 51

A variety of nucleophiles were reacted with complex **103** and they were all found to be effective at inducing stereocontrol in the PKR. With isopropanol as the nucleophile, complex **104** was reacted with 20 equivalents of norbornadiene **21** and yielded product **105** in 75 % yield with an enanantiomeric excess of 100 % (*Scheme 52*).



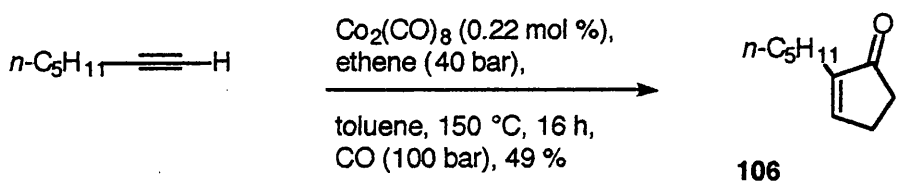
Scheme 52

Christie and co-workers also found that when the opposite enantiomer of the cobalt–molybdenum complex was reacted, regardless of the nucleophile used, the opposite enantiomer was isolated.

There have been many interesting and diverse routes towards enantioselectve synthesis in the Pauson-Khand reaction, but a universal strategy has yet to be unearthed.

1.18 Catalytic Pauson-Khand Cyclisations

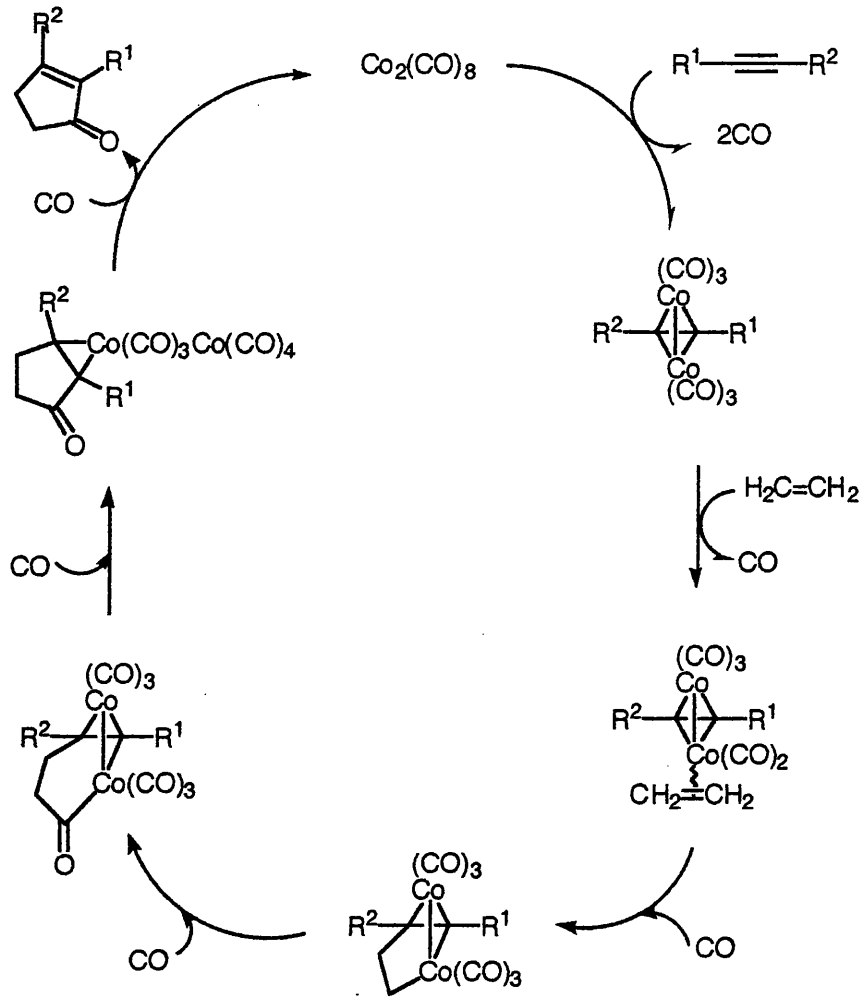
The main disadvantage of the traditional PKR was that a stoichiometric amount of dicobalt octacarbonyl was essential and this made the reaction very expensive. The next challenge was to attempt to develop an efficient catalyst. The Pauson group began work on catalysis[13] in the late 1980s but did not have much success. Rautenstrauch and co-workers developed a catalytic system but found that harsh conditions were needed (*Scheme 53*).[56] Although the yields were not very high they got a turnover number of about 220 with excellent regioselectivity and a 98 – 99 % yield of **106** was isolated.



106

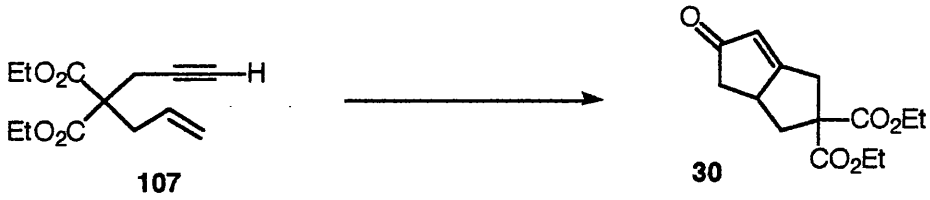
Scheme 53

Rautenstrauch and his group have suggested a possible mechanism[56] for the catalytic cycle. Until the second to last step it is identical to the mechanism proposed for the stoichiometric reaction.[1] However, in the catalytic cycle, $Co_2(CO)_8$ is regenerated (*Scheme 54*).



Scheme 54

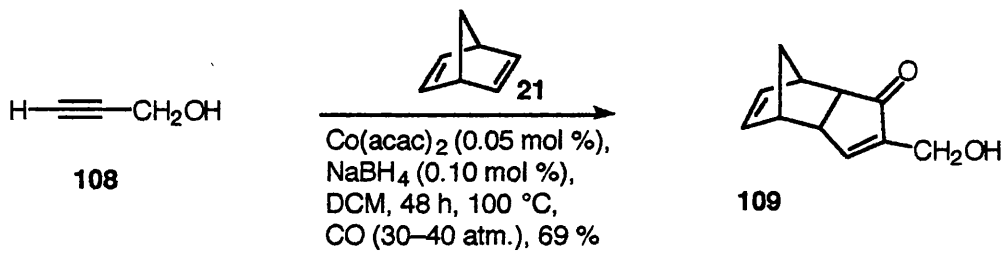
Jeong *et al.* took up the gauntlet to attempt to find a practical, catalytic version of the intramolecular PKR to yield cyclopentenones **30**.[57] One of the problems with developing a catalytic system was that the cobalt species formed either metal clusters or carbonyl species, such as $Co_4(CO)_{12}$, which were inactive towards alkyne substrates. The addition of phosphine and phosphite ligands seemed to inhibit the formation of these unreactive cobalt species. They found that by adding a catalytic amount of dicobalt octacarbonyl (3 mol %) with a co-catalyst of triphenylphosphite (10 mol %) to substrate **107** in DME at 120 °C for 24 h under 1 atmosphere of carbon monoxide, **30** was formed in a high yield of 82 % (*Scheme 55*). The reaction was effective with a variety of substrates whereas in the previous case,[56] the conditions were only effective in the reaction shown in *Scheme 53*.



107 **30**

Scheme 55

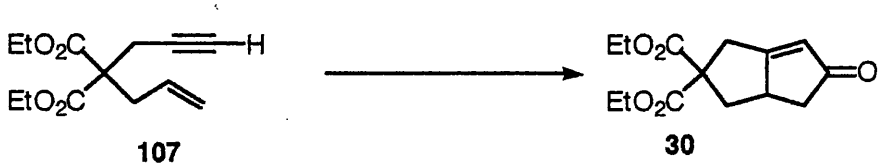
Lee and Chung also reported a catalytic version of the PKR.[58] They thought that a system could be catalytic if it could generate, *in situ*, low valent cobalt which could complex with dienes and alkynes or could produce cobalt carbonyls under carbon monoxide. Several cobalt salts were screened and when a mixture of alkyne **108**, alkene **21**, $Co(acac)_2$ and $NaBH_4$ in DCM were combined, the corresponding cyclopentenone derivative **109** was obtained in high yield (*Scheme 56*).



108 **109**

Scheme 56

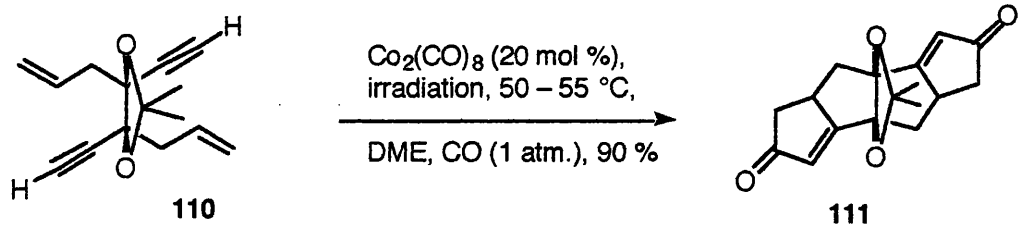
Pagenkopf and Livinghouse felt that very harsh conditions were required for the catalytic versions of the PKR and aimed to develop a milder catalytic cycle.[59] For many years it has been known that various metal carbonyl complexes undergo photoinduced CO dissociation.[23] Livinghouse and co-workers found that high-intensity visible light effectively promoted catalytic PKR at 50 – 55 °C under 1 atmosphere of carbon monoxide.[60] When ester **107** was subjected to irradiation at 50 °C with 5 mol % $Co_2(CO)_8$ in DME for 12 hours, product **30** was obtained in 95 % yield (*Scheme 55*).



107 **30**

Scheme 55

Livinghouse and co-workers then went on to apply their catalytic conditions in the tandem cyclisation of precursor **110** to form tetracycle **111** (*Scheme 57*).



110 111

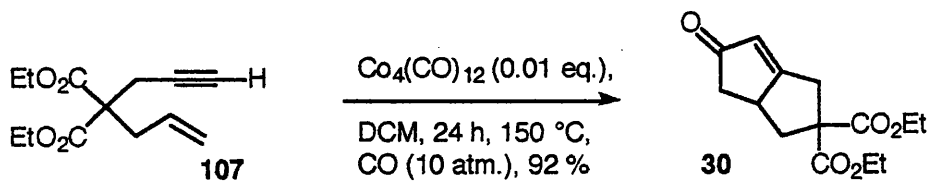
Scheme 57

Kim and Chung later used the cobalt cluster $Co_4(CO)_{12}$ as a catalyst precursor.[61] As previously discussed,[57] the formation of this complex hindered the ability of the reaction to be catalytic. However high pressures of carbon monoxide caused the complex to break down to become an active cobalt species. When phenylacetylene **94** was reacted with norbornadiene in the presence of 0.005 equivalents of $Co_4(CO)_{12}$ in DCM at 150 °C for 1.5 hours under 10 atmospheres of carbon monoxide, a yield of 97 % of **22** was isolated. In this case the turnover number was 194 (*Scheme 58*).[61]

94 **22**

Scheme 58

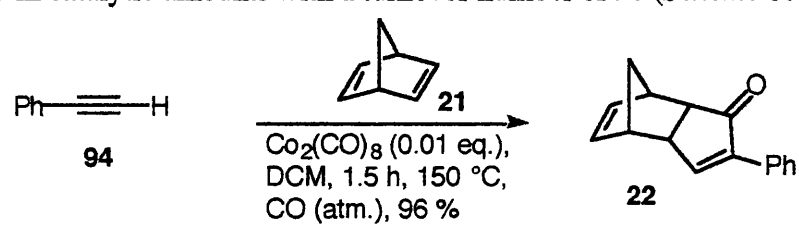
The intramolecular reactions required longer reaction times, more $Co_4(CO)_{12}$ and the turnover number was only 92 but the yields were very high (*Scheme 59*).



107 **30**

Scheme 59

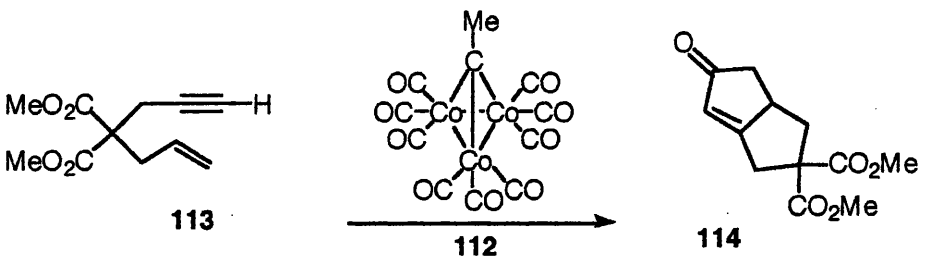
Under their optimised conditions, Kim and Chung discovered that $Co_2(CO)_8$ could also be used in catalytic amounts with a turnover number of 96 (*Scheme 60*).[61]



94 **22**

Scheme 60

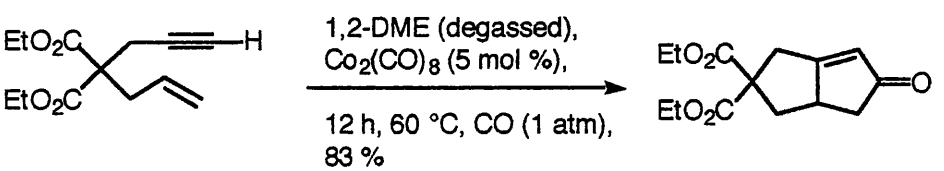
Sugihara and Yamaguchi developed the idea of using cobalt clusters and reported a catalytic route using the methylidynetricobalt nonacarbonyl cluster **112**.[62] Following a well known procedure, the cluster was prepared by reaction of dicobalt octacarbonyl with trihaloalkanes. When substrate **113** was reacted with 0.02 equivalents of methylidynetricobalt nonacarbonyl **112** in the presence of toluene at 120 °C under 7 atmospheres of carbon monoxide for 10 hours, product **114** was isolated in a yield of 98 % (*Scheme 61*).



Scheme 61

Methylidynetricobalt nonacarbonyl **112** was found to be more reactive and more stable to oxidation than the parent dicobalt octacarbonyl. The conditions were also very effective for both inter- and intra-molecular Pauson-Khand cyclisations.

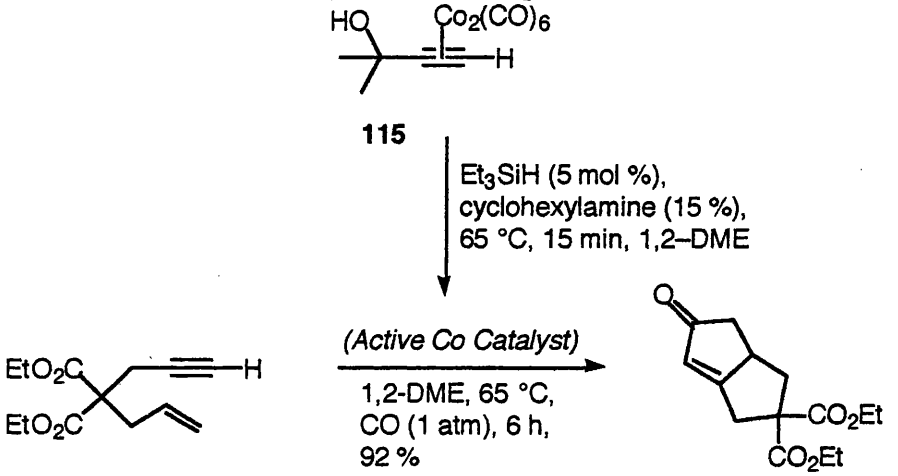
Livinghouse and co-workers also reported that very high purity $Co_2(CO)_8$ alone worked as a catalyst but that it had a very strong thermal dependence.[63] The optimum temperature range was between 60 – 70 °C and this appears to be one of the mildest catalytic versions of the Pauson-Khand cyclisation reported (*Scheme 62*).



Scheme 62

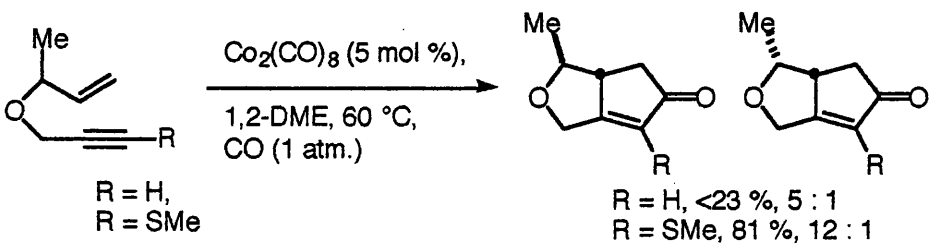
Livinghouse and co-workers argued that the need for $Co_2(CO)_8$, which is labile to both heat and oxygen, in a very high state of purity, constitutes an experimental disadvantage to this procedure.[64] They thought that the identification of chemically robust dinuclear complexes would greatly enhance the practical attractiveness of the catalysed PKR. Selected shelf stable, $Co_2(CO)_6$-alkyne complexes **115** were found to serve as sources of active catalysts for carbonylative enyne cyclisations.[64] In a previous

paper, Hosokawa and Isobe noted that Et_3SiH was a useful reagent for the conversion of $Co_2(CO)_6$-alkyne complexes **115** into vinylsilanes *via* reductive decomplexation.[65] Livinghouse's group used this chemistry in the hope that the (carbonyl)cobalt by-product generated in those reactions would exhibit catalytic activity.[64] A series of $Co_2(CO)_6$-alkyne complexes in combination with Et_3SiH as $Co_2(CO)_8$ surrogates in the catalytic PKR were tested. The example below shows the best $Co_2(CO)_8$ surrogate found in which 5 mol % of the alkyne-cobalt complex **115** was used (*Scheme 63*).



Scheme 63

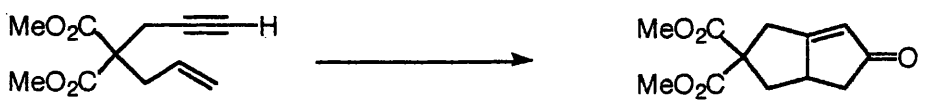
Belanger and Livinghouse then went on to examine the effect of the substituent on the alkyne since it has been shown to affect the rate and stereocontrol of the PKR.[60] They found that when a sulfide was at the terminal position of the alkyne as opposed to hydrogen, the yield and stereoselectivity of the reactions usually increased (*Scheme 64*).



Scheme 64

Sugihara and Yamaguchi applied the same reasoning to finding a catalyst[66] that they had used to identify an efficient promoter.[24] Combining the theory that hard ligands facilitate the PKR with the work by Lee and Chung that found that reactions conducted under CO regenerate the active cobalt species,[58] Sugihara found that by including an additive with dicobalt octacarbonyl, the reaction became catalytic.[66]

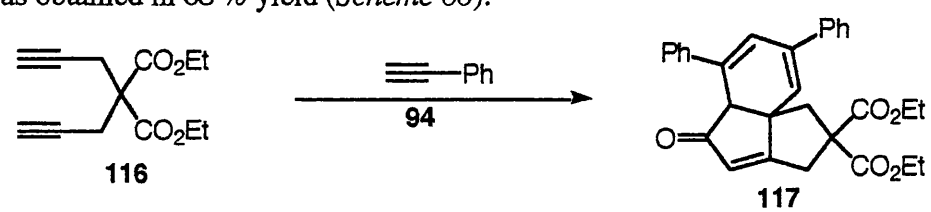
During the search for an efficient Lewis base, cyclohexylamine was tested. Although this primary amine was one of the most effective promoters in the stoichiometric reaction,[24] it was one of the worst additives in the catalytic cyclisation.[66] However, in the catalytic reaction, secondary and tertiary amines were found to be acceptable additives with diisopropylethylamine being the most efficient. The main implication of the finding was that the reaction mechanism appeared to differ between the stoichiometric and catalytic reactions. Although alcohols promoted the catalytic cyclisation, alcohols with chelatable substituents, such as ethylene glycol and 2-methyoxyethane, killed the catalytic process. They tested a range of hard Lewis bases with catalytic amounts of dicobalt octacarbonyl and found 1,2-dimethoxyethane to be the best additive (*Scheme 65*). When 0.01 equivalents of $Co_2(CO)_8$ was combined with 0.04 equivalents of DME in toluene at 120 °C for 10 hours under 20 atmospheres of carbon monoxide, **114** was isolated in a yield of 93 %. When water was used as a promoter under otherwise identical conditions, product **114** was obtained in a yield of 63 %.



114

Scheme 65

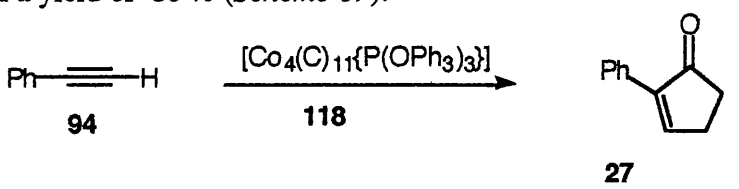
Chung and co-workers demonstrated that their catalytic route could be used to sythesise novel 5-5-6 tricyclic organic compounds *via* a tandem [2+2+1] and [2+2+2] cycloaddition reaction.[67] They found that when substrate **116** was reacted with 2 equivalents of phenylacetylene **94** in the presence of 5 mol % of $Co_2(CO)_8$ and heated in DCM at 130 °C for 18 hours under 30 atmospheres of carbon monoxide, product **116** was obtained in 68 % yield (*Scheme 66*).



116 **117**

Scheme 66

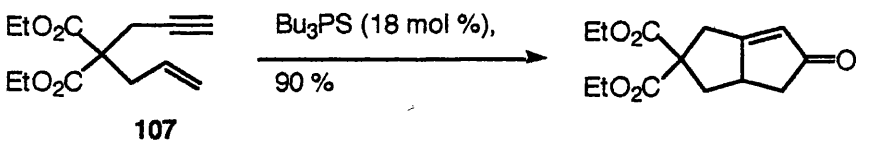
Jeong and Hwang have utilised supercritical ethylene both as a solvent and as a reagent in the catalytic PKR.[68] When phenylacetylene **94** was placed in a steel bomb at 34 °C with an initial 110 atmospheres of ethylene and 5 atmospheres of carbon monoxide with 3 mol % of catalyst **118**, then heated to 85 °C for 46 hours, product **27** was isolated in a yield of 80 % (*Scheme 67*).



Scheme 67

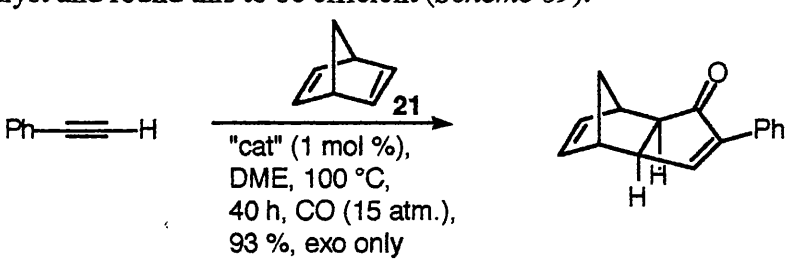
The advantage of this method is that under these conditions even a low pressure of CO (5 atm.) was sufficient for the reaction to occur.

Saigo and co-workers have also developed a mild phosphane sulfide / dicobalt octacarbonyl catalyzed PKR.[69] Their approach involved the addition of 18 mol % of a phosphane chalcogenide with 3 mol % of dicobalt octacarbonyl to substrate **107** in benzene at 70 °C for 7 hours under 1 atmosphere of carbon monoxide (*Scheme 68*).



Scheme 68

Lee and Chung tested 1,5-cyclooctadiene(indenyl)cobalt(I) complex (*Figure 10*) as a catalyst and found this to be efficient (*Scheme 69*).[70]



Scheme 69

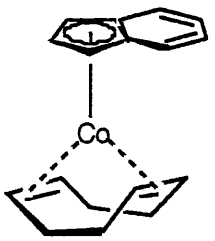
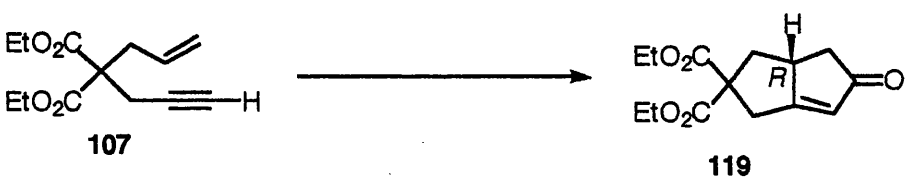


Figure 10

Although the above reaction has been rendered asymmetric, it has already been observed by Pauson that the *exo* product tends to be favoured in reactions involving a cyclic alkene.[11] When the reaction was applied to intramolecular reactions, good yields were obtained but the enantiomeric excess was not reported.[70]

Pauson and co-workers found mono- and bidentate phosphines to be useful additives in the stoichiometric Pauson-Khand cyclisations.[14] However, Hiroi *et al.* were the first group to use substoichiometric amounts of chiral phosphine ligands to induce enantioselectivity in the intramolecular catalytic PKR.[71] When substrate **107** was reacted with 0.2 equivalents of $Co_2(CO)_8$, 0.2 equivalents of (*S*)-BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) in DCE at reflux for 17 hours under a carbon monoxide atmosphere, product **119** in the *R*-configuration was isolated in 62 % yield with an enantiomeric excess of 91 % (*Scheme 70*).

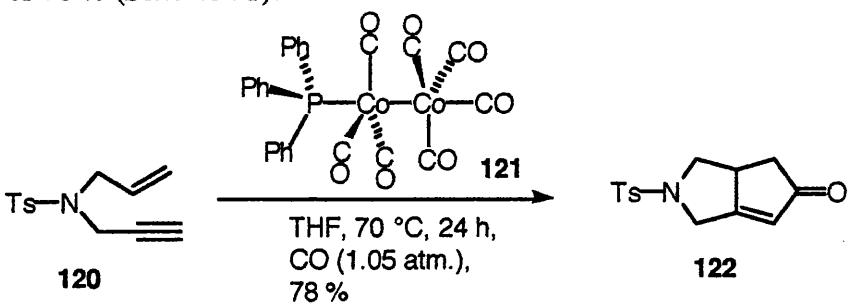


Scheme 70

The disadvantage of this method was that when there was a substituent on the alkyne component the enantioselectivity decreased significantly. The reaction only showed a significant degree of enantioselectivity in the intramolecular reaction.

As previously commented by Livinghouse and co-workers, the need for rigorously purifying dicobalt octacarbonyl prior to use constitutes an experimental disadvantage.[64] They proceeded to develop shelf-stable precursors and found these to be effective promoters. Krafft and co-workers continued this theme but found that by thoroughly base-washing glassware prior to use and using an additive, such as cyclohexylamine, the need for high purity dicobalt octacarbonyl was eliminated.[72]

Gibson and co-workers have also developed a range of stable catalysts for the PKR.[73] They synthesised phosphine and phosphite derivatives of dicobalt octacarbonyl and tested them using standard Pauson-Khand substrate **120**. When substrate **120** was combined with 5 mol % of the catalyst **121** and heated to 70 °C for 24 hours in THF under an atmosphere of carbon monoxide, product **122** was isolated in a yield of 78 % (*Scheme 71*).



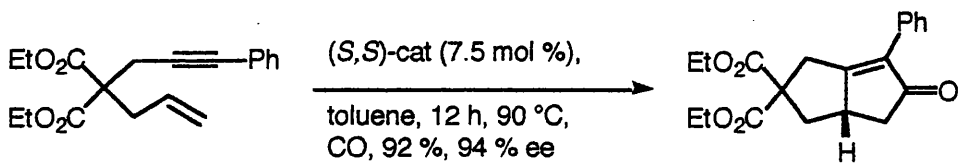
Scheme 71

The monophosphine cobalt complex was considerably more stable than $Co_2(CO)_8$ and was easily prepared from dicobalt octacarbonyl and triphenylphosphine. The stability of the complex made it easier to handle and measure and renders its reactions much more reliable.

Again there have been many fascinating attempts to find a general catalytic version of the Pauson-Khand reaction but there has yet to be found a general route with total enantiocontrol.

1.19 Other Metals for Asymmetric Catalysis

In 1996 Hicks and Buchwald developed the first asymmetric catalyst for the intramolecular Pauson-Khand type reaction.[74,75] The catalyst was (*S,S*)-(EBTHI)Ti(CO)$_2$, [EBTHI = ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)] (*Figure 11*) which was generated *in situ* from (*S,S*)-(EBTHI)TiMe$_2$ (*Scheme 72*). The bicyclic compounds were obtained in high yields with excellent enantioselectivity and a wide range of functionality, such as esters, amines and ethers, could be tolerated. Even more surprisingly, 1,1-disubstituted alkenes - whose reluctance to cyclise under "normal" PKR conditions constituted an experimental disadvantage - cyclised successfully under the conditions used by Hicks and Buchwald.



Scheme 72

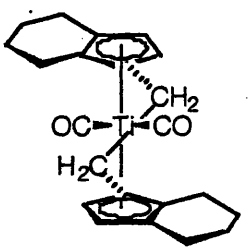


Figure 11

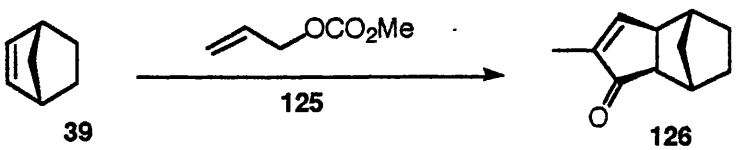
It was the first example where a substoichiometric amount of metal which was not cobalt was used in the reaction and many others have since used different metals in Pauson-Khand type reactions.

1.20 Ruthenium Based Catalysts

Murai and co-workers have used Ru$_3$(CO)$_{12}$ as a catalyst in the transformation of 1,6-enynes to bicyclo[3.3.0]octenones.[76] They found that when 0.02 equivalents of the catalyst was combined with substrate **123** in dioxane at 160 °C under 10 atmospheres of carbon monoxide for 20 hours, product **124** was obtained in 86 % yield (*Scheme 73*).

Scheme 73

Kondo and co-workers have also used ruthenium as their catalyst but they opted to use $[RuCl_2(CO)_3]_2$ with an amine additive to conduct the intermolecular PK type reactions effectively.[77] The amine additive was essential to the effectiveness of the transformations as there was no reaction without it. Where the PKR involves the combination of an alkyne and an alkene, the procedure of Kondo and co-workers uses two alkenes. When allyl methyl carbonate **125** was reacted with norbornene **39** in the presence of 2.5 mol % of $[RuCl_2(CO)_3]_2$ and 10 mol % of triethylamine in THF at 120 °C for 5 hours under 3 atmospheres of carbon monoxide, the corresponding *exo* cyclopentenone **126** was isolated in 80 % yield with a diastereomeric excess of 100 % (*Scheme 74*).

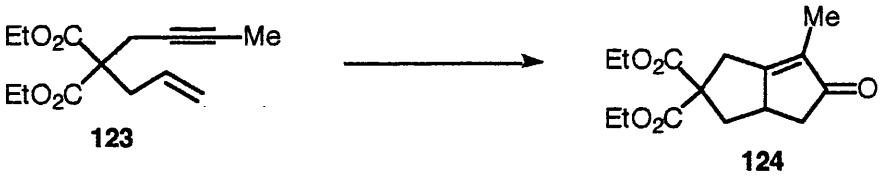


Scheme 74

In the PKR all the atoms that were present in the starting materials were present in the product ; however, in this case, the ester group was lost.

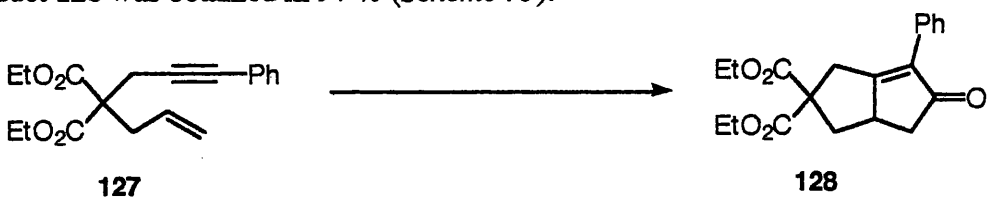
1.21 Rhodium Based Catalysts

Jeong *et al.* have developed the first catalytic intramolecular PK type reaction using rhodium and under only one atmosphere of carbon monoxide.[78] Different catalysts were tested, including Wilkinson's catalyst, but *trans*-$[RhCl(CO)(dppe)]_2$ was found to be the catalyst of choice due to its stability and the operational simplicity of the reaction. When substrate **123** was combined with 5 mol % *trans*-$[RhCl(CO)(dppe)]_2$ in toluene at 110 °C for 40 hours under one atmosphere of carbon monoxide, product **124** was isolated in 97 % yield (*Scheme 73*).



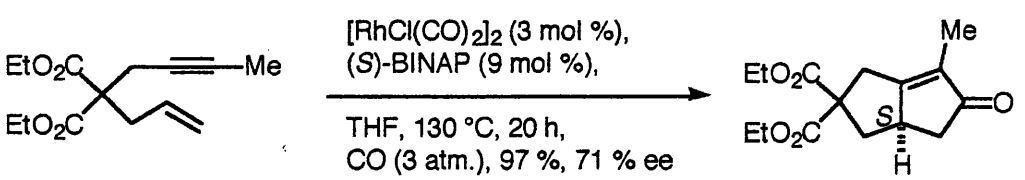
Scheme 73

Narasaka and co-workers also decided to use rhodium as the central metal in the intramolecular PK type cyclisations.[79] Rhodium was used since it belongs to the same group in the periodic table as cobalt and the Narasaka group hoped that it would have the same promoting ability. When substrate **127** was combined with 5 mol % of $[RhCl(CO)_2]_2$ in THF at 90 °C for 9 hours under one atmosphere of carbon monoxide, product **128** was obtained in 97 % (*Scheme 75*).



Scheme 75

Jeong *et al.* then proceeded to develop a catalytic asymmetric version of the intramolecular Pauson-Khand reaction.[80] While (*S*)-BINAP has been added as a chiral additive in PKR with $Co_2(CO)_8$,[71] This was the first example where it was added to a different metal.[80] They believed that the addition of (*S*)-BINAP to $[RhCl(CO)_2]_2$ resulted in the *in situ* formation of $[Rh(CO)(S)\text{-BINAP}]^+$ which then bound to the 1,6-enyne and resulted in controlling the stereoselectivity in the PK type reactions (*Scheme 76*).

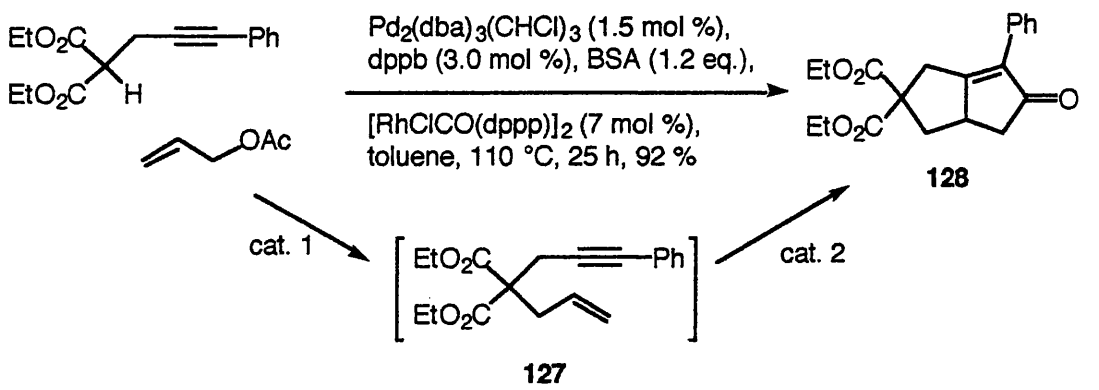


Scheme 76

However, the yields and enantiomeric excesses were very dependent on the pressure of the carbon monoxide gas and it had to be fine-tuned for each individual substrate.

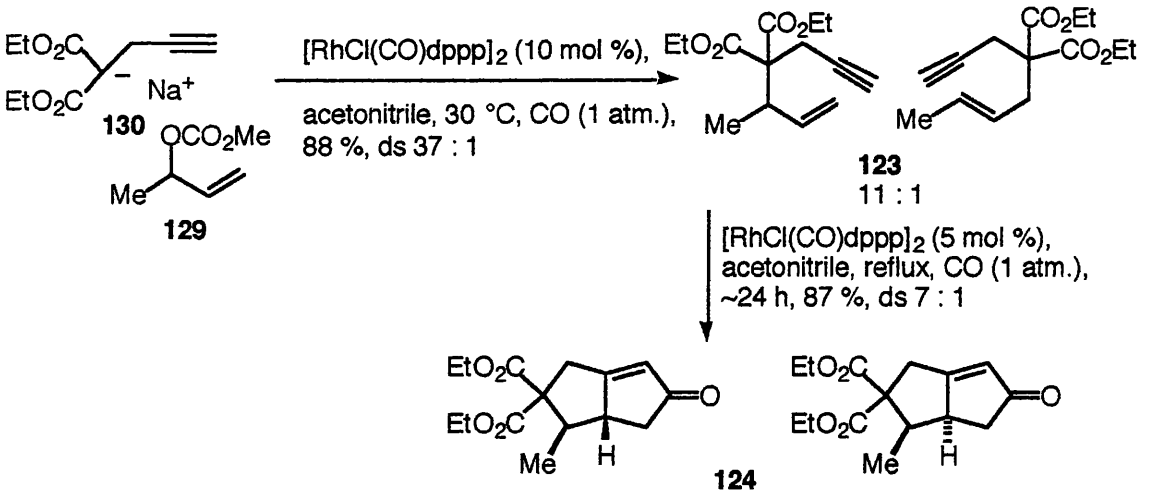
The next impressive strategy of Jeong and co-workers was the development of a one pot preparation of bicyclopentenones from propargyl malonates and 2 equivalents of allylic acetates *via* a tandem action of catalysts.[81] The number of steps required was

reduced since the substrate was synthesised *in situ* before further reaction to yield the bicyclopentenone. The first palladium catalyst formed intermediate **127** before reaction with the rhodium catalyst formed the bicyclopentenone **128** in 92 % yield over 2 steps (*Scheme 77*).



Scheme 77

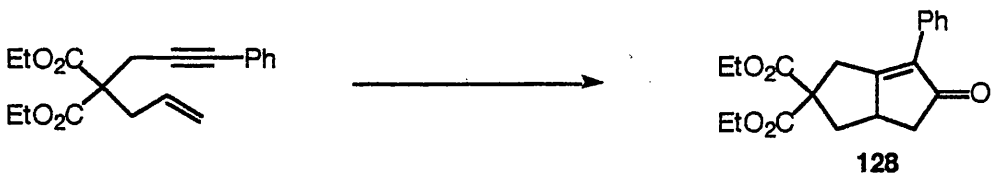
Evans and Robinson took the idea of Jeong and co-workers[81] and developed it into an asymmetric version of the catalytic intramolecular PK type reaction.[82] However, they decided to use one catalyst to conduct both synthetic transformations using only the temperature to modulate the catalytic activity. They also hoped that this approach would allow them to increase the molecular complexity of the bicyclic adduct by introducing a stereogenic centre at C-2 which they hoped would control the diastereoselectivity in the PK type reaction. When substrate **129** was reacted with 5 mol % of $[RhCl(CO)dppp]_2$ and 1.2 equivalents of the sodium salt of **130** in acetonitrile at 30 °C under one atmosphere of carbon monoxide, intermediate **123** was obtained in a yield of 88 % with a diastereoisomeric ratio of 37 : 1 (determined by gas liquid chromatography (GLC)). The reaction mixture was then heated at reflux for approximately 24 hours before **124** was isolated in 87 % yield as a 7 : 1 mixture of diastereoisomers (*Scheme 78*).



Scheme 78

1.22 Iridium Based Catalysts

Shibata and Takagi went on to look at another metal and found iridium to be an effective catalyst in the enantioselective asymmetric intra- and inter-molecular PK type reaction.[83] The chiral iridium catalyst was easily prepared *in situ* from 10 mol % of $[Ir(COD)Cl]_2$ and 20 mol % of (*S*)-tolBINAP, both of which are commercially available and air-stable. The reaction proceeded at reflux in toluene under one atmosphere of carbon monoxide to give a yield of 74 % of **128** with an enantiomeric excess of 84 % (*Scheme 75*).



Scheme 75

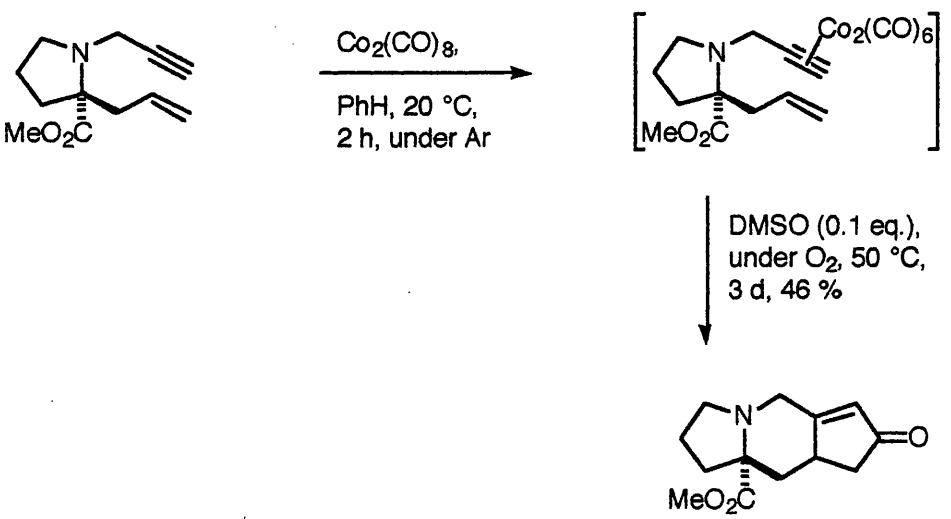
The PKR is one of the most commonly used cyclisations. Many research groups have attempted to develop general routes, asymmetric routes and catalytic routes towards the cyclopentenone products with a variety of success. The remainder of this thesis details our attempts to find a mild, general and eventually a catalytic route to the Pauson-Khand reaction products and we also had a variety of success along the way.

Chapter 2

2.1 Introduction

Pauson-Khand cyclisations of cobalt complexes have been attempted using many different conditions[17] and promoters.[4] Amine *N*-oxides have been researched as promoters,[16] but we decided to focus on the use of amines. Sugihara and co-workers have already demonstrated that amines promote the reaction well.[24]

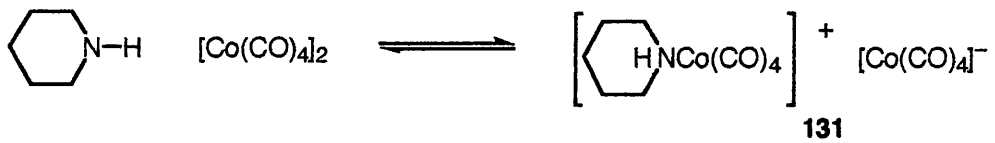
It is widely believed that the oxygen from the amine *N*-oxide attacks one of the carbon monoxide ligands to produce carbon dioxide which leaves and creates a vacant site at the cobalt atom (refer to *scheme 5* on page 3).[1] The alkene inserts into the vacant site and the PKR then proceeds. Pauson and co-workers hoped that the use of sulfoxides would be milder and would merely labilise the carbon monoxide ligands so that oxidative destruction of the cobalt complex would not occur, thus creating a possible approach to a catalytic process.[17] DMSO worked well under air (*Scheme 79*) and very recently Tanimori and co-workers developed reaction conditions using substoichiometric amounts of DMSO.[84]



Scheme 79

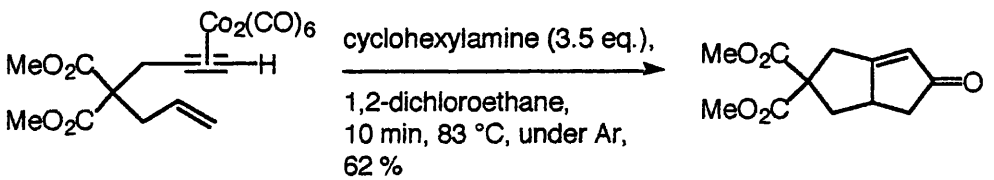
It has been well documented that hard Lewis bases, such as amines, can labilize the existing ligand on low-valent organotransition metals, such as cobalt.[25] Heiber and Schulten reported that ammonia can act as a Lewis base with $Co_2(CO)_8$, causing disproportionation of the carbonyls, leading to formation of $[Co(NH_3)_6][Co(CO)_4]_2$.[85]

Wender and co-workers have also shown that piperidine can reversibly react with $Co_2(CO)_8$ forming the anionic-cationic complex **131** (*Scheme 80*).[86] Complex **131** can then be readily attacked by a neutral alkene or by a basic or neutral amine.



Scheme 80

Sugihara and co-workers knew that hard ligands, containing a nitrogen or oxygen atom, labilised the carbon monoxide ligands attached to the cobalt atom and would aid the ligand substitution reaction.[24] If the hard ligands react with $Co_2(CO)_6$(alkyne) complexes in the presence of alkenes, the substitution of CO ligands by alkenes may also be facilitated. The co-ordinated alkyne is also made reactive by the labilising effect of the hard ligands, therefore the PKR may be promoted. It was found that primary amines promoted the reactions well (*Scheme 81*) but that tertiary amines retarded the reaction.



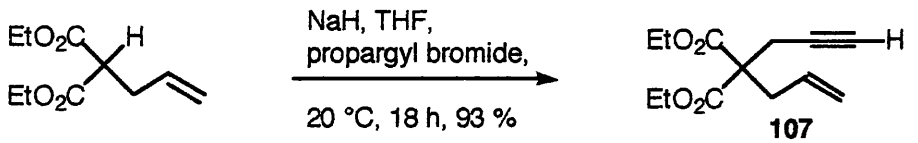
Scheme 81

We decided to look at the effect of promoting the PKR with a variety of amines in an attempt to develop a mild route towards the cyclopentenone products that did not require the reactions to be conducted under an atmosphere of carbon monoxide. It was hoped that an enantioselective route and a catalytic route would be successfully developed and applied to a variety of substrates.

2.2 Preparation of Starting Materials

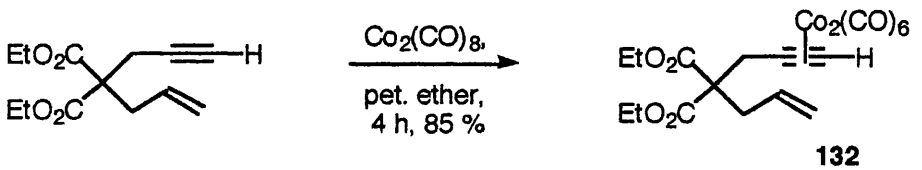
A standard substrate **107** that is commonly employed in PKR was used in order to compare our results with those already in the literature. However, problems were encountered during the synthesis of diethyl 6-hepten-1-yne-4,4-dicarboxylate **107**.

Product **107** was obtained in varying yields and purity when the literature procedure was followed.[87] Changing the base from LDA to sodium hydride gave a far more reproducible reaction and resulted in product **107** being obtained in consistently high yields of > 90 % (*Scheme 82*).



Scheme 82

Cobalt complex **132** was synthesised following a procedure developed by Pauson[11] (*Scheme 83*) and was purified using column chromatography on silica gel. The complex **132** was stable in air for about fifteen minutes but could be stored easily for long periods in the freezer under an atmosphere of nitrogen.



Scheme 83

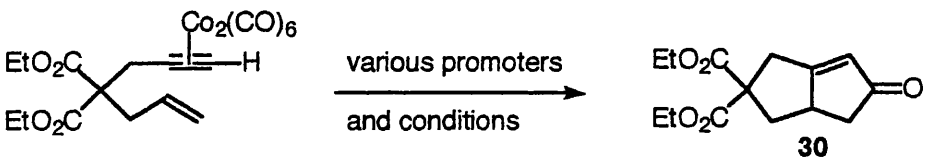
However, characterisation of complex **132** proved difficult. ^{1}H NMR spectroscopy gave broad signals because of the presence of paramagnetic cobalt residues. When **132** was diluted with $CDCl_3$, filtered through a pad of silica gel and cotton wool, a clean ^{1}H NMR spectrum was obtained. In the ^{1}H NMR spectrum of the starting material, the alkyne hydrogen appeared as a triplet at δ 2.00, however, in the cobalt complex, the alkyne hydrogen appeared as a singlet at δ 5.98. The ^{1}H NMR data obtained were in good agreement with the literature values.[11] ^{13}C NMR spectroscopy was more difficult. An extended ^{13}C NMR spectrum was run. Complex **132** precipitated from the $CDCl_3$ solution very quickly but eventually a satisfactory spectrum was obtained. Low resolution mass spectrometry confirmed the presence of a compound of the expected mass. I.R. spectroscopy confirmed the presence of carbon monoxide ligands with peaks at 2093, 2051, and 2020 cm^{-1}.

2.3 Results and Discussion

The main advantage of using amines over amine *N*-oxides is that there is a wider range of commercially available amines, thus simplifying the procedure. Also, cobalt complexes are more tolerant of amines than amine *N*-oxides, which tend to cause oxidative degradation.[17]

2.3.1 Varying the Nature of the Amine

A series of reactions were conducted under a wide variety of conditions to find the optimum requirements for cyclisation (*Scheme 84, Table 1*). Initially the amine component was varied.



Scheme 84

Table 1

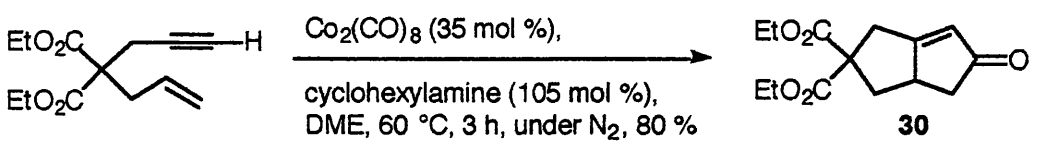
Reaction	Starting Material	Promoter	Yield of 30 (%)
1[a]	1.08 g, 2.06 mmol	–	29
2[b]	1.83 g, 3.49 mmol	NMO	47
3	0.96 g, 1.83 mmol	NMM	57
4[ac]	0.74 g, 1.38 mmol	NMM	38
5	1.08 g, 2.06 mmol	Triethylamine	36
6	1.25 g, 2.39 mmol	Diisopropylamine	49
7	0.72 g, 1.37 mmol	Cyclohexylamine	27
8	0.76 g, 1.45 mmol	DABCO	41
9	1.04 g, 1.98 mmol	TMEDA	42
10	1.28 g, 2.44 mmol	Pyridine	42
11[b]	0.45 g, 0.86 mmol	$NMO.H_2O$	75
12[b]	1.19 g, 2.27 mmol	NMM	49[e]
13[d]	0.91 g, 1.74 mmol	–	31[f]

Unless stated otherwise, 3 equivalents of promoter were added, the solvent was toluene (25 ml) and the reaction mixture was stirred at 20 °C under air for 4 days.

[a]No amine was added. [b]Methanol (5 ml) was added. [c]7.5 equivalents of NMM were added. [d]Methanol (15 ml) was added. [e]3 % of **133** (page 53) was isolated. [f]8 % of **133** (page 53) was isolated.

Table 1 effectively demonstrates that a wide variety of amines can promote the Pauson-Khand cyclisation. *N*-Methylmorpholine was tested since the *N*-oxide of this amine was one of the most commonly used promoters in the PKR[1] and a yield of 57 % of **30** was obtained (reaction 3). A blank experiment was also run, no amine was added and a poor 29 % yield was isolated (reaction 1). From these two results it was obvious that the amine was essential for promotion of these reactions. It should be noted that a major advantage of our method is that the reaction can be carried out under air instead of the more commonly used atmospheres of argon,[16] nitrogen[14] or carbon monoxide.[4]

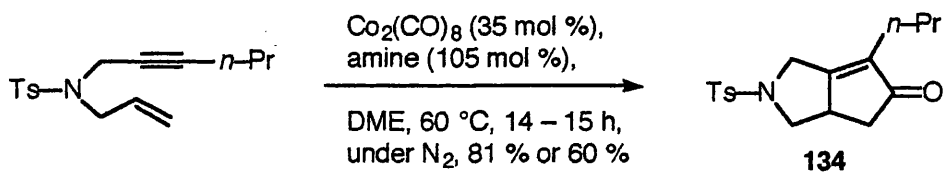
When conducting amine *N*-oxide promoted reactions, the groups of Kerr,[54] Crowe[16] and Laschat[53] usually added 6 – 10 equivalents of promoter. 7.5 equivalents of NMM were added but instead of increasing the yield, a lower yield of 38 % was obtained (reaction 4). It was thought that the excess amine may be reacting too quickly resulting in decomposition of the complex as opposed to cyclisation. Thereafter, 3 equivalents of promoter were subsequently used. Krafft and Bonaga also commented that in their catalytic amine-promoted Pauson-Khand reactions 3 equivalents of amine to 1 equivalent of $Co_2(CO)_8$ were crucial to the efficiency of the cyclisation procedure but no explanation for this was proposed (*Scheme 85*).[88]



Scheme 85

Table 1 shows that primary, secondary, tertiary and aromatic amines can promote the reaction to some extent and this was effectively demonstrated by reactions 5, 6 and 10. Triethylamine (reaction 5) was used because its availability makes it a highly attractive reagent. However, this tertiary amine gave a disappointing yield of only 36 %. Sugihara and co-workers found that when triethylamine was used as a solvent

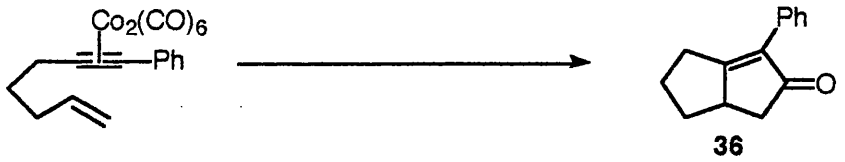
under their reaction conditions, only starting material was recovered.[24] They also found that primary amines with secondary alkyl groups seemed to promote the reactions most effectively and that when isopropylamine was used, a yield of 68 % of **30** was isolated. Diisopropylamine (reaction 6) was chosen since it was a secondary amine with bulky alkyl substituents and is a cheap commercial amine. A respectable yield of 49 % was obtained and diisopropylamine could be a useful promoter of the PKR. Cyclohexylamine, a primary amine with a secondary alkyl group, was the promoter of choice under Sugihara's conditions.[24] Surprisingly, it gave the poorest yield of only 27 % (reaction 7) which is equivalent to no promoter being added (reaction 1). An aromatic amine was used to see if there was any enhancement in the promoting ability, however pyridine (reaction 10) gave a yield of only 42 % of **30**. Very recently, Krafft and co-workers have found that pyridine was not as effective as cyclohexylamine in their substoichiometric PKR.[89] When 105 mol % of cyclohexylamine was added, 81 % of **134** was isolated and when 105 mol % of pyridine was added, 60 % of **134** was obtained (*Scheme 86*).



134

Scheme 86

Although a highly plausible mechanism exists for the amine *N*-oxide promoted PKR,[1] this has yet to be extended to the amine promoted reaction. It has been well documented that promoters containing hard ligands, such as nitrogen or oxygen atoms, labilize the CO ligands in metal-carbonyl complexes facilitating ligand substitution reactions.[25] Sugihara and co-workers felt that if the hard ligands reacted with $Co_2(CO)_6$(alkyne) complexes in the presence of alkenes, then the substitution of CO ligands by the alkenes might also be facilitated, and the PKR would occur.[24] It was found that 3.5 equivalents of cyclohexylamine in DME at 83 °C under argon for 5 minutes gave the optimum yield of 99 % of **36** (*Scheme 17*).



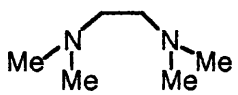
36

Scheme 17

It was speculated that the amine might be acting as an electron donor. 1,4-Diazabicyclo[2.2.2]octane (DABCO) (*Figure 12*) was used as it is a highly hindered base.[90] Its lone pairs are completely unavailable to facilitate the reaction. If the amine was indeed acting as an electron donor then the reaction time should be increased and the yield should be decreased. However, a yield of 41 % (reaction 8) was obtained and the role of the amine is still unclear.

N,N,N',N',-Tetramethylenediamine (TMEDA) (*Figure 13*), has been used to stabilise and activate organometallic reagents.[91] TMEDA is a diamine, therefore co-ordination by both nitrogens with elimination of two carbonyls is entropically favoured. It was used in the hope of increasing the yields and shortening the reaction times of the PKR. Unfortunately a yield of only 42 % (reaction 9) was recorded.

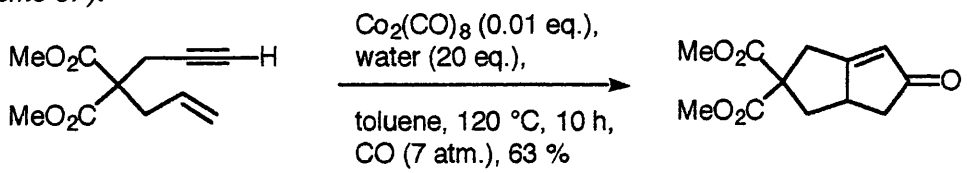
DABCO
Figure12



TMEDA
Figure 13

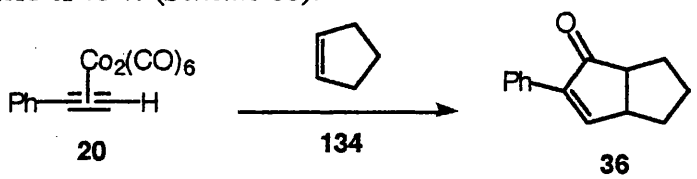
Reactions 2 and 3 have already compared the use of NMM versus NMO as promoters of the Pauson-Khand reaction. However, Kerr and co-workers comment that it was always the dihydrate of TMANO.$2H_2O$ and the monohydrate of NMO that was used to promote the PKR.[20] Therefore, a comparison between NMO.H_2O and NMM was required. NMO.H_2O is insoluble in toluene and had to be dissolved in MeOH before it could be added to the reaction mixture. Although the yield obtained from using NMO.H_2O (reaction 11) is 18 % higher than the equivalent result using NMM (reaction 3) our study involving amines was continued. Since alcohols are known to promote the PKR,[17] the water molecule of the monohydrate may also participate in the reaction. Although we did not run an experiment using water as a promoter, Kerr and

co-workers may have but it has not been reported in the literature. However, Sugihara and Yamaguchi have shown that water effectively promotes their catalytic PKR (*Scheme 87*).[66]



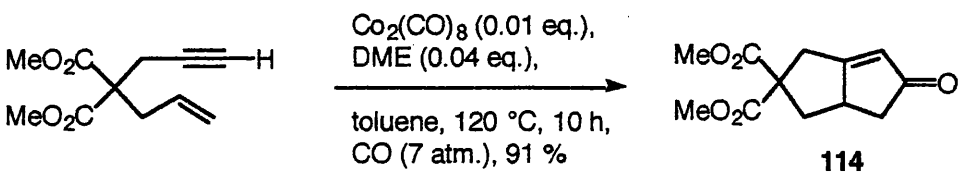
Scheme 87

Pauson and co-workers had demonstrated that MeOH and MeCN effectively promoted PKR.[17] When 10 equivalents of methanol and cyclopentene **134** were reacted with substrate **20** in refluxing DCM for 3 days under air, product **36** was obtained in a yield of 75 % (*Scheme 88*).



Scheme 88

Sugihara and co-workers have also shown that alcohols can promote the PKR. In their original communication using stoichiometric amounts of the cobalt complex with 1,4-dioxane and ethanol as promoters, only starting material was recovered.[24] However, when a catalytic version of the reaction was developed, they found that alcohols were as effective at promoting the reactions as amines (*Scheme 89*).[66]



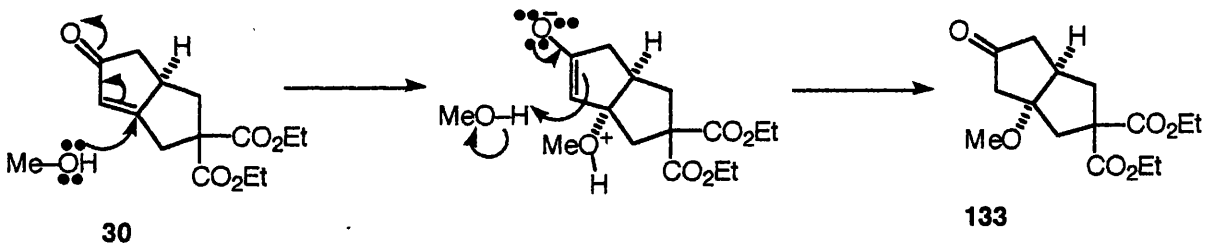
Scheme 89

DME (0.04 eq.) in toluene was shown to be the best promoter and a yield of 91 % of **114** was obtained. Benzyl alcohol, 1,4-dioxane and water all promoted the reactions to some extent but alcohols with chelating substituents, such as 2-methoxyethanol and ethylene glycol stopped the catalytic process.

Since amines[24] and alcohols[17] have been shown to promote the PKR effectively, alcohols were also examined under our conditions. Methanol was used as the promoter (reactions 12 and 13). In reaction 12, the addition of both amine and

alcohol led to a lower yield of 49 % compared to the amine alone (reaction 3) but traces of a by-product were detected. The amount of alcohol added was tripled while the amine was omitted and the yield was 31 % (reaction 13). This led to an increase in by-product **133** by 3 (reaction 12) to 8 % (reaction 13).

Two compounds **30** and **133** were identified by ^{1}H and ^{13}C NMR spectroscopy. However it was impossible to separate them using column chromatography. The by-product **133** has only been observed in reaction mixtures where methanol is present. GC-MS identified peaks relating to two compounds **30** and **133**, the major one was the cyclopentenone **30** and the minor one was 32 mass units higher. It was suggested that methanol was adding to the cyclopentenone in a Michael type addition (*Scheme 90*).



Scheme 90

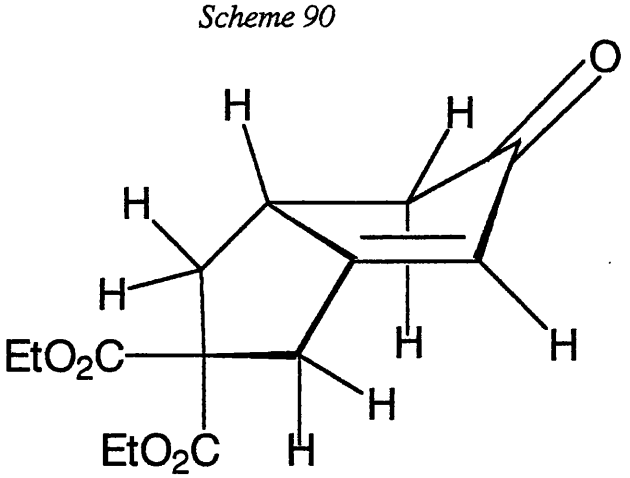
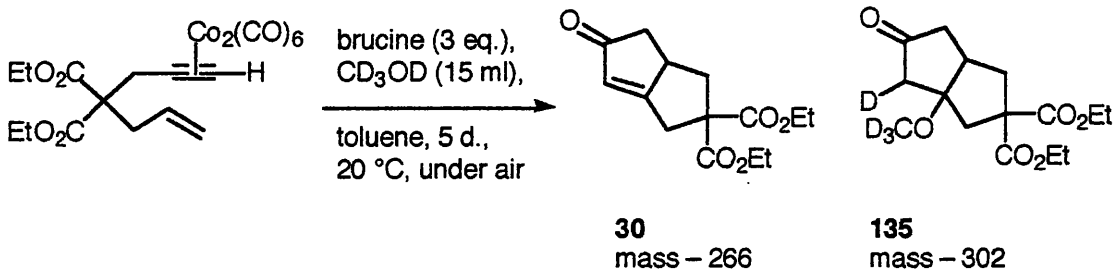


Figure 14

It is thought that the methanol adds to the same side as the proton from studying a molecular model (Chem 3D Pro) of the compound (*Figure 14*). It is the preferred site for attack as attack from the other side is sterically hindered due to the conformation of the molecule.

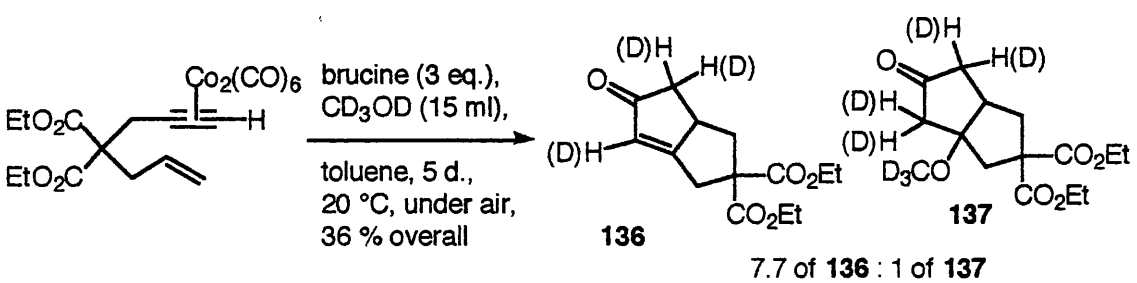
2.3.2 Pauson-Khand Cyclisations in Deuteriated Solvent

The PKR was conducted using CD_3OD to show that methanol was indeed adding across the double bond as speculated in *Scheme 90*. The expected products **30** and **135** are shown (*Scheme 91*).



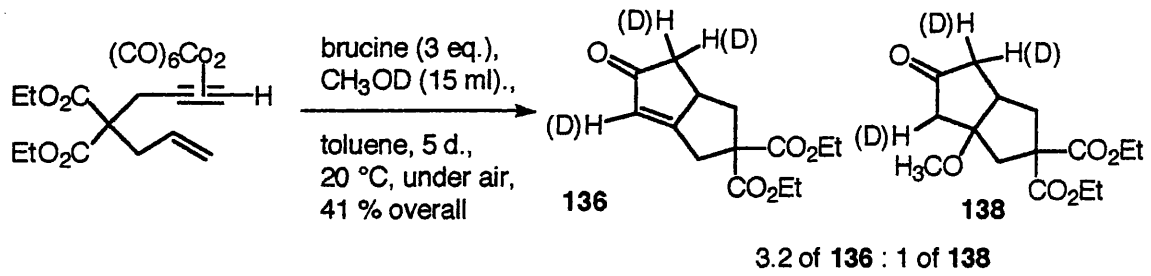
Scheme 91

The two products **30** and **135** that formed were inseparable so GC-MS was used to identify the product by mass and to determine the yield of each. In the first case we expected to see two peaks relating to compounds of mass 266 (product **30**) and 302 (product **135**). However, peaks relating to 269 (product **136**) and 305 (product **137**) were observed (*Scheme 92*). The reaction conditions clearly allow the acidic protons next to the carbonyl group to be rapidly exchanged for deuterium atoms. It was deduced that compound **30** had exchanged three protons for three deuteria to give a mass of 269, product **136**. Then addition of CD_3OD across the double bond would gave a mass of 305, product **137**. The overall yield was 36 % (7.7 of **136** : 1 of **137**). ^1H NMR spectroscopy confirmed the absence of a singlet at δ 5.92, showing that the hydrogen of the double bond had been exchanged by a deuterium atom. ^{13}C NMR spectroscopy showed the characteristic broadening associated with the signal from the O–CD_3 group.



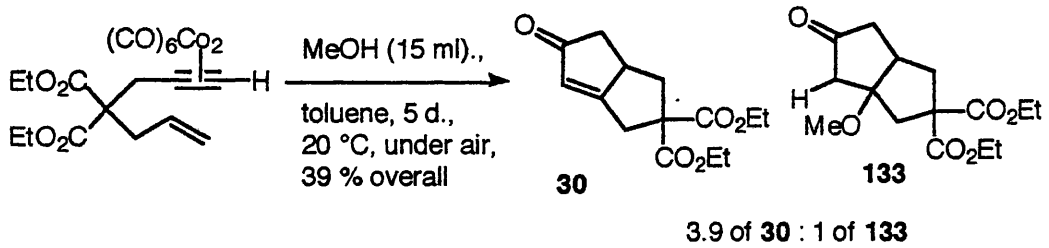
Scheme 92

When using CH_3OD, two peaks relating to compounds of mass 269 for **136**, and 302 for **138** were observed (*Scheme 93*). The overall yield was 41 % (3.2 of **136** :1 of **138**).



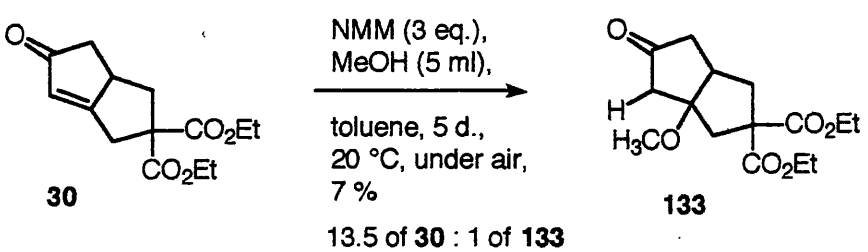
Scheme 93

In an attempt to rationalise the formation of the by-product **133**, the reaction was carried out without any amine present (*Scheme 94*). However, the yield of both **30** and by-product **133** was determined to be 39 % overall (3.9 of **30** : 1 of **133**), therefore the amine was not participating in the formation of by-product **133**.



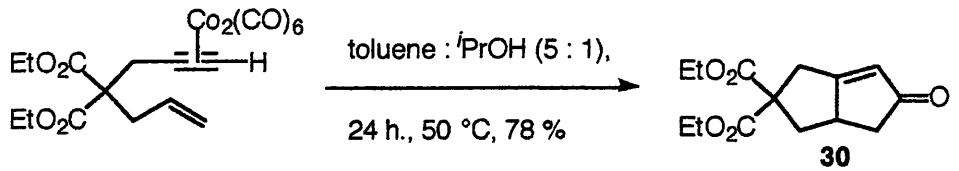
Scheme 94

The reaction between compound **30** and methanol was conducted without any cobalt present, (*Scheme 95*). However, a mixture of both starting material **30** (93 % yield) and by-product **133** (7 % yield) was isolated. Therefore, formation of the by-product **133** occurs after cyclisation as might be expected.



Scheme 95

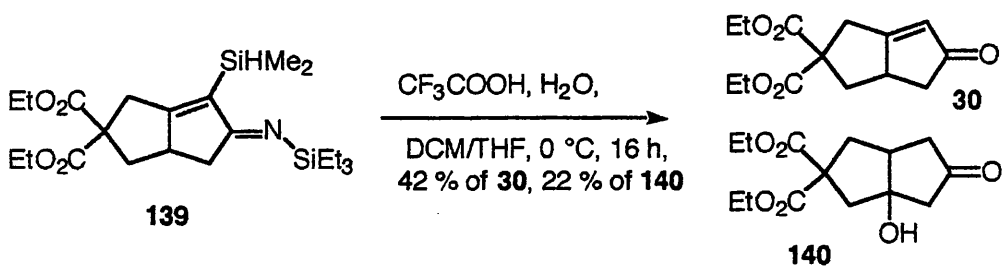
When isopropanol, a bulky and poor nucleophile compared to methanol, was added as a promoter, formation of the undesired by-product **133** was not observed but higher yields of **30** were obtained (*Scheme 96*).



Scheme 96

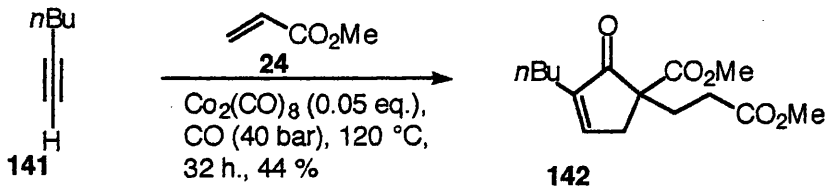
As far as we are aware, there are no other reports of methanol adding across the double bond in a Michael type addition to yield the same product that we isolate in any of the amine *N*-oxide promoted reactions.

The closest impurity isolated was by Buchwald and co-workers when they attempted to convert intermediate **139** into the desired cyclopentanone by an alternative route to cyclopentanones using a titanium based catalyst.[87] After reaction there is an acidic work-up and water added across the double bond in a Michael addition reaction giving a mixture of products (*Scheme 97*).



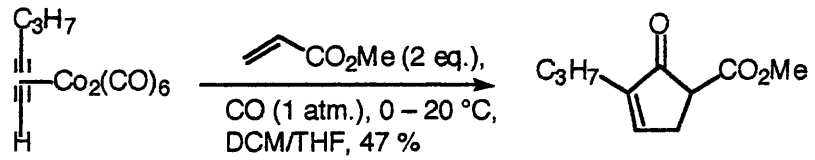
Scheme 97

Whilst Costa and Mor were attempting to induce the normally unreactive electron-deficient alkenes to cyclise, they found that addition of at least two equivalents of alkene **24** to one equivalent of alkyne **141** led to the formation of the unusual cyclopentenone **142** (*Scheme 98*).[92] Product **142** was believed to have formed by Pauson-Khand reaction followed by Michael-type addition of alkene **24** to the initially formed cyclopentenone.



Scheme 98

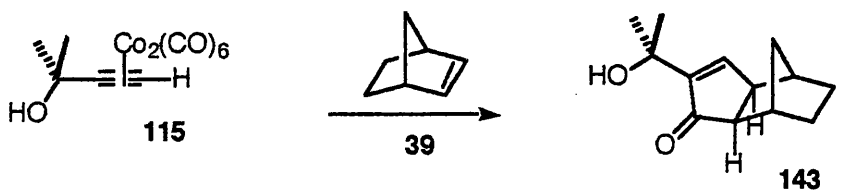
Cazes and co-workers found that the Michael-type addition by-product **142** could be prevented from forming when the reactions were conducted at 0 – 20 °C with 6 equivalents of NMO (*Scheme 99*).[19]



Scheme 99

2.3.3 Promotion of the Pauson-Khand Cyclisations By Chiral Amines

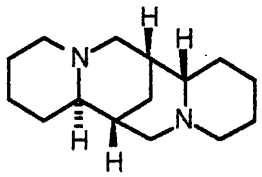
Since its discovery in 1973, there have been many attempts to induce enantioselectivity in the PKR. As previously mentioned, Kerr and co-workers used brucine *N*-oxide (*Figure 9*) as a chiral promoter[54] and found that it induced asymmetry in the reaction (*Scheme 100*).



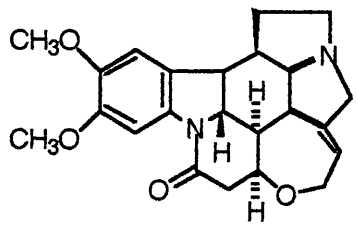
Scheme 100

Kerr and co-workers reacted hexacarbonyl dimethylpropargyl alcohol dicobalt **115** with norbornene **39** in the presence of 6 equivalents of brucine *N*-oxide in THF/CH_2Cl_2 at -20 °C for 48 hours. The desired product **143** was isolated in a yield of 78 % with a diastereomeric ratio of 32 : 68, *exo* : *endo*.

(-)-Sparteine (*Figure 14*) has been widely used to induce stereoselectivity in organic synthesis.[93] There were attempts to induce some stereocontrol in the PKR using (-)-sparteine (*Figure 14*, reaction 1) and brucine (*Figure 15*) both of which are naturally occurring chiral amines.



(-)-Sparteine
Figure 14



Brucine
Figure 15

A series of reactions using (-)-sparteine (*Figure 14*) and brucine (*Figure 15*) as chiral promoters were conducted (table 2).

Table 2

Reaction	Starting Material	Promoter	Solvent	Yield of 30 (%)
1	1.01 g, 1.93 mmol	(–)-Sparteine	toluene	55
2	0.75 g, 1.43 mmol	Brucine	toluene : MeOH 5 : 3	48[a]
3	0.67 g, 1.28 mmol	Brucine	toluene : ^{i}PrOH 5 : 3	34
4[b]	1.21 g, 2.31 mmol	Brucine	toluene : MeOH 5 : 1	3

Unless stated otherwise, 3 equivalents of promoter were added and the reaction mixture was stirred at 20 °C under air for 4 days.

[a]10 % of **133** was isolated. [b]Cooled to -78 °C.

Brucine (*Figure 15*) was added at -78 °C to attempt to induce enantioselectivity (reaction 4) however, with a yield of only 3 % there was not enough product to test.

In order to determine the enantiomeric excess, using the product from the brucine reaction (reaction 3), a chiral shift reagent was employed. (*R*)-(-)-1-(9-Anthryl)-2,2,2-trifluoroethanol was chosen (*Figure 16*). However, when one or more equivalents of the chiral shift reagent were added to compound **30** no splitting of signals was observed in the ^{1}H NMR spectrum. An advantage of the chiral shift

reagent chosen was that it contained fluorine. ^{19}F NMR spectra with one or two equivalents of the chiral shift reagent added to the compound showed no splitting of the signals, implying that this particular shift reagent was not interacting with **30**. Another chiral shift reagent was used, europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate (*Figure 17*). However, this also proved unsuccessful so it had to be assumed that there was no enantioselectivity in these reactions. In a last attempt to determine the enantiomeric excess, the optical rotation of the (-)-sparteine (*Figure 14*) product **30** was measured (reaction 1). Adrio and Carretero have reported that the optical rotation of product **30** is $[\alpha]_D = +88$.[48] Unfortunately, using optical rotation, the enantiomeric excess of product **30** was determined to be zero.

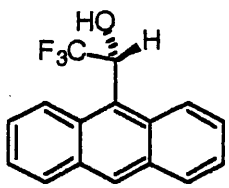


Figure 16

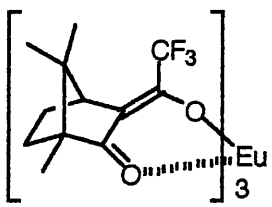


Figure 17

The lack of enantioselectivity could have been due to methanol promoting the reaction in preference to brucine. Brucine is a hindered base and a poor nucleophile which would not be able to displace a carbonyl ligand from the cobalt complex easily.

2.3.4 Effect of Thermal Promotion on The Pauson-Khand Cyclisations

Pauson had already reported that the PKR could be thermally promoted[2,11] and the reactions with *N*-oxides as promoters were also sometimes heated.[20] Hence, the effect of a combination of thermal and amine promotion was studied (*Table 3*).

Table 3

Reaction	Starting Material	Promoter	Solvent	Yield of 30 (%)
1[a]	0.92 g, 1.76 mmol	–	toluene	39
2[a]	0.97 g, 1.85 mmol	–	toluene : ^{i}PrOH 5 : 1	78

3	0.66 g, 1.26 mmol	NMM	toluene	65
4	0.97 g, 1.85 mmol	NMM	toluene : MeOH 5 : 1	61
5	0.97 g, 1.85 mmol	NMM	toluene : ^{i}PrOH 5 : 1	84
6	0.64 g, 1.22 mmol	NMM	DCM	25
7[b]	1.02 g, 1.95 mmol	NMM	DCM : MeOH 5 : 1	65

Unless stated otherwise, 3 equivalents of promoter were added and the reaction mixture was stirred at 50 °C under air for 24 hours.

[a]No promoter was added. [b]Heated at 25 – 30 °C.

As always, a blank experiment was required. Heating the reaction mixture to 50 °C, without any promoter (reaction 1) gave a yield of 39 %, which was a 10 % increase over conducting the reaction at room temperature (*Table 1*, reaction 1). Warming the reactions to 50 °C led to a general increase in yields with a shortened reaction time of less than 24 hours as opposed to 4 days (*Table 1*). When using 3 equivalents of NMM a respectable yield of 65 % was obtained (reaction 3). Again this was approximately 10 % higher than the corresponding reaction at room temperature (*Table 1*, reaction 3).

Pauson and co-workers[17] have already commented that alcohols promote the reaction and we have also demonstrated this (*Table 1*, reaction 13). When methanol was added in conjunction with the amine, the yield was 61 % (reaction 4). This was comparable to the yield obtained with just the amine (reaction 3). However, when isopropanol was added with the amine, the yield increased significantly to 84 % (reaction 5). Unsurprisingly, isopropanol also acted alone as a promoter of the PKR giving a yield of 78 % (reaction 2).

There are many examples of the PKR being conducted in DCM so this solvent was examined.[16,94] When the reaction mixture was heated to reflux, the yield was very poor at 25 % (reaction 6). However, when MeOH was added and the mixture was warmed to 25 – 30 °C, the yield increased to 65 % (reaction 7). The low yield from

reaction 6 may be a result of the complex decomposing too quickly in the presence of heat before it had an opportunity to cyclise. The same yield was obtained from conducting the reaction in toluene at 50 °C with 3 equivalents of promoter (reaction 3) as it was when substrate **29** was warmed in DCM : MeOH (reaction 7). Therefore the yield of **30** was not solvent dependent and both toluene and DCM were used throughout the remainder of these studies.

2.3.5 Increasing Reaction Time

The next set of results show the effect of doubling the duration of the reactions (*Table 4*).

Table 4

Reaction	Starting Material	Promoter	Solvent	Yield of 30 (%)
1	0.96 g, 1.83 mmol	NMM	toluene	41
2	0.93 g, 1.77 mmol	NMM	toluene : MeOH 5 : 1	66
3	0.96 g, 1.83 mmol	NMM	DCM : ^{i}PrOH 5 : 1	57
4[a]	0.96 g, 1.83 mmol	NMM	DCM : MeOH 5 : 1	72[b]

Unless stated otherwise, 3 equivalents of promoter were added and the reaction mixture was stirred at 50 °C under air for 48 hours.

[a]Heated at 25 – 30 °C. [b]12 % of **144** (page 64) was isolated.

Surprisingly, doubling the reaction time from 24 hours to 48 hours, had no effect on the yield, 41 % (reaction 1) compared to 39 % (*Table 3*, reaction 1). Adding methanol (reaction 2) gave a comparable result of 66 %, compared to 61 % (*Table 3*, reaction 4). The only slight increase in yield was observed in reaction 4 (72 %) compared to the corresponding result in reaction 7, *Table 3* (65 %). Even adding isopropanol (reaction 3) only gave a yield of 57 %, as opposed to 78 % (*Table 3*,

reaction 2). Therefore doubling the reaction time does not increase the yield of **30**. The optimum length of time for these PKR was assumed to be less than 24 hours.

2.3.6 Pauson-Khand Reactions Conducted in DCM

Various solvents have been used in the PKR, DCM has been commonly applied[16,94] so it was used in our experiments (*Table 5*) in an attempt to maximise the yield of **30**.

Table 5

Reaction	Starting Material	Promoter	Solvent	Yield of 30 (%)
1	1.10 g, 2.10 mmol	NMM	DCM	54 %
2	0.74 g, 1.41 mmol	NMM	DCM : MeOH 5 : 1	63 %

Unless stated otherwise, 3 equivalents of promoter were added and the reaction mixture was stirred at 20 °C under air for 4 days.

Changing the solvent to DCM and stirring at room temperature for 4 days gave a respectable yield of 54 % (reaction 2) compared to the equivalent reaction in toluene, which gave a yield of 57 % (*Table 1*, reaction 3). The addition of methanol increased the yield to 63 % (reaction 3) compared to the identical reaction in toluene which gave a yield of 49 % (*Table 1*, reaction 12). Although there is very little difference in the yields obtained when using DCM and toluene, toluene became the solvent of choice since it could be heated to higher temperatures.

2.3.7 Pauson-Khand Reactions Under Nitrogen

PKR are generally conducted under an inert atmosphere of nitrogen[14] or argon[16] or under carbon monoxide.[12] The reactions (*Table 6*) were conducted under nitrogen to determine if the yield of **30** increased.

Table 6

Reaction	Starting Material	Promoter	Solvent	Time	Temp. (°C)	Yield of 30 (%)
1	1.20 g, 2.29 mmol	NMM	toluene	4 d	20	41
2[a]	0.27 g, 0.52 mmol	–	toluene	23 h	20 → 130	0
3[b]	0.76 g, 1.45 mmol	NMM (6 eq.)	toluene : MeOH 12 : 2	23 h	–78 → 20	21[c]
4[d]	0.26 g, 0.50 mmol	NMM (9 eq.)	toluene : MeOH 5 : 1	23 h 21 h	20 → 100	30[e]
5	0.42 g, 0.80 mmol	DABCO	toluene : MeOH 5 : 1	24 h 24 h	20 → 100	19[f]

Unless stated otherwise, 3 equivalents of promoter were added and the reaction mixture was stirred under nitrogen.

[a]No promoter was added. [b]6 equivalents of promoter were added. [c]6 % of **144** was isolated. [d]9 equivalents of promoter were added. [e]30 % of **144** was isolated. [f]62 % of **144** was isolated.

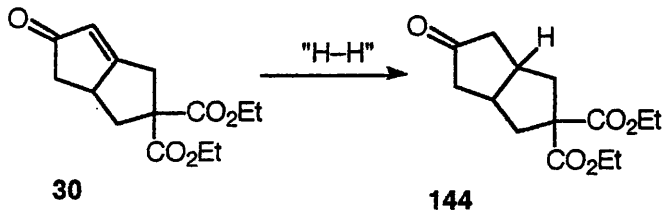
It was commonly believed that the cobalt complex would decompose in air, despite the fact that the cobalt complexes are stable enough to purify using column chromatography on silica gel. PKR are commonly conducted under carbon monoxide.[12,18] From the scheme of the mechanism it can be seen that one molecule of carbon monoxide is required to insert into the cobalt complex to yield the desired cyclopentenone. The groups of Jeong[57] and Sugihara,[66] for example, felt that

conducting the reactions under carbon monoxide would encourage the reaction to go to completion.

Table 6 shows that when the reactions were conducted under nitrogen, instead of increasing the yields, the yields decreased. Stirring the reaction mixture under nitrogen for 4 days at 20 °C gave a yield of 41 % of **30** (reaction 1). The yield is low compared to the identical reaction conducted under air which gave 57 % of **30** (*Table 1*, reaction 3). Although there is no evidence, there is a possibility that oxygen from the atmosphere or moisture could oxidise the amine to the amine *N*-oxide and this could be how the amines promote the PKR.

The groups of Kerr[54] and Laschat[53] often cool the reaction mixture to less than -50 °C to add the amine *N*-oxide and then warm the reaction mixture to room temperature and obtain the desired cyclopentenone products in excellent yield. When using the amine, however, cooling the reaction mixture to -78 °C for 2 hours, followed by warming to 20 °C for 21 hours gave a poor yield of the desired product (21 %, reaction 3). When the reaction mixture was cooled to -78 °C for 2 hours, followed by warming to 20 °C for 21 hours and then heating to 100°C for 21 hours (reaction 4) the yield remained poor (30 %). Refluxing the reaction mixture under nitrogen also gave a surprising result as no product was isolated. This result is unusual since Pauson and co-workers have reported that reactions can be promoted by heat[2] but Livinghouse and co-workers achieved their best results when reactions were conducted between 50 – 60 °C.[63]

When DABCO was used instead of NMM, the yield was very low at 19 % (reaction 5). It has been demonstrated that, when using amines as promoters, the reactions actually give higher yields of **30** when conducted under air instead of under nitrogen. This is another contributing factor that makes our reaction conditions even more favourable. However, throughout these reactions (reactions 3, 4 and 5) a by-product **144** had been isolated. Product **144** had only been observed when the reaction mixture was heated at reflux and when methanol was present in the reaction mixture.

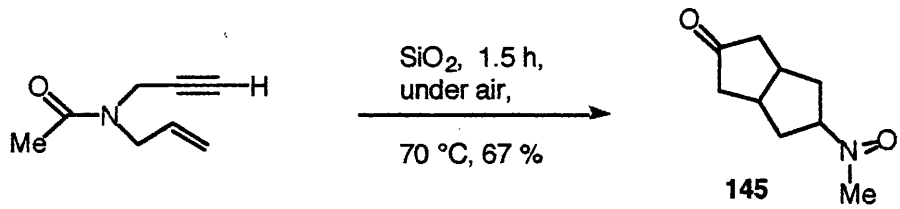


30 144

Scheme 101

The cyclopentenone **30** was believed to form first, followed by reduction to form the cyclopentanone **144** but it is not clear where the hydrogen atoms come from (*Scheme 101*). The cyclisation was attempted using DABCO, a sterically hindered amine,[90] as a promoter (*Table 1*, reaction 8). Since the role of the amine is not clear, DABCO (*Figure 12*) was used to attempt to determine if the amine was acting as a hydrogen atom transporter in cyclopentanone **144** formation. The reaction was repeated using DABCO (3 eq.) in toluene : MeOH, 5 : 1, stirring at room temperature and under nitrogen for 24 hours, the reaction mixture was then heated to 100°C and stirred for a further 24 hours. The desired product **30** was isolated in 19 % yield and the cyclopentanone **144** was isolated in a yield of 62 %. The role of the amine is still unclear. The other possibility was that the hydrogen atom was coming from methanol but no work has been done to determine if this was indeed the case. Other less hindered amines are more likely to give proton transport but no other alcohols were examined with this concept in mind.

Chung's group have mentioned the formation of by-product **144** but not in very high yields and their by-product formed whilst oxygen was being bubbled through the reaction mixture.[18] Brown and Pauson have isolated the product **145** as the sole product in one of their reactions (*Scheme 102*).[23]



145

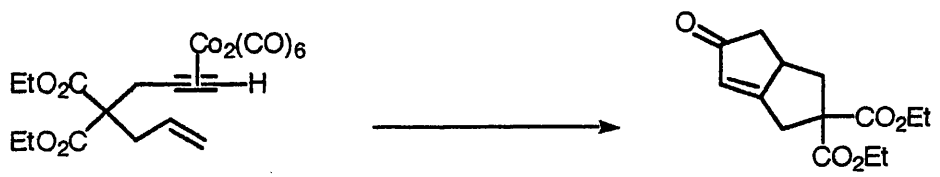
Scheme 102

They repeated the reaction with a deuterium atom as the terminal group on the acetylene but the results were inconclusive. They noted that the reduction depends on a number

of factors: the free acetylenic hydrogen; the reaction conditions; and the presence of the *N*-acyl group. They are not entirely sure where the hydrogen comes from. It was proposed that it may be from the solvent but the by-product formed even in the presence of benzene. Benzene is an unlikely hydrogen source and it was therefore suggested that the hydroxy groups on silica or alumina appear to be the only likely source for reduction, presumably at the expense of cobalt (0).

2.3.8 Use of Optimum Conditions on Other Substrates

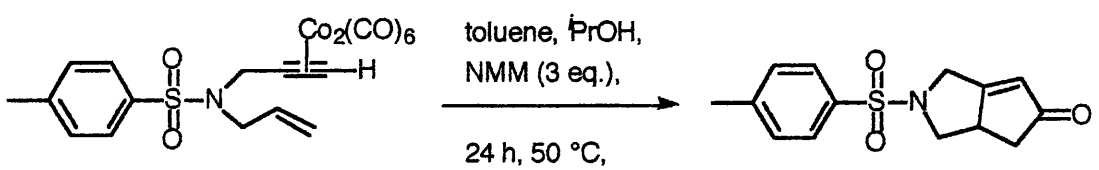
A set of optimised conditions for the PKR has been developed. It was found that heating cobalt complex **29** to 50 °C in 5:1 toluene / isopropanol with 3 equivalents of NMM for 24 hours under air gave the highest yields of **30**. When these conditions were applied to the test compound, hexacarbonyl allylprop-2-ynylmalonic acid diethyl ester dicobalt **29**, a yield of 84 % of **30** was obtained (*Scheme 14*).



29 **30**

Scheme 14

However, only using one substrate does not make the procedure general. Hexacarbonyl 4-methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide dicobalt **146** was synthesised in good yield and subjected to the optimised conditions (*Scheme 103*).

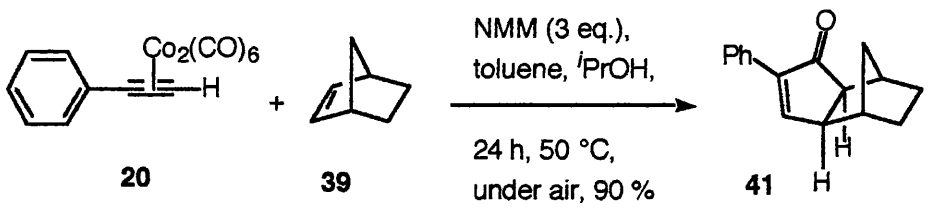


146 **122**

Scheme 103

2-(Toluene-4-sulfonyl)-2,3,4a,4-tetrahydro-1H-cyclopenta[c]pyrrol-5-one **122** was isolated in good yield (62 %). Another common set of reagents for testing the

intermolecular PKR is hexacarbonyl phenylacetylene dicobalt **20** with norbornene **39** (*Scheme 104*).



20 **39** **41**

Scheme 104

Under the optimised conditions, 2-phenyl-3a,4,5,6,7,7a-hexahydro-4,7-methano-inden-1-one **41** was obtained in 90% yield as solely the *exo*-isomer.

2.4 Conclusions

1. Sugihara's group found that only primary amines promoted the reaction.[24] However, we found that primary, tertiary amines and pyridine all promoted the reaction to some extent. This has cost benefits as amines are more readily available than their corresponding *N*-oxides.

2. The Michael-type addition product **133** was identified and a plausible route to its formation was proposed.

3. The cyclopentanone **144** was isolated. However the source of this reduction product remains the subject of considerable speculation.

4. There were several attempts to induce enantioselectivity in the PKR. However these proved unsuccessful.

5. A set of optimum conditions for the use of the amine promoter was developed. This meant that the PKR could be easily conducted in air, making the reaction easier to perform and therefore more accessible.

6. The optimum conditions were found to be applicable and effective in both inter- and intra-molecular PKR.

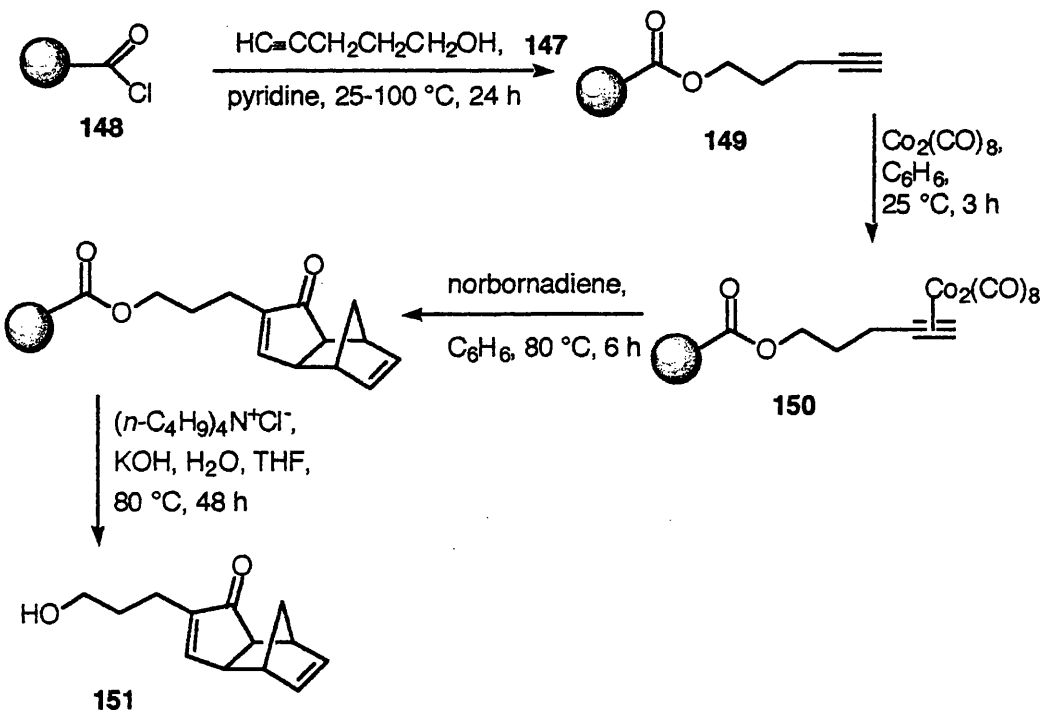
Chapter 3

Solid Phase Pauson-Khand Reactions

3.1 Introduction

There have been many advancements in the Pauson-Khand reaction; for instance, the use of promoters,[16] enantioselectivity[31] and catalysis.[57]

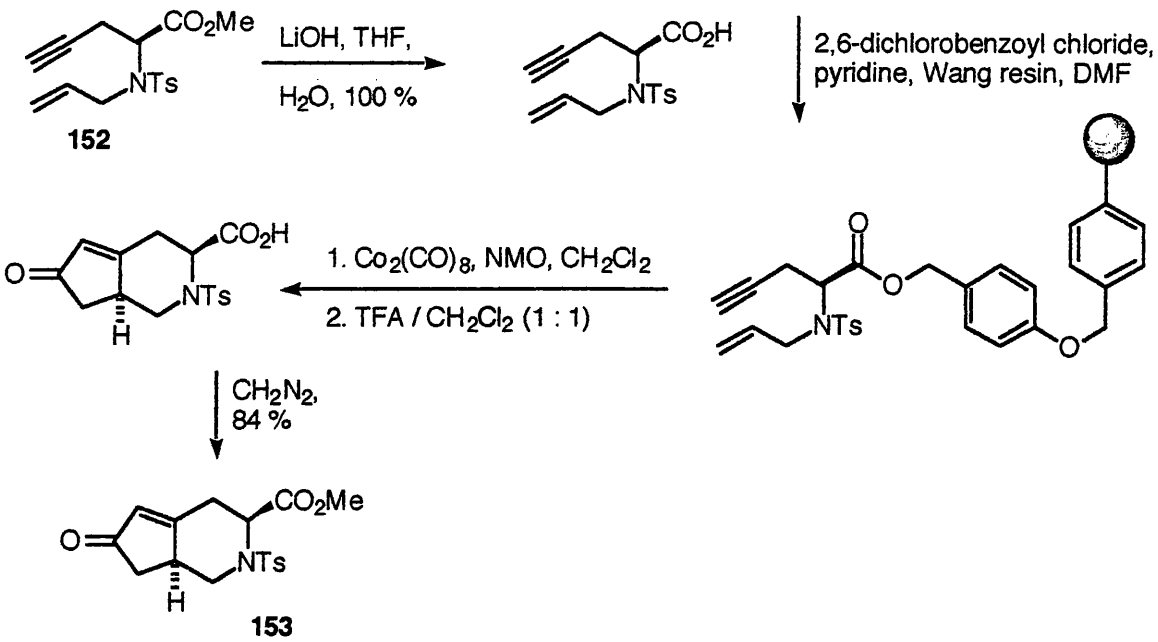
However, one of the most interesting advances is the use of solid phase synthesis in the PKR.[4] Schore originally attached ω-alkynol **147** to a 2%-cross-linked Merrifield polymer that had been modified by conversion into the aroyl chloride **148**.[97] Ester formation with 4-pentyn-1-ol **147** gave the necessary polymer-linked substrate **149** (*Scheme 105*).



Scheme 105

Reaction of **149** with $Co_2(CO)_8$ gave the desired cobalt complex **150**, which underwent the PKR with norbornadiene **21** in benzene at 80 °C. Product **151** was obtained in 69 % yield after cleavage of the ester linkage. The corresponding yield obtained from the solution phase reaction was less than 10 % of **151**.

Bolton has reported a highly efficient synthesis of 1H-[2]-pyrindinone ring systems using the PKR conducted on solid support (*Scheme 106*).[96,98]

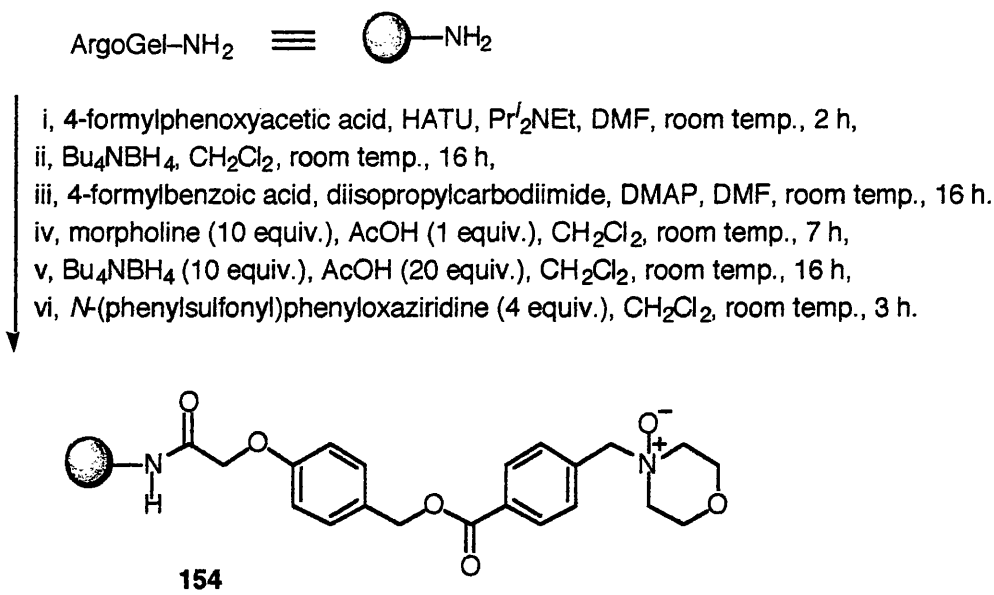


Scheme 106

Bolton attached the alkyne and alkene component **152** to Wang resin and conducted the intramolecular PKR in nearly quantitative yield, before forming ester **153** in 84 % yield as a single diastereoisomer.[96]

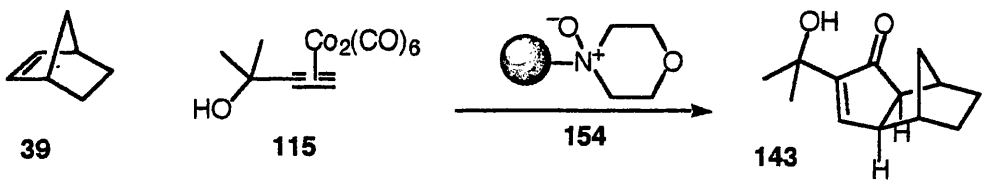
More recently, Kerr and co-workers reported that an amine *N*-oxide bound to a solid support could promote PKR in excellent yield with major advantages over solution phase cyclisations.[99] Since amine *N*-oxides are expensive, recycling the resin can reduce the cost of the reaction. Purification of the product is also simplified as, after filtration, essentially pure product is isolated. However, the major advantage is that the oxidised cobalt residues stick to the solid phase resin and can be washed off later, making the route attractive to industry.

Kerr and co-workers originally used a six step synthesis to build his amine *N*-oxide **154** onto the solid support (*Scheme 107*).



Scheme 107

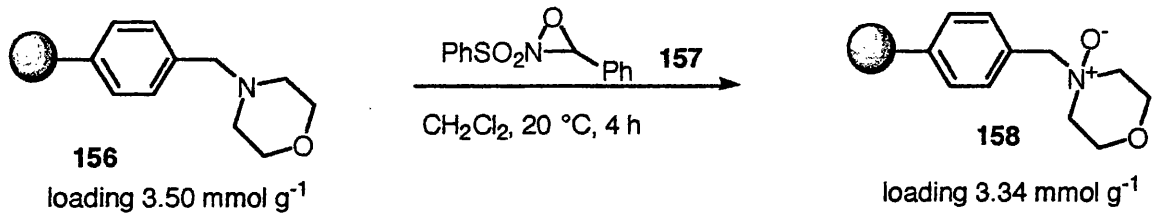
Hexacarbonyl(2-methylbut-3-yn-2-ol)dicobalt **115** was reacted with norbornene **39** and 6.7 equivalents of amine *N*-oxide resin **154** at room temperature for 30 minutes in THF. The desired product **143** was obtained in a yield of 91 % (*Scheme 108*).



Scheme 108

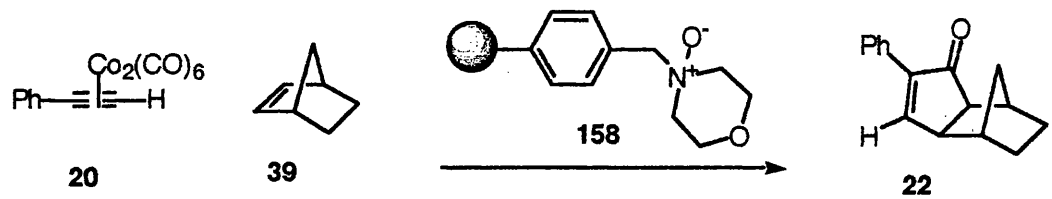
The PK products were obtained in good yields and the resin could be recycled up to five times with no loss in yield of **143**.

The main problem with the initial polymeric support of the Kerr group was that it had a very low loading of only 0.4 mmol g^{-1} ; therefore a large quantity of resin needed to be used in each reaction. They proceeded to use the readily available 2 % divinylbenzene (DVB) cross linked morpholinomethyl polystyrene resin **156** with a high loading of 3.5 mmol g^{-1}.[100] Four equivalents of Davis' reagent (*N*-phenyl-sulfonyl oxaziridine) **157** were used to oxidise the morpholinomethyl resin **156** to the amine *N*-oxide **158** (*Scheme 109*).



Scheme 109

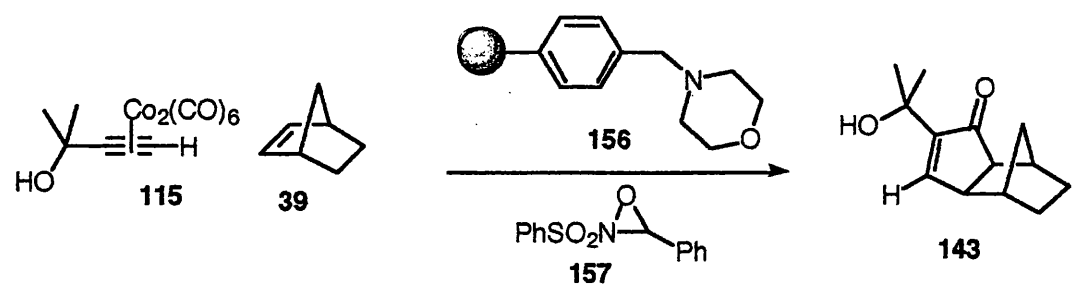
Kerr and co-workers then used his polymer supported *N*-oxide **158** as a promoter in the Pauson-Khand reaction (*Scheme 110*).



Scheme 110

Reacting hexacarbonyl phenylacetylene dicobalt **20** with norbornene **39** in the presence of 10 equivalents of the polymer supported *N*-oxide **158**, in DCM at room temperature for 24 hours afforded the desired product **22** in 97 % yield.

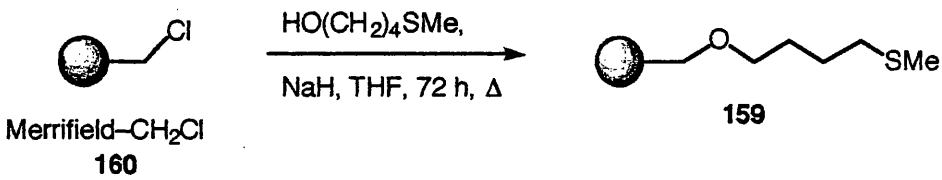
Kerr and co-workers also demonstrated that the *N*-oxide **158** does not have to be preformed.[100] The solid supported amine **156** can be oxidised *in situ* and then the PKR proceeds smoothly (*Scheme 111*).



Scheme 111

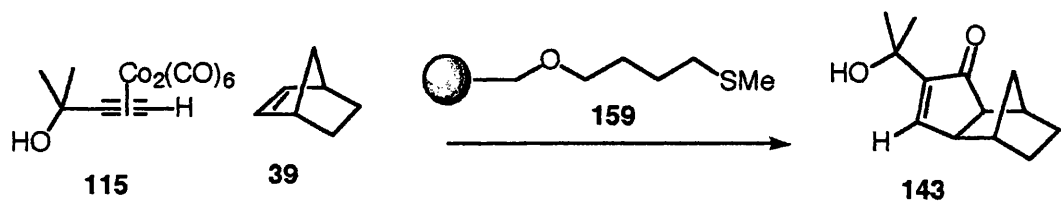
Reaction of hexacarbonyl dimethylpropargyl alcohol dicobalt **115** with norbornene **39** in the presence of 7 equivalents of polymer supported amine **156**, 10 equivalents of Davis' reagent **157** at room temperature in DCM for 45 minutes gave the desired product **143** in 95 % yield. Again, the resin **156** can be recycled up to five times with no major loss in yield. Kerr and co-workers also state that in the presence of either the polymer supported amine or Davis' reagent alone, no reaction occurs.

Sulfides have been commonly used as promoters of the PKR.[27] Pauson and co-workers originally used DMSO and found this to be efficient.[17] More recently Sugihara and co-workers showed that *n*-butyl methyl sulfide was an excellent promoter of both the inter- and intra-molecular PKR.[27] Kerr and co-workers have gone on to demonstrate that polymer supported alkyl methyl sulfides are also efficient promoters of the PKR.[101] The supported sulfide **159** was synthesised in a single step from Merrifield type resin **160** and 4-(methylthio)butan-1-ol *via* a chemically robust ether link (*Scheme 112*).



Scheme 112

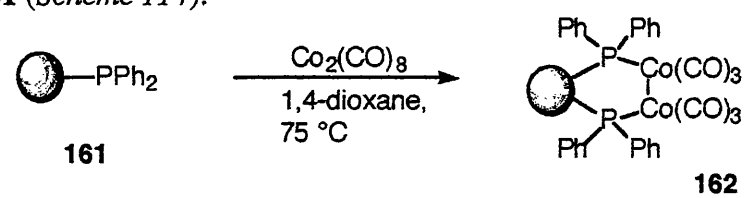
The odour-free solid supported sulfide **159** was found to be an excellent recyclable promoter of the PKR (*Scheme 113*).



Scheme 113

Reaction of hexacarbonyl dimethylpropargyl alcohol dicobalt **115** with norbornene **39** in the presence of 3.5 equivalents of polymer supported sulfide **159** at 83 °C for 30 minutes in DCE gave the desired product **143** in 92 % yield, (*Scheme 113*). Again, the resin can be recycled up to five times with no major loss in yield.

Gibson and her group built the cobalt complex onto a solid supported phosphine **161** (*Scheme 114*).[102]



Scheme 114

The advantage was, that by attaching the cobalt complex to the solid phase resin, the cobalt complex **162** became more air stable and less toxic than the corresponding solution phase cobalt complex. Another major advantage was that the cobalt complexed solid phase resin **162** could be used in catalytic amounts (*Scheme 55*).

30

Scheme 55

A maximum yield of 49 % of **30** was obtained when using 5 mol % of the cobalt complexed solid phase resin **162** at 70 °C for 24 hours in THF under 50 mbar of carbon monoxide.

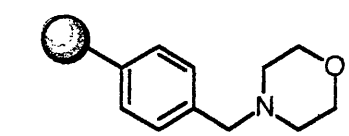
Kerr used a solid phase resin with an amine **156** and oxidised it to the amine *N*-oxide **158** using Davis' reagent **157**.[100] Based on our work using amines as promoters of the Pauson-Khand cyclisation, as demonstrated in Chapter 2, we decided to use a simple amine based solid phase resin to promote the reactions.

3.2 Results and Discussion

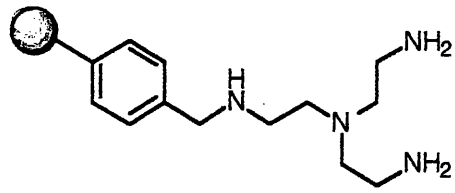
Three different resins were used to promote the Pauson-Khand reaction. *N*-Methylmorpholine was found to be a good promoter for the solution phase PKR. Therefore morpholinomethyl resin **156** was used because it was the solid supported equivalent of NMM. (Whilst our work was ongoing, Kerr and co-workers also used resin **156** in their more recent publication.[100])

Polyamine resin **163** [tris-(2-aminoethyl)-amine polystyrene high loading (HL)] was used since it had four nitrogens attached; two primary, one secondary and one tertiary. Three equivalents of resin were initially used. The results from Chapter 2 previously demonstrated that primary, secondary and tertiary amines all promoted the solution phase PKR. Since there were four nitrogens attached to the resin we were able to reduce the number of equivalents of resin used, thus making the reaction even more favourable. Wang resin **164** (*p*-benzyloxybenzyl alcohol resin) was used to test the promoting ability of a solid supported alcohol. Pauson and co-workers initially

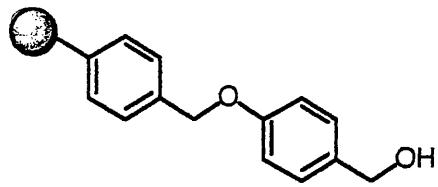
demonstrated that alcohols can promote the reactions[17] and we also supported this finding in Chapter 2.



Morpholinomethyl Resin **156**

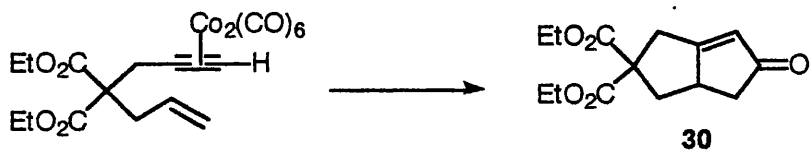


Polyamine Resin **163**



Wang Resin **164**

In an attempt to find the optimum reaction conditions for the solid phase chemistry, different solvents, temperatures and co-solvents were used. The standard Pauson-Khand substrate **29** was used to measure the efficiency of our reactions (*Scheme 14, Table 7*).



29 **30**

Scheme 14

3.2.1 Effect of Time on the Pauson-Khand Reaction

Table 7

Reaction	Starting Material	Resin 156	Yield of 30 (%)
1[a]	207 mg, 0.40 mmol	–	50
2	195 mg, 0.37 mmol	3 eq.	60
3	200 mg, 0.38 mmol	6 eq.	56

Unless stated otherwise, the promoter was morpholinomethyl resin **156**, the solvent was THF and the reaction mixture was heated at 40 °C for 6 hours.

[a]No promoter was added.

In order to find the optimum number of equivalents of solid supported amine required for the reaction, several studies were conducted.

After 6 hours shaking there was very little difference between using 3 and 6 equivalents, with yields of 60 % (reaction 2) and 56 % (reaction 3) obtained. The yields were still very low after only six hours hence a longer reaction time was necessary. One of the major advantages that Kerr and co-workers found with solid phase synthesis was that, after filtration, the products were almost pure.[100] Unfortunately, we still had to purify the products using column chromatography on silica gel. Kerr and co-workers state that the oxidised cobalt residues stick to the solid phase resin.[100] However, under our reaction conditions no oxidising agent is used, therefore only a small percentage of the cobalt residues stick to the resin.

The reaction time was increased to 18 hours and the number of equivalents of resin **155** used was varied (*Table 8*). The substrates from *Scheme 14* were used.

Table 8

Reaction	Starting Material	Resin 156	Yield of 30 (%)
1[a]	199 mg, 0.38 mmol	–	51
2	199 mg, 0.39 mmol	3 eq.	76
3	195 mg, 0.37 mmol	6 eq.	69
4	205 mg, 0.39 mmol	10 eq.	60

Unless stated otherwise, the promoter was morpholinomethyl resin **156**, the solvent was THF and the reaction mixture was heated at 40 °C for 18 hours.

[a]No promoter was added.

Krafft and Bonaga found that a large excess of cyclohexylamine was detrimental to the efficiency of their amine-promoted catalytic PKR but did not suggest a reason for this observation.[88] It has been shown in Chapter 2 that when the number of equivalents of NMM was increased from 3 to 7.5, the yield dropped from 57 %

(*Table 1*, reaction 3) to 38 % (*Table 1*, reaction 4). Table 8 demonstrates that the same phenomenon happens with solid supported amines. When the number of equivalents of resin was increased, there was a decrease in yield. Reaction 2 gave a yield of 76 % when 3 equivalents were used, reaction 3 gave a yield of 69 % with 6 equivalents and reaction 4 shows that a yield of 60 % was obtained when 10 equivalents of resin were used. As previously mentioned in Chapter 2, there was a possibility that the complex could have been reacting too quickly with too many equivalents of amine present. The complex could be decomposing as opposed to cyclising in the presence of the solid phase amines.

The reaction time was increased to 24 hours and the number of equivalents of resin **156** used was varied (*Table 9*). The substrates from *Scheme 14* were used.

Table 9

Reaction	Starting Material	Resin 156	Yield of 30 (%)
1[a]	214 mg, 0.41 mmol	–	66
2	200 mg, 0.38 mmol	3 eq.	81
3	105 mg, 0.20 mmol	6 eq.	84
4[b]	205 mg, 0.39 mmol	3 eq.	72

Unless stated otherwise, the promoter was morpholinomethyl resin **156**, the solvent was THF and the reaction mixture was heated at 40 °C for 24 hours.

[a]No promoter was added. [b]5 ml (159 mol. equiv.) of isopropanol were added.

Allowing the reaction to run for 24 hours resulted in a small increase in the yield of **30**. Yields of 81 % (reaction 2) and 84 % (reaction 3) were isolated, compared to yields of 76 % (*Table 8*, reaction 2) and 69 % (*Table 8*, reaction 3) when the reaction was run for 18 hours. Contrary to the solution phase reactions, adding isopropanol as a co-solvent did not increase the yields (reaction 4) with a yield of 72 % obtained compared to 81 %, under identical conditions without the alcohol (reaction 2).

Unsurprisingly, and in common with the solution phase reactions, solid phase reactions run at room temperature gave lower yields than those that were heated. When the reaction was conducted at 20 °C for 4 days with 3 equivalents of promoter, a poor yield of only 50 % of **30** was isolated.

The PKR can be thermally promoted without the presence of any additive[2] and this was again demonstrated in reactions 1 in Tables 7 – 9. Yields of 50, 51 and 66 % were obtained after 6, 18 and 24 hours shaking at 40 °C.

From the results in Tables 7, 8 and 9, it was decided that 3 equivalents of resin **156**, 40 °C and 18 hours were the desired combination for optimum results.

3.2.2 Effect of Solvent on the Pauson-Khand Reaction

The effect of solvent in the solid phase PKR was examined (*Table 10*). Again, the substrates from *Scheme 14* were used.

Table 10

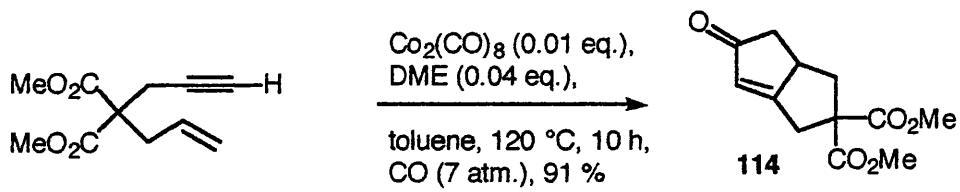
Reaction	Starting Material	Resin 156	Solvent	Yield of 30 (%)
1[a]	217 mg, 0.41 mmol	–	DCE	58
2	198 mg, 0.38 mmol	3 eq.	DCE	75
3[a]	223 mg, 0.43 mmol	–	DME	82
4	200 mg, 0.38 mmol	3 eq.	DME	82

Unless stated otherwise, the promoter was morpholinomethyl resin **156** and the reaction mixture was heated at 40 °C for 18 hours.

[a]No promoter was added.

There are many examples where DCM is used as the solvent in PKR.[18] In our solution phase experiments, it was found to be efficient. However, this solvent could not be heated to 40 °C therefore DCE was used instead. When no promoter was added the yield was 58 % (reaction 1). However, when 3 equivalents of resin **156** were added, the yield increased significantly (75 %, reaction 2).

Adding a promoter to a reaction conducted in DME was shown to have no additional effect (reactions 3 and 4). This is not really surprising given that DME has been shown to be an effective promoter of the PKR in its own right.[66] Sugihara and Yamaguchi demonstrated that substoichiometric quantities of $Co_2(CO)_8$ could be used with small amounts of DME in toluene as an additive to effect the cyclisations (*Scheme 88*).[66]



Scheme 88

However, when they conducted their substoichiometric reactions in DME, a yield of only 9 % of the desired product **114** was obtained.

The yields of **30** obtained from using either THF (*Table 7*, reaction 2) or DCE (*Table 9*, reaction 2) were nearly identical at 76 and 75 % but THF was used as the preferred solvent.

3.2.3 Effect of Temperature

Table 11 shows the effect of increasing the temperature from 40 °C to 50 °C.

Table 11

Reaction	Starting Material	Resin 156	Solvent	Yield of 30 (%)
1[a]	196 mg, 0.37 mmol	–	THF	60
2	215 mg, 0.41 mmol	3 eq.	THF	65
3	204 mg, 0.39 mmol	10 eq.	THF	78
4[a]	235 mg, 0.45 mmol	–	DME	84
5	214 mg, 0.41 mmol	3 eq.	DME	84
6	208 mg, 0.40 mmol	10 eq.	DME	82

Unless stated otherwise, the promoter was morpholinomethyl resin **156** and the reaction mixture was heated at 50 °C for 18 hours.

[a]No promoter was added.

The optimum temperature for the solution phase PKR was found to be 50 °C. Until now, the solid phase reactions had been conducted at 40 °C for fear of destroying the resin at higher temperatures. Table 11 shows the effect of heating the resin to 50 °C for 18 hours in THF. Increasing the temperature from 40 °C to 50 °C had no significant effect on the yields (*Table 9*, reactions 1, 2 and 3 compared to *Table 11*, reactions 1, 2 and 3) except when 10 equivalents of resin were used. The yield of **30** increased from 51 % to 60 % when no promoter was present (*Table 11*, reaction 1 and *Table 8*, reaction 1). The yield of **30** decreased from 76 to 65 % (*Table 11*, reaction 2 and *Table 8*, reaction 3) when 3 equivalents of resin **156** were used. The yield increased by 18 % when 10 equivalents of **156** were used (*Table 11*, reaction 3 and *Table 8*, reaction 5). The resin **156** may be destroyed at the higher temperature of 50 °C so when 10 equivalents of **156** were added, there was more chance for some of the resin to survive the harsh reaction conditions and thus a higher yield of **30** was obtained. Although the yield of 78 % was obtained using 10 equivalents of resin **156** (*Table 11*, reaction 3) this was comparable to the yield of 76 % obtained when 3 equivalents of resin **156** were used at 40 °C. Therefore there was no advantage to be gained in increasing the temperature by 10 °C.

3.2.4 Effect of Other Solid Phase Promoters

The other solid phase promoters were then examined (*Table 12*). The substrates from *Scheme 14* were used.

Table 12

Reaction	Starting Material	Resin 163	Time	Yield of 30 (%)
1	201 mg, 0.38 mmol	1 eq.	18 h	76

2	204 mg, 0.39 mmol	3 eq.	18 h	73
3	204 mg, 0.39 mmol	3 eq.	24 h	69
4[a]	208 mg, 0.40 mmol	3 eq.	24 h	45

Unless stated otherwise, the promoter was polyamine resin **163**, the solvent was THF and the reaction mixture was heated at 40 °C.

[a]5 ml (159 mol. equiv.) of isopropanol were added.

In chapter 2, it was shown that primary, tertiary and aromatic amines all promoted the solution phase PKR. Use of polyamine resin **163** proved successful and when only one equivalent of **163** was added the yield of **30** was 76 % (reaction 1). Adding isopropanol as a co-solvent had no effect on increasing the yields and in one particular case lowered it (entry 3 vs. entry 4). The optimum conditions for this resin **163** have been found to be 1 equivalent of resin **163** at 40 °C in THF for 18 hours giving a yield of 76 % (reaction 1) which is comparable to using 3 equivalents of resin **156** under the same conditions, 76 % (*Table 8*, reaction 3).

Although excellent results had been achieved when resin **163** was heated to 40 °C (*Table 12*), it was decided to see if the reaction could be conducted at lower temperatures, thus making the reaction conditions even milder (*Table 13*).

Table 13

Reaction	**Starting Material**	**Resin 163**	**Time**	**Yield of 30 (%)**
1	210 mg, 0.40 mmol	3 eq.	24 h	21
2[a]	207 mg, 0.40 mmol	3 eq.	24 h	19
3	209 mg, 0.40 mmol	3 eq.	2 days	38
4[a]	200 mg, 0.38 mmol	3 eq.	2 days	33
5	195 mg, 0.37 mmol	3 eq.	4 days	47
6[a]	199 mg, 0.38 mmol	3 eq.	4 days	45

Unless stated otherwise, the promoter was polyamine resin **163**, the solvent was DCM and the reaction mixture was shaken at 20 °C.

[a]5 ml (159 mol. equiv.) of isopropanol were added.

Table 13 demonstrated that when the reactions were conducted at 20 °C in DCM, the yields of **30** were very low. Isopropanol addition had little effect (entry 2 vs. entry 1). This effect has been observed previously when morpholinomethyl resin was used (*Table 9*, reactions 2 and 4) and seems unusual since in the solution phase reactions the isopropanol had a significant enhancing effect. Increasing the reaction time from 2 days to 4 days increased the yield from 38 % (reaction 3) to 47 % (reaction 5) and increasing the temperature from 20 °C to 40 °C significantly increased the yield from 21 % (reaction 1) to 69 % (*Table 12*, reaction 3).

The last solid phase resin to be investigated was Wang resin **164**, the only resin used that had a terminal hydroxyl group instead of an amine (*Table 14*). The substrates from *Scheme 14* were used.

Table 14

Reaction	Starting Material	Resin 164	Time	Yield of 30 (%)
1	200 mg, 0.38 mmol	3 eq.	24 h	15
2	200 mg, 0.38 mmol	3 eq.	2 days	26
3	200 mg, 0.38 mmol	3 eq.	4 days	30

Unless stated otherwise, the promoter was Wang resin **164**, the solvent was DCM and the reaction mixture was shaken at 20 °C.

Table 14 demonstrated that when the reactions were run at 20 °C for varying lengths of time, the yields were very much lower than the corresponding yields from the polyamine resin **163** under the same conditions. When run for 24 hours, Wang resin **164** gave a yield of 15 % (reaction 1) compared to a yield of 21 % (*Table 13*,

reaction 1) when the polyamine resin **163** was the promoter. All the yields are higher with the polyamine resin **163** than with the Wang resin **164** at 20 °C. The yields obtained from the Wang resin **164** could be lower since there is only one functional group that can react but in the polyamine resin **163** there are four functional groups that are available to promote the reaction.

However, all three resins were comparable when the reaction mixture was heated to 40 °C for 18 hours in THF giving yields of 76 % when Wang resin **164** was used, 77 % (*Table 8*, reaction 2) when morpholinomethyl resin **115** was used and 73 % (*Table 12*, reaction 2) when polyamine resin **163** was used.

3.3 Conclusions

1. These results are the first examples of solid supported amines and alcohols being used as promoters in the Pauson-Khand cyclisation. This opens up the possibility of recycling the resin and developing simpler purification techniques, thus making the reaction simple and cost effective.

2. Many different reaction conditions, including solvents, temperatures and duration, were examined.

3. Optimum conditions were found to be 3 equivalents of resins **156** and **164**, and 1 equivalent of resin **163** shaking at 40 °C for 18 hours in THF, yielding **30** in high yields.

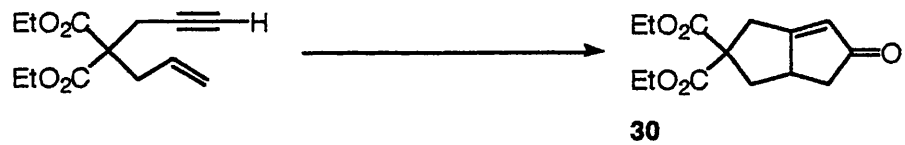
Chapter 4

Substoichiometric Pauson–Khand Reactions

4.1 Introduction

Classic Pauson–Khand reactions require a stoichiometric amount of dicobalt octacarbonyl which is both expensive and highly toxic.[5] PKRs utilising a substoichiometric amount of dicobalt octacarbonyl are highly favourable. Successful use of substoichiometric quantities of dicobalt octacarbonyl in conjunction with either $P(OPh)_3$,[57] ultraviolet light[59] or high pressures of carbon monoxide[56] have been reported.

Livinghouse and co–workers have reported that very high purity $Co_2(CO)_8$ was used in substoichiometric amounts (5 mol %).[63] The reaction was conducted at 60 – 70 °C in DME for 12 hours under one atmosphere of carbon monoxide. This was one of the mildest substoichiometric versions of the PKR reported giving a yield of 83 % of **30** (*Scheme 55*).



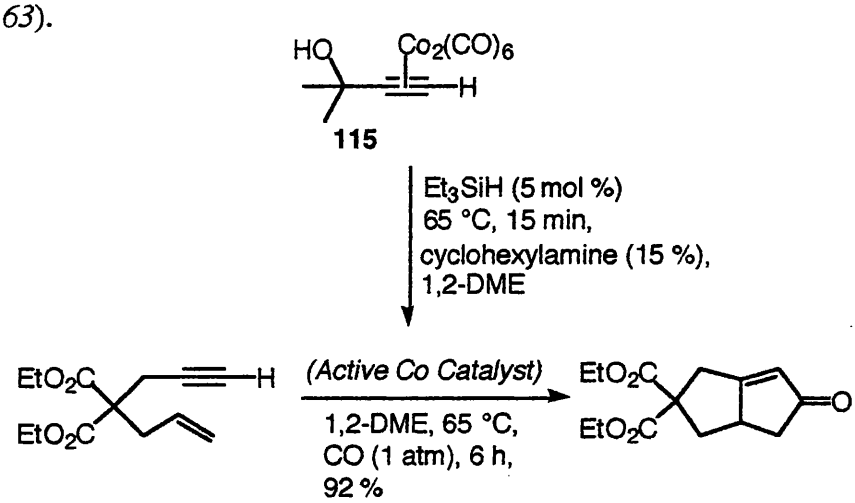
30

Scheme 55

Another advantage to this method was that the need to pre-form and isolate the cobalt complex had been eliminated, since the cobalt complex formed *in situ*. Therefore the PKR sequence was only one step, instead of the traditional two.

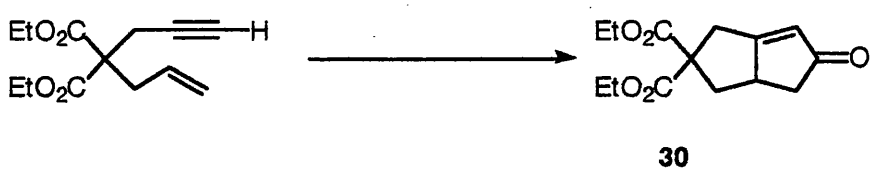
Livinghouse and co-workers argued that the need for $Co_2(CO)_8$, which is labile to both heat and oxygen, in a very high state of purity, constitutes an experimental disadvantage to this procedure.[64] The identification of chemically robust dinuclear complexes would greatly enhance the practical attractiveness of the catalysed PKR. Selected shelf stable, $Co_2(CO)_6$–alkyne complexes were found to serve as sources of active catalysts for carbonylative enyne cyclisations (*Scheme 63*). Previously, Hosokawa and Isobe noted that Et_3SiH was a useful reagent for the conversion of $Co_2(CO)_6$–alkyne complexes into vinylsilanes *via* reductive decomplexation.[65] Livinghouse's group used Isobe's chemistry in the hope that the (carbonyl)cobalt by-

product generated in those reactions would exhibit catalytic activity.[64] A series of $Co_2(CO)_6$–alkyne complexes in combination with Et_3SiH were tested as $Co_2(CO)_8$ surrogates in the catalytic PKR. The example below shows the most effective $Co_2(CO)_8$ surrogate when 5 mol % of the alkyne-cobalt complex **115** was used (*Scheme 63*).



Scheme 63

Based on Livinghouse's work, Krafft and co-workers have demonstrated that carefully base-washed glassware eliminated the need for high purity dicobalt octacarbonyl.[72] The reaction was carried out using a substrate concentration of 0.2 M in DME with 5 mol % $Co_2(CO)_8$ and 10 mol % cyclohexylamine under one atmosphere of carbon monoxide at 70 °C for 2.5 hours and a yield of 94 % of **30** was obtained (*Scheme 55*).



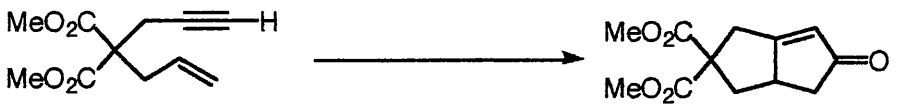
30

Scheme 55

However when no amine was added and the amount of $Co_2(CO)_8$ was doubled to 10 mol %, the yield actually decreased by 14 % to give 80 % of **30**.

Sugihara and Yamaguchi showed that substoichiometric quantities of $Co_2(CO)_8$ could be used with small amounts of DME or water as additives to effect the cyclisations.[66] The reaction was carried out using a cobalt complex concentration of 0.4 M in toluene with 0.01 molar equivalents of $Co_2(CO)_8$ and 0.04 molar equivalents

of DME at 120 °C for 10 hours under 7 atmospheres of carbon monoxide and a yield of 91 % of **114** was obtained (*Scheme 65*).



114

Scheme 65

The only disadvantage was that the reactions have to be performed under 7 atmospheres of carbon monoxide.

Sugihara and co-workers found that cyclohexylamine was the amine of choice in the stoichiometric reactions[24] but was one of the worst additives in the substoichiometric reactions.[66] Krafft and Bonaga have found that an additive, such as cyclohexylamine, increases the yields of the PKR.[88]

Krafft and Bonaga have recently described the use of substoichiometric amounts of $Co_2(CO)_8$ in conjunction with an amine promoter.[88] An example is shown in *Scheme 55*.

30

Scheme 55

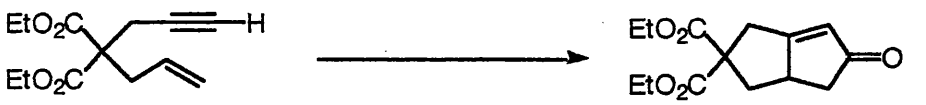
The reaction was carried out using a catalyst concentration of 0.02 M in DME with 35 mol % $Co_2(CO)_8$ and 105 mol % cyclohexylamine under a nitrogen atmosphere at 60 °C and a yield of 80 % of **30** was obtained. This is only the second example of a substoichiometric reaction being performed under nitrogen[103] instead of under carbon monoxide.[56] In the majority of cases, the catalytic reactions are conducted under an atmosphere of carbon monoxide in the belief that the carbon monoxide regenerates the active cobalt precursor.[104]

Krafft and Bonaga found that the addition of cyclohexylamine increased the yields in most cases.[88] However, there was no way to determine in advance whether the addition of cyclohexylamine would result in enhancement of the yields, although in

most cases it did. They speculated that the amine may be a catalyst carrier which has the effect of increasing the longevity of the intermediate complexes. Although the mechanism of the amine-promoted PKR has not been determined, it is thought that the amine displaces a CO ligand, thus forming a stable complex until the alkene inserts and displaces either another CO ligand or the amine. This is different to amine *N*-oxide promotion in that the oxygen reacts with the carbon monoxide ligand to form carbon dioxide which then leaves, thus creating a vacant site around the cobalt atom, which the alkene proceeds to occupy (refer to mechanism (*Scheme 5*), page 3).[1]

4.2 Results and Discussion

Combining the work by Krafft and Bonaga[88] and the solid phase work by the group of Kerr,[100] we also attempted to develop a substoichiometric version of the PKR. Using a solid phase amine that could be recycled would make the reaction more efficient and using less dicobalt octacarbonyl would make the reaction more cost effective. The number of equivalents of both the polymer supported amine and the dicobalt octacarbonyl were varied. Different solvents were examined and a variety of other substrates were tested. Based on the results from Chapter 3, the reactions were conducted under air at 40 °C for 18 hours using morpholinomethyl resin **156** (*Scheme 55*, *Table 15*).



107 **30**

Scheme 55

4.2.1 Effect of Varying the Molar Equivalents of Promoter and Dicobalt Octacarbonyl on the Catalytic Pauson-Khand Reaction

Table 15

Reaction	Starting Material	Resin 156	$Co_2(CO)_8$	Solvent	Yield of 30 (%)
1	250 mg, 1.05 mmol	105 mol %	70 mol %	THF	68

2	250 mg, 1.05 mmol	105 mol %	35 mol %	THF	67
3	101 mg, 0.42 mmol	105 mol %	10 mol %	THF	8
4[a]	130 mg, 0.55 mmol	105 mol %	–	THF	0
5	101 mg, 0.42 mmol	50 mol %	35 mol %	THF	75
6[b]	130 mg, 0.50 mmol	–	36 mol %	THF	36
7	102 mg, 0.43 mmol	105 mol %	35 mol %	DME	61
8	101 mg, 0.42 mmol	50 mol %	35 mol %	DME	84
9	104 mg, 0.44 mmol	50 mol %	20 mol %	DME	27
10[b]	103 mg, 0.43 mmol	–	35 mol %	DME	85

Unless stated otherwise, the promoter was morpholinomethyl resin **156**, the dicobalt octacarbonyl was freshly sublimed and the reaction mixture was heated at 40 °C for 18 hours.

[a]No dicobalt octacarbonyl was added. [b]No promoter was added.

Halving the amount of $Co_2(CO)_8$ from 70 mol % to 35 mol % (reactions 1 and 2) had no effect on the yield. When 10 mol % of dicobalt octacarbonyl was added, only 8 % of the product **30** was obtained (reaction 3). This result was interesting since the yield was stoichiometric with respect to the cobalt complex. When THF was used as the solvent, without any $Co_2(CO)_8$, no product **30** was isolated (reaction 4) and without any promoter present the yield was low (36 %, reaction 6). A maximum yield of **30**

was obtained when all reagents were present with 50 mol % of resin **155**, 35 mol % of $Co_2(CO)_8$ and heating at 40 °C for 18 hours in THF (reaction 5). Surprisingly, the yields almost match the number of molar equivalents of $Co_2(CO)_8$ that have been added (reactions 1, 3 and 6). However in the case where 35 mol % of $Co_2(CO)_8$ has been added the yield more than doubles to 75 % (reaction 5) and 67 % (reaction 2). Krafft and Bonaga comment that the substrate concentration of 0.2 M in solvent is crucial to the reaction.[88] Our reactions were also conducted using a substrate concentration of 0.2 M, however, the concentration of the other reactants might also be important. From the results in table 15, it was assumed that the optiumum ratio for the substoichiometric solid phase reactions is 0.2 M substrate concentration with either a 3 : 1 or 1.5 : 1 ratio of amine promoter to dicobalt octacarbonyl.

DME is a commonly used solvent in PKR. Although it was not used for the solution phase work it was used in the solid phase experiments. However, it has been demonstrated that DME must be promoting the reaction (reaction 10) when a yield of 85 % of **30** was obtained. Throughout their work on amine additives, Krafft and co-workers have shown that when no amine was added in her experiments a yield of 80 % was obtained compared to 94 % when the amine was added.[104] Sugihara and Yamaguchi found that when DME was added to a reaction conducted in toluene, it acted as a promoter.[66] However when Sugihara conducted the substoichiometric reactions in DME, a yield of only 9 % of the desired product **114** was obtained.

When the amount of resin **156** was halved from 105 mol % to 50 mol %, the yield increased from 61 % (reaction 7) to 84 % (reaction 8) therefore only 50 mol % of resin **156** was required to achieve the maximum result. Again this is a surprising result. There are no clear reasons why the yield should increase when the amount of solid phase resin is halved but it is possible that with more solid phase resin, the beads could form several layers at the top of the solvent and maybe the beads nearer the top don't actually come into contact with the 35 % of the substrate **107** that must have already formed the cobalt complex **29**. The beads were shaken but always floated at the top of the solvent. Perhaps using a larger vessel that allowed the beads to form a single layer may have provided the answer. Although the solvent was DME instead of THF,

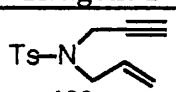
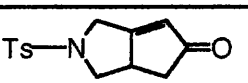
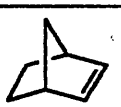
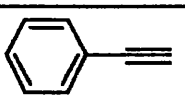
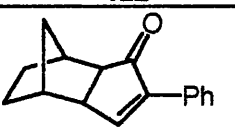
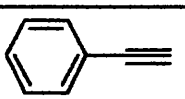
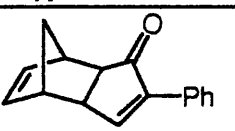
again the percentage of molar equivalents of dicobalt octacarbonyl used was reflected in the yield. Reducing the amount of $Co_2(CO)_8$ from 35 mol % to 20 mol % caused the yield to drop from 84 % (reaction 8) to 27 % (reaction 9). When no solid phase promoter was added to DME, the yield was high at 85 % (reaction 10) so it was expected that that high yield would be constant in the DME reactions. However, reactions 7 and 9 gave lower yields. It could be that the solid phase resin is hindering the DME promoted reaction so when the amount of resin is halved, there is less to compete with the DME so the yield increases.

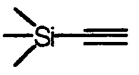
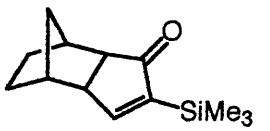
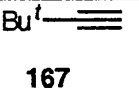
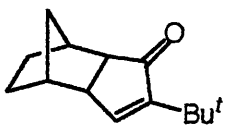
The optimum reaction conditions were assumed to be 18 hours shaking at 40 °C, in THF with 50 mol % of morpholinomethyl resin **156** and 35 mol % of $Co_2(CO)_8$.

4.2.2 Other Substrates

In order to assess the versatility of the substoichiometric reactions with the solid phase promoter **156**, a variety of substrates were tested. The yields were variable. Unless stated otherwise, 1 equivalent of each reagent was used, 35 mol % of $Co_2(CO)_8$, 50 mol % of morpholinomethyl resin **156** were shaken in THF at 40 °C for 18 hours (*Table 16*).

Table 16

Reaction	Reagent 1	Reagent 2	Product	Yield (%)
1	 **120**	–	 **122**	17
2	 **39**	 **94**	 **41**	78
3	 **21**	 **94**	 **22**	58

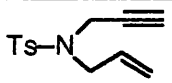
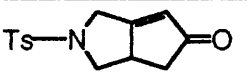
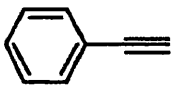
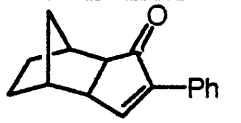
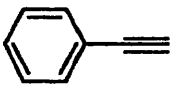
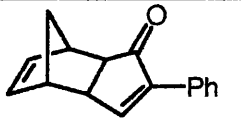
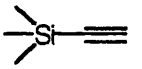
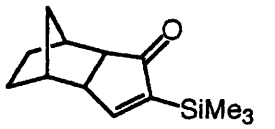
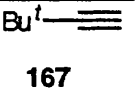
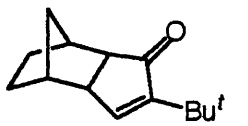
4	 **39**	 **165**	 **166**	13
5	 **39**	 **167**	 **168**	75

The commonly used intramolecular Pauson–Khand substrate **120** cyclised to give **122** in a poor yield of 17 % (reaction 1). The intermolecular substrates tend to react well. The alkyne and alkene components are held together therefore they are in close proximity and chances of reaction are increased. However, in this instance, the substrate did not react well. Usually the cobalt complexes are pre-formed and isolated but under these conditions, the cobalt complex has to form *in situ* and the bulky tosyl group may hinder the complex formation. The other commonly used set of intermolecular substrates norbornene **39** and phenylacetylene **94** cyclised effectively to yield 78 % of **41** (reaction 2). Norbornene and norbornadiene tend to be used since they are strained alkenes and these are known to be very reactive in the PKR.[1] Electron rich alkynes, such as phenylacetylene, are also commonly used since they are reactive in the PKR.[11,38] **22** was obtained in a moderate yield of 58 % from norbornadiene **21** and phenylacetylene **94** (reaction 3). The reaction between norbornene **39** and (trimethylsilyl)acetylene **165** gave **166** in a poor yield of only 13 % (reaction 4). **168** was isolated in a very good yield of 75 % from norbornene **39** and 3,3-dimethyl-1-butyne **167** (reaction 5). These two yields show that by replacing a carbon atom with a silicon atom, the reactivity of the substrate is greatly reduced. We have clearly demonstrated that a variety of substrates cyclised in a range of yields.

To give a comparison, the same conditions and substrates were used but the reactions were conducted in DME instead of toluene. From Table 15, it was shown that DME was also promoting the reactions so high yields of substrates **122**, **41**, **22**, **166** and **168** were expected under these conditions.

Unless stated otherwise, 1 equivalent of each reagent was used, 35 mol % of $Co_2(CO)_8$, 50 mol % of morpholinomethyl resin **156** were shaken in DME at 40 °C for 18 hours (*Table 17*).

Table 17

Reaction	Reagent 1	Reagent 2	Product	Yield (%)
1	 **120**	–	 **122**	49
2	 **39**	 **94**	 **41**	69
3	 **21**	 **94**	 **22**	92
4	 **39**	 **165**	 **166**	23
5	 **39**	 **167**	 **168**	52

An increase in the yields when DME was used as the solvent had been expected. However, this was not always the case and the results were unpredictable.

When 4-methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide **120** was cyclised, a yield of 49 % of **122** was isolated (reaction 1). This is a huge increase over the reaction in THF which yielded only 17 % (*Table 17*, reaction 1). The reaction between norbornene **39** and phenylacetylene **94** gave **41** in a good yield of 69 % (reaction 2). This was comparable to the reaction in THF, which yielded 69 % (*Table 17*, reaction 2). **22** was isolated in a moderate yield of 58 % (*Table 17*, reaction 3) in THF. However when DME was used, the yield increased significantly to give an excellent yield of 92 % (reaction 3). The reaction between norbornene **39** and (trimethylsilyl)acetylene **165** gave **166** in a yield of 23 % (reaction 4). Surprisingly, the

same reaction in THF gave a lower yield of 13 % (*Table 17*, reaction 4). The reaction between norbornene **39** and 3,3-dimethyl-1-butyne **167** gave **168** in a moderate yield of 52 % (reaction 5). Again, surprisingly this is lower than the same reaction in THF, which gave a good yield of 75 % (*Table 17*, reaction 5).

THF (*Figure 18*) and DME (*Figure 19*) have different structures. THF is cyclic with one oxygen atom, DME is a chain with two methoxy groups. We have previously demonstrated that alcohols can promote the PKR and methanol and isopropanol were very effective. However, there is only one oxygen atom in THF which is locked in a cyclic ring. However, DME has two flexible methoxy groups. They might be able to chelate to the cobalt complex, thus making the cobalt complex more soluble, therefore more reactive.[54] However, there are two cases where the use of DME leads to lower yields of product. Entry 2 in Table 17 is lower but only by 10 %. However, entry 5 in Table 17 is lower by 23 %, it may be that the bulky *tert*-butyl group on the alkyne **167** prevents chelation by DME.

Figure 18

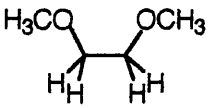
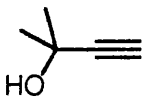
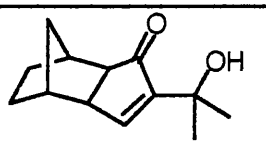
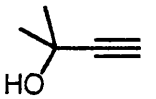
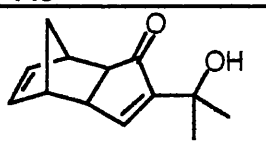
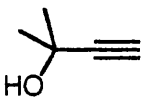
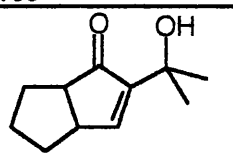
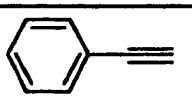
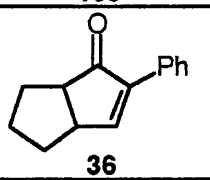
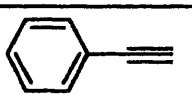
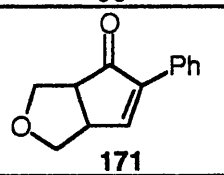
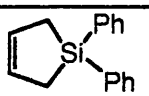
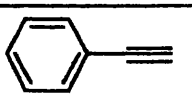
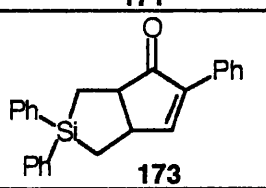


Figure 19

The successful cyclisation of a variety of substrates that are known to be unreactive in the PKR would show that the reaction conditions developed were completely robust so it was decided to attempt the cyclisations using the developed optimum conditions. The reactions were conducted in DME since it also appears to have some promoting ability.[66] As before, the reactions were carried out using 1 equivalent of each reagent, 35 mol % of $Co_2(CO)_8$, 50 mol % of resin **156** and shaken at 40 °C for 18 hours in DME (*Table 18*).

Table 18

Reaction	Reagent 1	Reagent 2	Product	Yield (%)
1	 **39**	 **108**	 **143**	0
2	 **21**	 **108**	 **109**	0
3	 **134**	 **108**	 **169**	0
4	 **170**	 **94**	 **36**	0
5	 **170**	 **94**	 **171**	0
6	 **172**	 **94**	 **173**	0

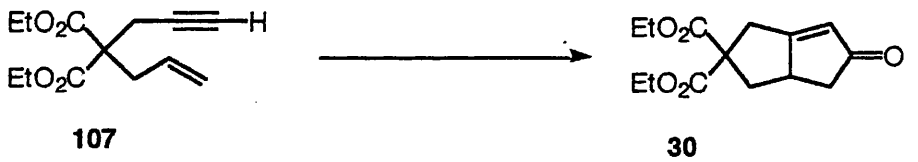
Kerr and co-workers successfully cyclised entries 1 – 3[99] but nothing was returned under our conditions. Belanger and Livinghouse had already demonstrated the unreactivity of cobalt-complexed **108** in the reaction involving shelf-stable cobalt-alkyne surrogates (*Scheme 63*).[64] They used 5 % of cobalt-complexed **108** as a pre-catalyst under one atmosphere of carbon monoxide and once the active catalyst formed, substrate **29** cyclised.

The alkynes in reactions 4, 5 and 6 are known to be very reactive in the PKR. Strained alkenes, such as norbornene are reactive in the PKR but cyclopentene and dihydrofuran are unstrained cyclic alkenes. However, they are exceptions and tend to

be reactive but usually at elevated temperatures[1] so the temperature of 40 °C must be too low to induce cyclisation in entries 4 and 5. As we have seen in the previous Table, when the silicon based alkyne **165** was used, only a small amount of product **166** was isolated therefore the silicon containing alkene was not expected to react very well.

4.2.3 Recycling of Morpholinomethyl Resin

The major advantage obtained from using a solid phase resin was that the resin could be recycled. The optimum conditions of 35 mol % of $Co_2(CO)_8$, 50 mol % of solid supported morpholinomethyl resin **156** at 40 °C for 18 hours in THF were used to conduct each reaction (*Scheme 55*). Following the procedure of Kerr and co-workers, the morpholinomethyl resin was washed after each reaction with a 2 : 1 mixture of THF : HCl (1M), followed by treatment of the resin with 10 % *N*-ethyl-di-iso-propylamine in DMF.[99] Rinsing with DCM and drying under nitrogen returned the solid phase resin (*Table 19*).



107 **30**

Scheme 55

Table 19

Run No.	Starting Material	Yield of 30 (%)
1	101 mg, 0.42 mmol	75
2	102 mg, 0.43 mmol	80
3	101 mg, 0.42 mmol	78
4	101 mg, 0.42 mmol	65
5	101 mg, 0.42 mmol	75

Unless stated otherwise, 35 mol % of freshly sublimed dicobalt octacarbonyl was used, the solvent was THF, 50 mol % of morpholinomethyl resin **156** was used and the reaction mixture was heated at 40 °C for 18 hours.

The first run gave a yield of 75 %. The resin **156** was then washed 3 times using the acid followed by the amine, rinsed using DCM and dried under nitrogen. The cycle was repeated and surprisingly the yield of **30** increased to 80 %. The resin **156** was washed 5 times using the acid and amine, rinsed with DCM and dried under nitrogen as before. The third cycle gave a yield of 78 %, and the resin **156** was washed 7 times using the acid and amine and treated as before. The fourth run yielded 65 % of **30** and the resin was washed 9 times using the acid and amine. The fifth run yielded 78 % of **30**. The last result seems surprising in that the yield should increase. However, Kerr and co-workers have also shown that the yields obtained from recycling of their solid supported *N*-oxide **158** can fluctuate but they make no comment as to why the yield should increase.[99]

Again, to give a comparison, the same series of experiments were conducted in DME (*Scheme 55, Table 20*).

Table 20

Run No.	Starting Material	Yield of 30 (%)
1	102 mg, 0.43 mmol	84
2	104 mg, 0.44 mmol	81
3	101 mg, 0.42 mmol	76
4	101 mg, 0.42 mmol	43
5	103 mg, 0.43 mmol	41

Unless stated otherwise, 35 mol % of freshly sublimed dicobalt octacarbonyl was used, the solvent was DME, 50 mol % of morpholinomethyl resin **156** was used and the reaction mixture was heated at 40 °C for 18 hours.

The yields of **30** are good for the first three runs but then the yield falls dramatically. This is surprising since we have shown that DME can promote the reaction without any amine present. However, the decrease in yields could be as a result of the resin still being slightly wet. Although Sugihara and Yamaguchi showed that a small amount of water could promote the reaction, they also showed that too much water would hinder the reaction.[66] The reactions would have to be repeated to determine what had actually happened; however, owing to time restrictions this was impossible.

4.3 Conclusions

1. The first Pauson–Khand reaction using substoichiometric amounts of solid supported amine and dicobalt octacarbonyl to be conducted under air has been succesfully developed.
2. The reaction is only one step, instead of having to preform the cobalt complex prior to reaction. The complex is formed *in situ*, again making the reaction very simple and high yielding.
3. Optimum conditions for the substoichiometric Pauson-Khand reaction were found to be reacting one equivalent of substrate with 50 mol % of solid supported amine **156** with 35 mol % of dicobalt octacarbonyl shaking for 18 hours at 40 °C in THF.
4. The optimum reaction conditions were successfully applied to both inter- and intramolecular Pauson-Khand cyclisations.
5. The resin was shown to be easily recycled at least five times without any loss in yield, again making the reaction even cheaper and more accessible.
6. The reaction was unsuccessful with challenging substrates for the PKR. However, only Kerr and co-workers have been successful using these substrates in the PKR.

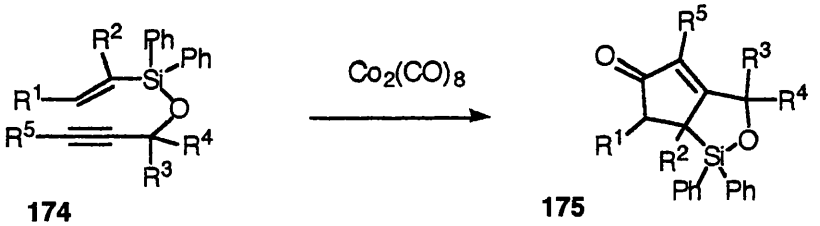
Chapter 5

Silicon–Oxygen Tethers in Pauson-Khand Reactions

5.1 Introduction

Clearly the intramolecular Pauson-Khand reaction has many advantages over the intermolecular reaction. However, there is one major drawback of the PKR that hinders its use in organic synthesis. In the case of a compound with an ether linkage **19**, or other bicyclic compounds, there is little potential for further reaction, (refer to *Schemes 7* and *8*).

The introduction of a linkage or tether as in **174** that could temporarily connect the alkene and alkyne components would mean that the beneficial effects of the intramolecular reaction could be utilised (*Scheme 115*). Subsequent removal of the tether would create scope for further functionalisation about the generated cyclopentenone system **175**.

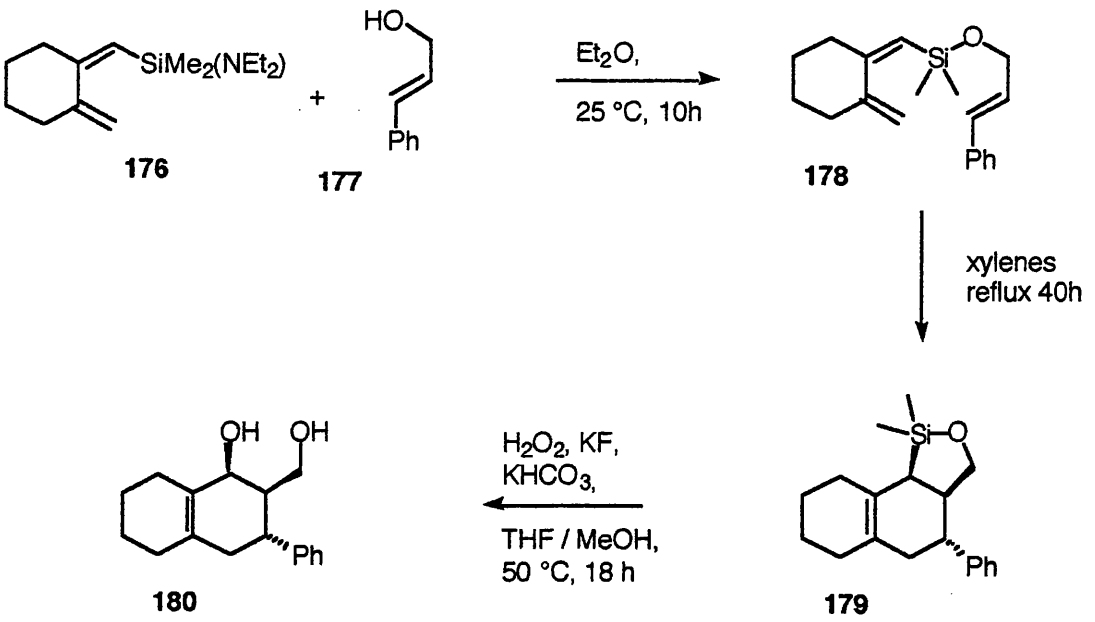


174 **175**

Scheme 115

Silicon based tethers are commonly used in a variety of intramolecular processes.[105] They make an attractive choice of tether, as a variety of procedures are available for their removal from organic systems. There are many examples of the silicon-oxygen tether being used in organic synthesis as a directing factor[105] but it has not yet been successfully applied to the PKR.

Tamao *et al* used a silicon tether,[106] where the tether removal permits functionalisation, in an intramolecular Diels Alder reaction (*Scheme 116*). The silicon tether precursor was produced by the condensation of the vinyl silane **176** with cinnamyl alcohol **177**. Diels Alder cyclisation of the triene yielded the siloxane **178** and oxidative cleavage was then used to remove the tether **179**, resulting in a 75% yield of the diol **180**.

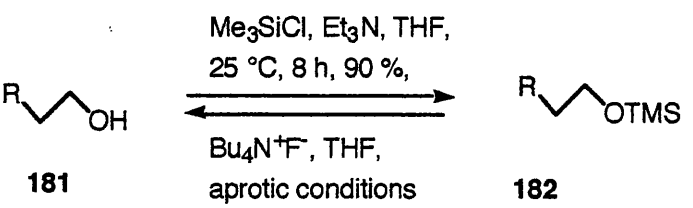


176 **177** **178** **180** **179**

Scheme 116

One of the aims of this research was to explore the application of a temporary silicon tether to the PK intramolecular cyclisation (*Scheme 115*). It was hoped that a five-membered cyclopentenone ring system could be synthesised *via* a bicyclic intermediate **175**, eventually yielding the product of the intermolecular reaction but gaining the advantages created by the intramolecular reaction, such as increased regio- and stereo-control.

Before this strategy could be investigated, the silicon-tethered substrates had to be synthesised. Silyl ethers are commonly used to protect hydroxyl functionality in organic synthesis.[107] Many silyl ethers have been developed and there are numerous examples of the formation and cleavage of these groups. Hydroxyl groups **181** are often protected using a trimethylsilyl ether **182** and there is a wide choice of routes available for the formation and cleavage of this group, for example see *Scheme 117*.[108]

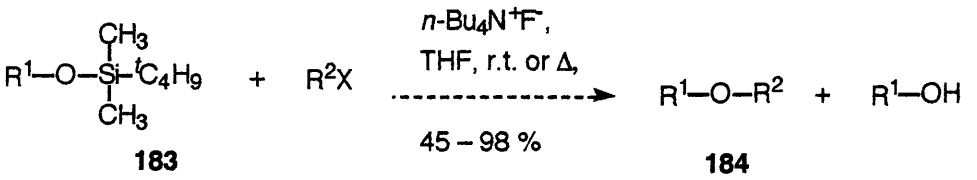


181 **182**

Scheme 117

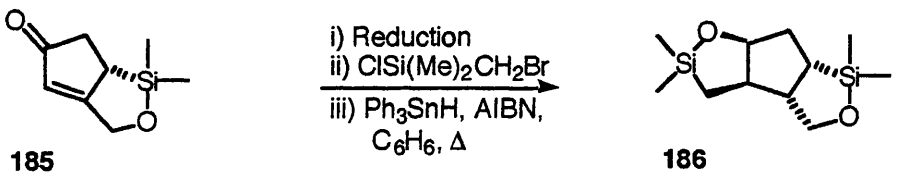
We intended to mask the hydroxyl functionality by forming C–Si or O–Si bonds and then conducting an intramolecular Pauson-Khand cyclisation (*Scheme 115*).

Another advantage that silyl ethers have over other hydroxyl protecting groups is that they can be further manipulated to yield a variety of functional groups without first deprotecting the alcohol.[107] Silyl ethers **183** have been directly converted into aldehydes,[109] ketones,[110] bromides,[111] acetates[112] and ethers[113] **184**, for example (see *Scheme 118*).



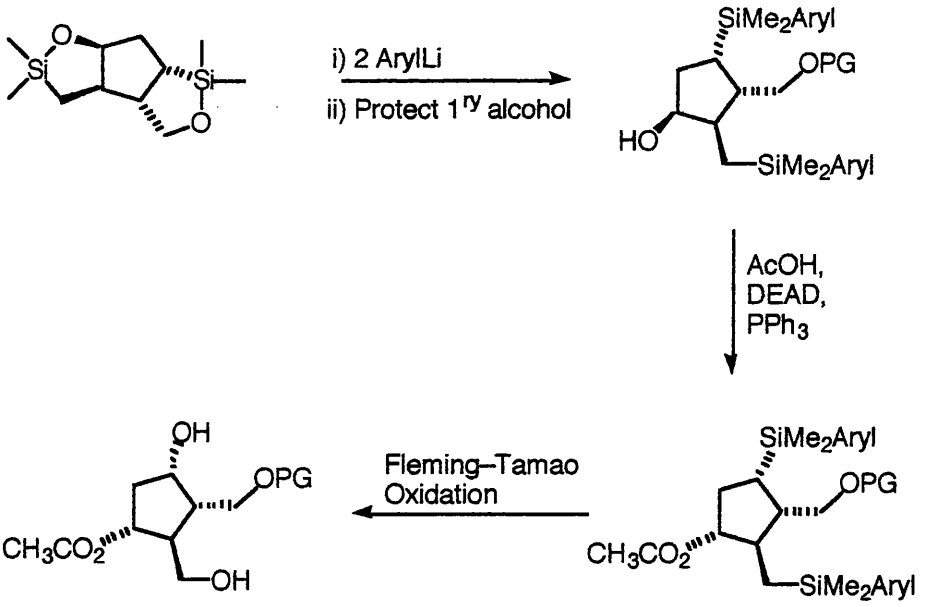
Scheme 118

The silicon-tethered substrates **185** could be further functionalised to introduce another silicon-oxygen bond **186**. This would lead to the formation of a tetrasubstituted cyclopentane skeleton (*Scheme 119*).



Scheme 119

It was hoped that eventually this methodology would be widely applied in synthesis. Carbocyclic nucleosides[114] and prostaglandins[6] are potential synthetic targets. A possible approach to the latter is outlined in *Scheme 120*.



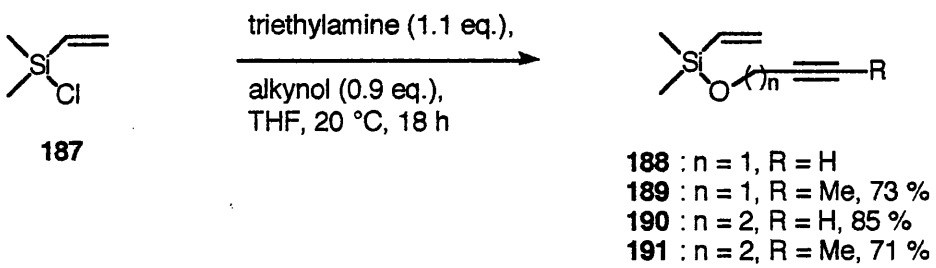
Scheme 120

5.2 Results and Discussion

In order to attempt the PKR, the starting materials had to be synthesised.

5.2.1 Preparation of Starting Materials

Following a procedure by Whitby and co-workers,[115] the silyl compounds were prepared by reaction of chlorodimethylvinylsilane **187**, triethylamine and the appropriate alkynol (*Scheme 121*). The reaction mixture was stirred under nitrogen for 18 hours in THF. Compounds **188, 189** and **190** are novel compounds.



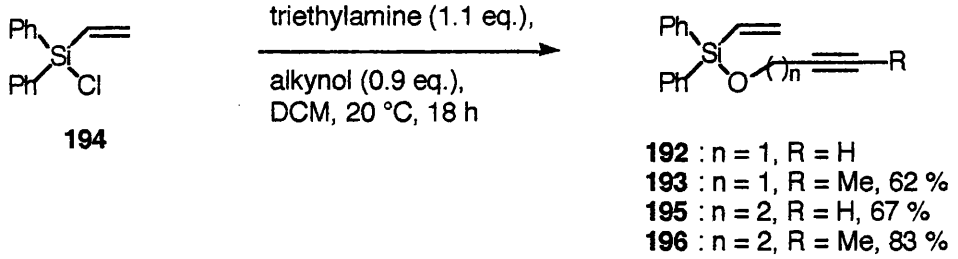
Scheme 121

Washing the compounds with saturated aqueous ammonium chloride caused decomposition, so the mixture was filtered twice through Celite to remove the salts. The solvent and triethylamine residues were removed using a rotary evaporator; however compounds **188, 189, 190** and **191** were so volatile that they evaporated. To

overcome this problem, removal of the impurities was attempted using fractional distillation. This proved unsuccessful since the mixture had to be heated to over 100 °C causing the compounds to polymerise. Some product did distil but it was still very impure. The use of a variable pressure rotary evaporator provided the solution to the problem. The vacuum pump was set to 50 mmHg and the majority of the solvent was removed in this manner. The vacuum pump was then attached to a Kugelrohr oven and was set to 30 mmHg. After two consecutive distillations at 70 – 90 °C, the desired product was isolated in good yields of over 71 %. Although there were many attempts, compound **188** was never obtained analytically pure. There were at least 2 – 3 % of starting materials present in the ^{1}H and ^{13}C NMR spectra.

The mass spectra of compounds **189** and **191** were interesting. When the methyl group was the terminal group on the alkyne, a methyl group was easily lost under the conditions required for mass spectrometry hence the peak observed relates to the mass of 154 or 168 minus a methyl group, giving a peak at *m/z* 139 or 153. However, this phenomenon was also observed when the mass spectrum of compound **190** with a terminal hydrogen on the alkyne was obtained. Again, the peak observed relates to the mass of 154 minus a methyl group giving a mass of 139. Therefore, it could not have been the terminal methyl group that was lost under the conditions required for mass spectrometry but must have been one of the methyl groups that was attached to the silicon. Whitby and co-workers did not seem to observe this feature and their mass spectral data were obtained using atmospheric pressure chemical ionisation (APCI).[115]

A second set of substrates that had phenyl groups attached to the silicon were also synthesised. The procedure by Saigo and co-workers[116] was followed but was slightly modified. Compounds **192** and **193** are novel. Chlorodiphenylvinylsilane **194**, triethylamine and the appropriate alkynol were combined (*Scheme 122*).



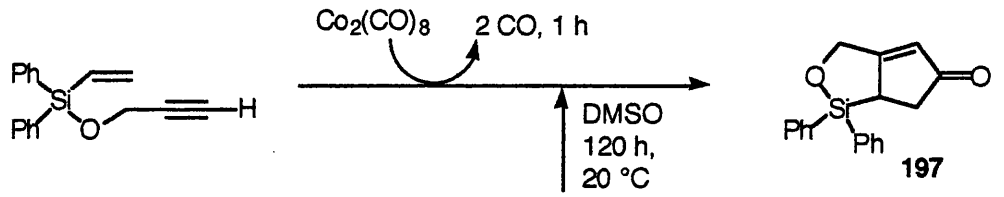
Scheme 122

When triethylamine was added to the appropriate alkynol followed by dropwise addition of chlorodiphenylvinylsilane **194**, a white precipitate immediately formed. The salt was easily removed by aqueous work–up using saturated aqueous ammonium chloride (Saigo and co-workers used saturated aqueous sodium hydrogen carbonate[116]) and the solvent was removed using a rotary evaporator. Purification of the compounds **192, 193, 194** or **195** was difficult and a variety of different techniques were used. Column chromatography on silica gel proved unsuccessful. Surprisingly the compounds survived this technique but because of the possibility of decomposition the compounds were eluted quickly therefore no separation occurred (Saigo and co-workers used flash column chromatography[116]). Purification was finally achieved by distillation using a Kugelrohr oven at 110 – 130 °C at 0.05 mmHg and eventually two consecutive distillations yielded products of high purity. After the first distillation the yield was over 90 %. However the compounds were not pure and the second distillation yielded the pure products in 62 – 83 %. The yields are much lower than expected because higher yields were compromised for high purity. Despite many attempts at purification, compound **192** was never obtained analytically pure. In the ^{1}H and ^{13}C NMR spectra at least 2 – 3 % of starting materials were observed.

The mass spectra of compounds **195** and **193** were unusual. In the case where the methyl group is at the terminal position of the alkyne **193** only one peak at *m/z* 278 was observed. Compound **193** was run using electron impact (EI) mass spectroscopy to obtain the accurate mass. However in the case where the hydrogen atom was the terminal group of the alkyne **195** two peaks were seen, one at 279 and the other at 278. Expansion of the spectrum showed two signals corresponding to two different ions at *m/z* 279 and *m/z* 278. Presumably the hydrogen atom is easily gained under the conditions required for mass spectrometry and hence two signals relating to compound

195 were observed. In order to obtain the accurate mass of **195** it was run in isobutane chemical ionisation (CI). Saigo and co-workers managed to get the accurate mass using EI and saw only one peak corresponding to an ion of *m/z* 278.[116] Compound **196** gave spectra in good agreement with the literature values.[116]

As mentioned in chapter 1, DMSO was found to be an efficient promoter of the Pauson-Khand reaction.[17] Previous work within the group on these cyclisations utilised a "one-pot" approach. The cobalt complex was prepared *in situ* and the promoter was added to the reaction mixture (*Scheme 123*).

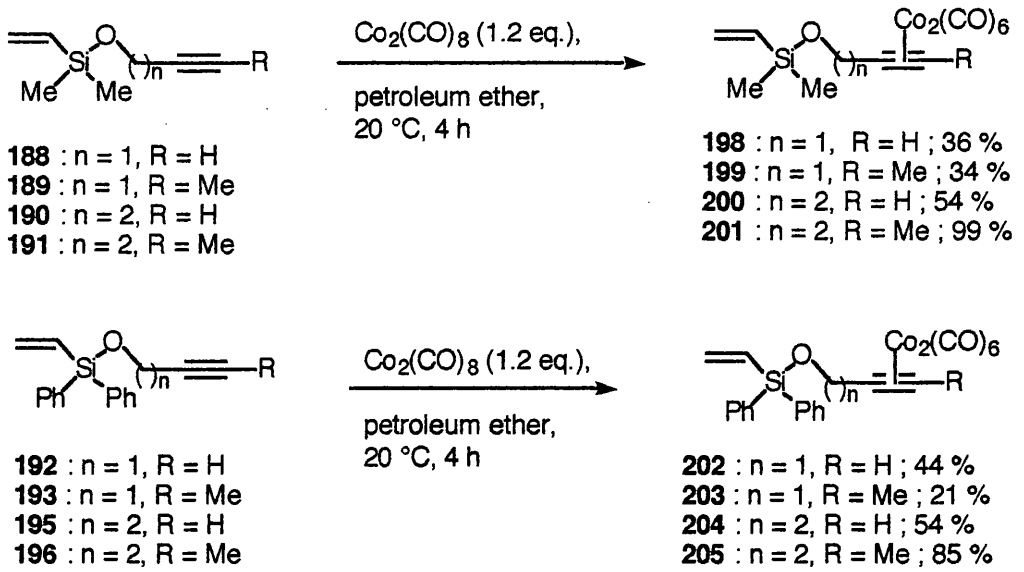


Scheme 123

It was hoped that compound **197** would be the product of the above reaction ; however none of the desired product **197** was isolated. From then on, the cobalt complexes **198**, **199**, **200**, **201**, **202** and **203** were isolated to determine whether or not the reaction was proceeding in the manner that had been anticipated.

5.2.2 Synthesis of Cobalt Complexes

Following a general procedure by Pauson,[11] substrates **188**, **189**, **190**, **191**, **192**, **193**, **195** and **196**, were treated stoichiometrically with dicobalt octacarbonyl to yield complexes **198**, **199**, **200**, **201**, **202**, **203**, **204** and **205**, (*Scheme 124*). Dicobalt octacarbonyl was dissolved in distilled petroleum ether and the appropriate substrate **188**, **189**, **190**, **191**, **192**, **193**, **195** and **196** was added dropwise and stirred for 4 hours at room temperature. Carbon monoxide gas could be seen bubbling off, a sign that complexation was occurring and the solution was then filtered through a pad of Celite to remove some of the excess cobalt.



188 : n = 1, R = H
189 : n = 1, R = Me
190 : n = 2, R = H
191 : n = 2, R = Me

198 : n = 1, R = H ; 36 %
199 : n = 1, R = Me ; 34 %
200 : n = 2, R = H ; 54 %
201 : n = 2, R = Me ; 99 %

192 : n = 1, R = H
193 : n = 1, R = Me
195 : n = 2, R = H
196 : n = 2, R = Me

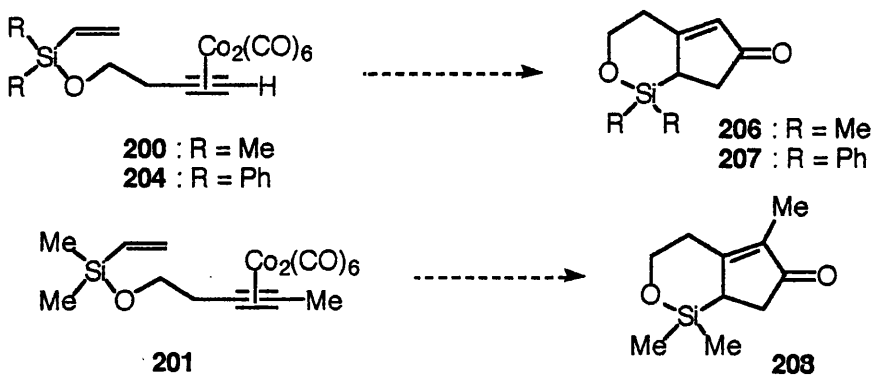
202 : n = 1, R = H ; 44 %
203 : n = 1, R = Me ; 21 %
204 : n = 2, R = H ; 54 %
205 : n = 2, R = Me ; 85 %

Scheme 124

Compounds **198**, **199**, **200**, **201**, **202**, **203**, **204** and **205** were purified using column chromatography on deactivated alumina. The compounds were reasonably stable in air for short periods and could be stored for a long time in the freezer when placed under nitrogen. The synthesis of hexacarbonyl 3,3-diphenyl-4-oxa-3-sila-1-octen-7-yne dicobalt **204** gave a crude yield of approximately 65 %. Compound **204** was purified using column chromatography run on neutral alumina and approximately 29 % of the pure compound **204** was isolated. Compound **204** looked to be decomposing slowly on the column. The procedure was repeated using 3,3-dimethyl-4-oxa-3-sila-1-octen-7-yne **190**. Prior to purification, 54 % of **200** was isolated ; however compound **200** completely decomposed on the column. In consequent runs of the experiment, complex **200** was filtered through Celite and then the Pauson-Khand cyclisation was attempted. The synthesis of hexacarbonyl 3,3-diphenyl-4-oxa-3-sila-1-nonen-7-yne dicobalt gave a yield of 99 %. Before complexation the alkyne peak in the ^{1}H NMR spectra was a triplet at δ 1.76. After complexation the alkyne peak shifted to become a singlet at δ 2.64. The ^{1}H NMR spectrum looked clean but this does not show the existence of any elemental cobalt or organocobalt residues. It is the formation of $Co_4(CO)_{12}$ and other cobalt by-products that are believed by the groups of Pauson[117] and Magnus[15] to hinder the Pauson-Khand cyclisations.

5.2.3 Attempted Cyclisations

Pauson-Khand cyclisations were attempted using amines as promoters. We had hoped that the amines might be milder promoters of the PKR and our products would stand a better chance of surviving the reaction conditions. The substrates in *Scheme 125* were used to test the Pauson-Khand cyclisations (*Table 21*).



Scheme 125

Table 21

Reaction	Starting Material	Promoter	Solvent	Yield (%)
1	**204**	NMM (3 eq.)	toluene	0
2	**200**	NMM (3 eq.)	toluene	0
3[a]	**201**	^{i}PrOH (17 eq.)	DCM	0
4[a]	**201**	–	^{i}PrOH	0

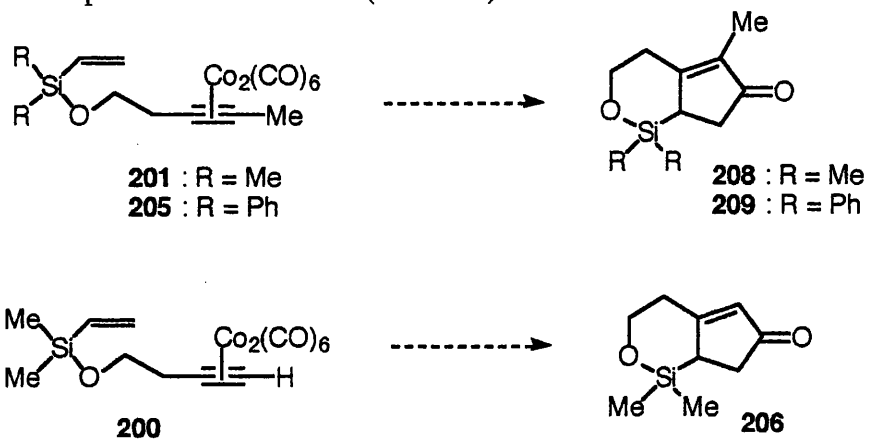
Unless stated otherwise the reaction mixture was stirred at 20 °C under air for 4 days.

[a]Conducted under nitrogen.

In Chapter 2, combining amine promoter and substrate and stirring at 20 °C for 4 days under air were the conditions used to test the different amine promoters. Whichever amine was used, some product was obtained (Chapter 2, *Table 1*). However, under these conditions with substrates **204** (reaction 1) and **200** (reaction 2) no trace of the desired products **206** or **207** were detected. DCM was shown to be as good a solvent as toluene (Chapter 2) and isopropanol was also shown to be an effective

promoter. Therefore, reaction 3 was conducted in DCM with isopropanol as the promoter but no product was obtained. It was hoped that using a solvent that was also a promoter, for example, isopropanol, might induce cyclisation, however no product **208** was isolated (reaction 4).

Using the substrates in *Scheme 126*, the effect of doubling the reaction time and varying the temperature was assessed (*Table 22*).



Scheme 126

Table 22

Reaction	Starting Material	Promoter	Solvent	Temp. (°C)	Yield (%)
1	**200**	NMM (3 eq.)	DCM : ^{i}PrOH	28	0
2	**205**	NMM (3 eq.)	toluene : ^{i}PrOH	50	0
3[a]	**201**	^{i}PrOH (36 eq.)	DCM	28	0

Unless stated otherwise, 3 equivalents of promoter were added and the reaction mixture was stirred under air for 48 hours.

[a]Stirred for 72 hours.

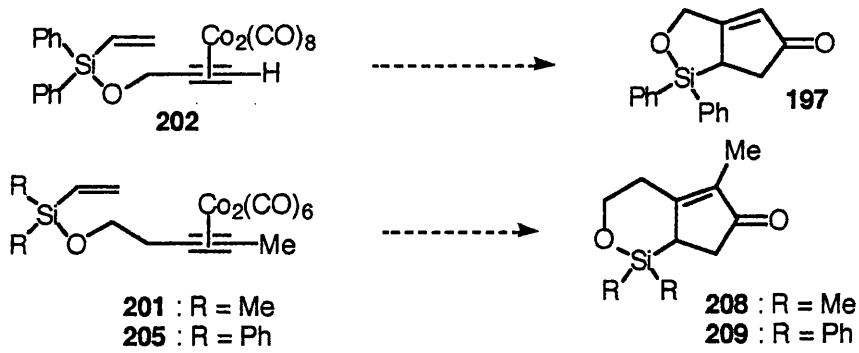
The optimum conditions for substrate **29** (ester) were found to be 50 °C for 24 hours in toluene : ^{i}PrOH with 3 equivalents of NMM, *Scheme 14*. The same conditions were applied to substrate **205** but the reaction time was doubled (reaction 2) unfortunately,

no product **209** was isolated. Even changing the solvent from toluene to DCM and lowering the temperature to a milder 28 °C proved unsuccessful (reaction 1). Isopropanol had been shown to be an efficient promoter for substrate **29** but when combined with DCM at 28 °C, no product **208** was detected (reaction 3).

High intensity ultrasound has been shown to be an efficient promoter of the Pauson–Khand reaction,[29] so the sonicator was set at 28 °C to induce cyclisation. The reaction was run for 2 hours in DCM : MeOH with 3 equivalents of NMM, however no product **208** was isolated. ^{1}H NMR spectra showed traces of starting material.

5.2.4 Use of TMANO.2H$_2$O

Another problem that was encountered with the cyclisation of the silyloxy compounds was that the compounds were acid sensitive so purification on both silica and alumina columns caused decomposition of either the unreacted starting material or product. It was difficult to remove the cobalt residues from complex **201** without using column chromatography. In the Nicholas reaction (Chapter 6) the cobalt residues were normally removed using cerium ammonium nitrate[118] but since this is acidic it could cleave the silicon-oxygen bond. Lewis acids were also commonly used to remove the cobalt protecting group but given that the siloxy compounds were acid sensitive, these were no use. It would have been useful to use a promoter with a dual purpose, that is, if it didn't cyclise the compound then it would remove the cobalt complex. The ^{1}H NMR spectra would be easier to interpret and the reactions could be followed more easily. Nicholas briefly mentioned that TMANO.2H$_2$O had been used in his reaction to remove the cobalt protecting group.[118] TMANO.2H$_2$O was also well known as a promoter in the PKR[18] so it was used in an attempt to induce cyclisation. It was thought that either the compound would cyclise or the cobalt complex would decompose. However, no cyclisation was observed and the cobalt complex was never completely removed (*Scheme 127, Table 23*).



Scheme 127

Table 23

Reaction	Starting Material	Promoter	Solvent	Time	Yield (%)
1[a,b]	**202**	NMO.H_2O	toluene : MeOH	20 h	0
2	**201**	TMANO.2H_2O	MeOH	17 h	0
3[c]	**205**	TMANO.2H_2O	^{i}PrOH : MeOH	2 h	0
4	**205**	TMANO.2H_2O	MeOH	16 h	0
5[d]	**205**	TMANO.2H_2O	MeOH	18 h	0

Unless stated otherwise, 10 equivalents of promoter were added and the reaction mixture was stirred at 20 °C under air.

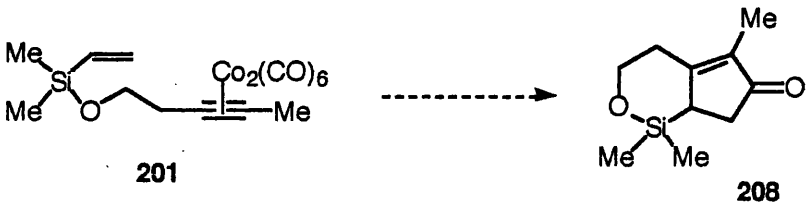
[a]3 equivalents of promoter were added. [b]Toluene : MeOH, 5 : 1. [c]^{i}PrOH : MeOH, 7 : 1. [d]Conducted under nitrogen.

The reactions involving TMANO.2H_2O had to be conducted in methanol to dissolve the amine *N*-oxide. Unfortunately even with the combination of amine *N*-oxide and alcohol promoters none of the compounds **201** or **205** cyclised (reactions 2, 3 and 4). The reaction was conducted under nitrogen in the hope that using standard Pauson–Khand conditions,[16] albeit in a different solvent, might induce cyclisation. Unfortunately, this approach was also unsuccessful (reaction 5). Even using NMO.H_2O in a combination of toluene and methanol was unsuccessful in obtaining any trace of **197** (reaction 1).

5.2.5 Use of Solid Phase Promoters

Whilst this work was ongoing, solid phase experiments using the ester substrate had been conducted (Chapter 3). The reaction conditions for the solid phase reactions were very mild and very effective. It was hoped that use of solid supported amines in the cyclisations of the silyl compounds would yield the desired products.

Morpholinomethyl resin **156** and polyamine resin **163** were used to induce cyclisation. Again morpholinomethyl resin **156** was used since it was effective in both the solution phase reaction and the solid phase experiments and polyamine resin **163** was used for its multiple nitrogens (*Scheme 126, Table 24*).



Scheme 126

Table 24

Reaction	Starting Material	Resin	Solvent	Yield (%)
1	**201**	**156**	THF	0
2	**201**	**156**	DCM	0
3	**201**	**163**	THF	0
4	**201**	**163**	DCM	0
5[a]	**201**	**163**	THF	0
6[a]	**201**	**163**	DCM	0

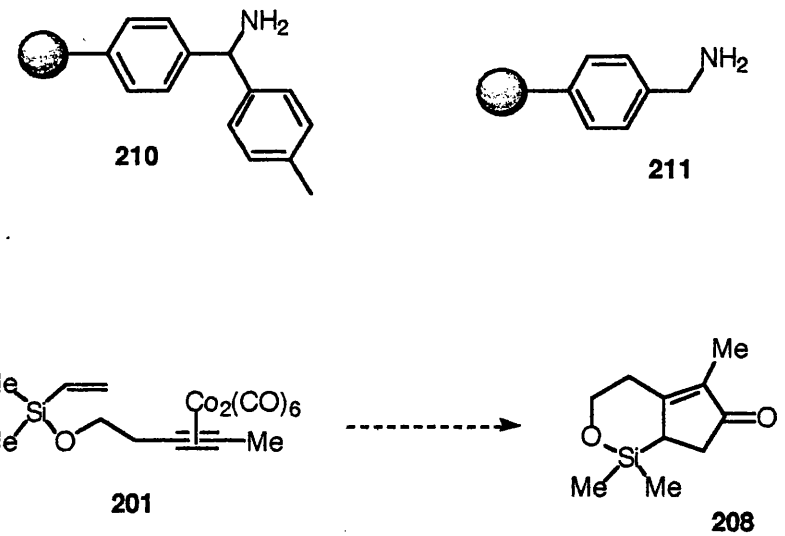
Unless stated otherwise, 3 equivalents of promoter were added and the reaction mixture was stirred at 20 °C under air for 4 days.

[a]Conducted under nitrogen.

When the reactions were carried out using morpholinomethyl resin **156** for 4 days at room temperature in either THF or DCM, the ester substrate **30** was isolated. However with substrate **201** no product was isolated (reactions 1 and 2). Again, the

ester substrate **30** was obtained when using polyamine resin **163** but when substrate **201** was used product **208** was not detected. The reactions were conducted under nitrogen in the unlikely event that the products were decomposing in air or in case it was hindering the reaction in some way. This would have been unusual since the opposite was observed in the solution phase reactions of the ester substrate. Even when the reactions were conducted under nitrogen, none of the desired product **208** was isolated (reactions 5 and 6).

Alternative solid phase resins were examined. Simple amine based solid phase amines, aminomethylated polystyrene resin **210** and aminomethyl polystyrene resin **211** were tested in the hope that they would induce cyclisation (*Scheme 126, Table 25*).



Scheme 126

Table 25

Reaction	Starting Material	Resin	Time	Yield (%)
1	**201**	**210**	4 days under N_2	0
2[a]	**201**	**210** ^{i}PrOH (6.7 eq.)	4 days, under N_2	0
3[b]	**201**	**211**	7 days	0

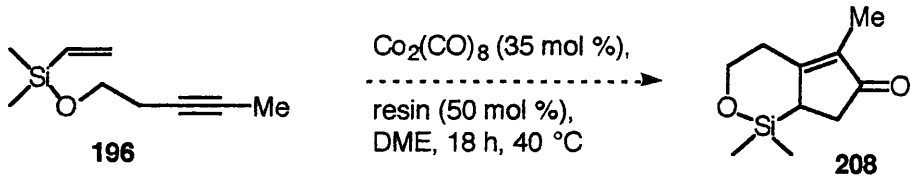
4[a,b]	**201**	**211** ^{i}PrOH (5.6 eq.)	7 days	0

Unless stated otherwise, 3 equivalents of promoter were added, the solvent was DCM and the reaction mixture was stirred at 20 °C under nitrogen.

[a]5 ml of isopropanol were added. [b]Conducted under air.

Although morpholinomethyl **156** and polyamine resin **163** were very successful when using substrate **29**, resin **211** was used in the hope that the very simple polymer supported amine might induce cyclisation. However, when the reaction was run for 4 days under nitrogen at 20 °C no product **208** was isolated (reaction 1). The solution phase reactions experienced a large increase in yield when isopropanol was added to the reaction mixture but there was no difference in the solid phase reactions. Despite these findings, isopropanol was added to these reactions in the hope that it might induce cyclisation when paired with the solid supported amine. Unfortunately adding isopropanol did not yield even a trace of the desired product **208** (reaction 2). The reaction time was increased to 7 days in case the reactions were taking longer than with the corresponding ester substrate **29**. Unfortunately, running the reactions for a longer reaction time with (reaction 3) and without isopropanol (reaction 4) yielded no product **208**.

We had almost accepted that these compounds were not going to cyclise. However, from the success of our catalytic PKR it was hoped that this might be the answer to the cyclisation of the silyl compounds. The major advantage was that the cobalt complex would be prepared *in situ* with no need to isolate the cobalt complex, therefore there would be no trace of elemental cobalt or the other unreactive cobalt cluster Co_4CO_{12}, that may have been preventing the cyclisation from occurring. Compound **196** was reacted with 35 mol % $Co_2(CO)_8$, 50 mol % morpholinomethyl resin **155** and heated for 18 hours in DME at 40 °C (*Scheme 128*). DME was used as opposed to THF since the reactions seemed to occur in DME with or without the resin, so the more effective solvent was used in this reaction.



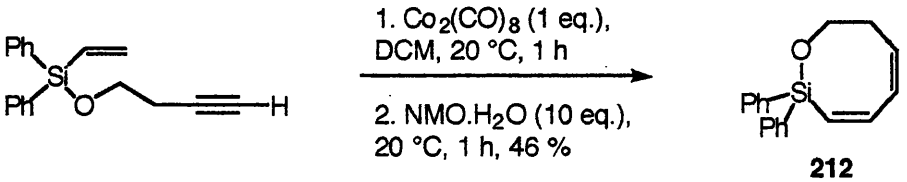
Scheme 128

Sadly, no trace of any product **208** was detected and work was ceased.

5.3 Conclusions

To our relief, we were not the only group who have tried and failed to induce these compounds to cyclise. Brown and Pauson attempted to cyclise the hexacarbonyldicobalt complexes of allyldimethylprop-2-ynylsilane and (allyloxy)dimethyl(prop-2-ynyloxy)silane.[23] However their initial attempts were unsuccessful and no further work has been reported. Verbal communication with Whitby has confirmed that he also tried to cyclise these compounds but has given up due to lack of success.

Saigo and co-workers have also attempted to cyclise these silicon substrates but were unsuccessful in obtaining the cyclopentenone products.[116] However, when they used standard Pauson-Khand conditions they isolated eight-membered cyclic dienylsilanes **212** (*Scheme 129*).



Scheme 129

They formed the cobalt complex *in situ* and then added 10 equivalents of $NMO.H_2O$, stirred the mixture for one hour at 20 °C and isolated **212** in 46 % yield. The stereochemistry of **212** was determined using ^1H NMR spectroscopy. The coupling constants were 14.8 Hz and 11.5 Hz, which seem high for *Z* sterochemistry but Saigo and co-workers felt that these values clearly showed that **212** has (3*Z*, 5*Z*)-stereochemistry. X-ray crystallography also determined the stereochemistry of the double bonds as *Z*.

Throughout our studies of these compounds no trace of the eight-membered cyclic dienylsilanes were detected.

1. Four novel compounds were synthesised and characterised.

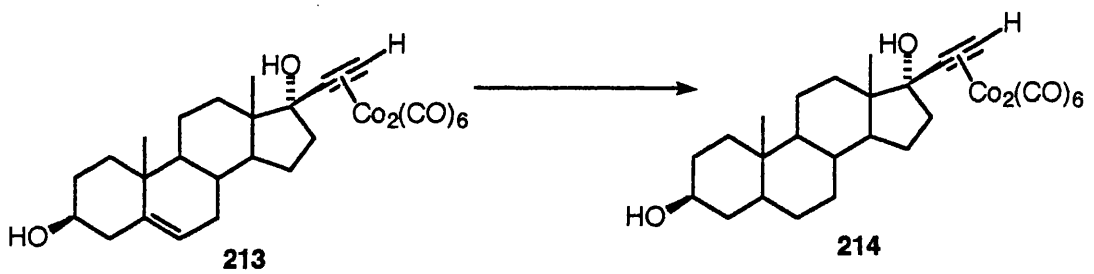
2. Despite many attempts and many different approaches, the silicon-oxygen tethered Pauson-Khand substrates did not cyclise.

Chapter 6

The Nicholas Reaction

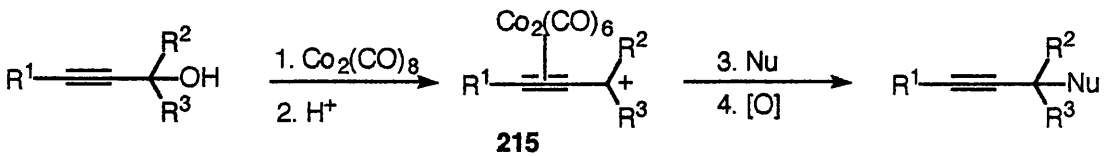
6.1.1 Background

In 1971, Nicholas and Petit detailed the use of dicobalt octacarbonyl as a protecting group of an alkyne.[119] Reactions were conducted on an organic compound containing a double and triple bond **213** and while the triple bond was protected, reactions could be carried out selectively on the double bond. The double bond was reduced using BH_3 followed by treatment with acetic acid to yield product **214** in 60 % yield (*Scheme 130*). The metal moiety could be easily removed in excellent yield at the end of the reaction sequence by oxidative degradation using $Fe(NO_3)_3.9H_2O$.



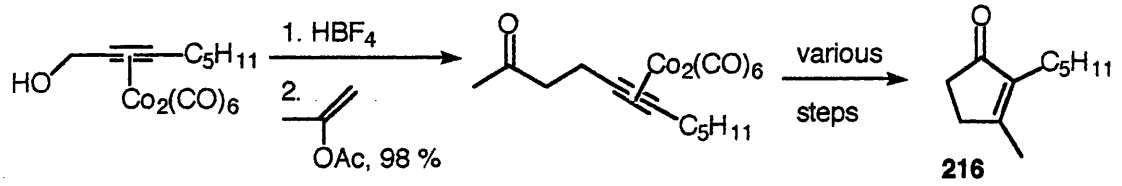
Scheme 130

The cobalt carbonyl bound to the triple bond was also found to have a stabilising effect on the carbocation produced on the α-carbon **215** created by reaction with a Lewis acid, such as boron trifluoroetherate.[119] The carbocation **215** was then susceptible to attack by a nucleophile and this reaction was named the Nicholas reaction (*Scheme 131*).[118]



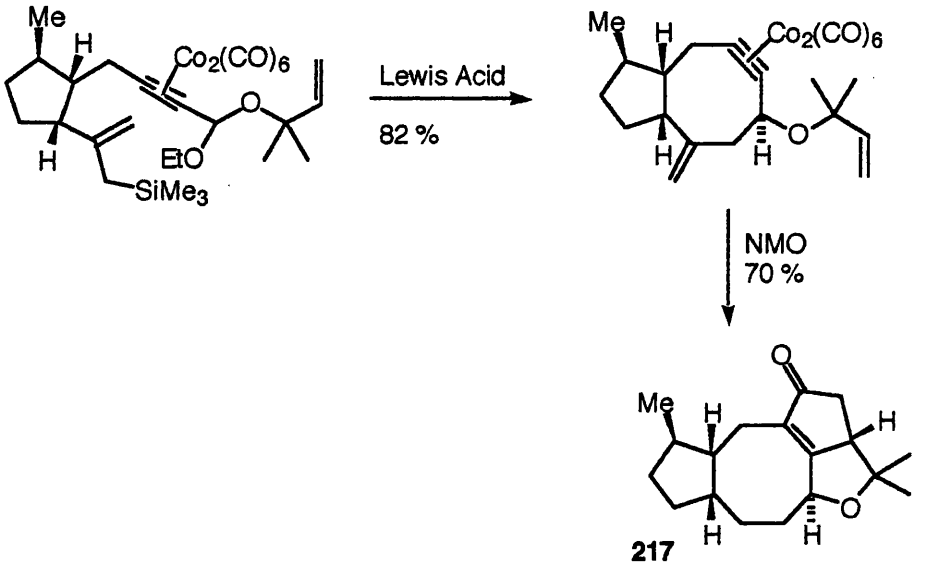
Scheme 131

The Nicholas reaction has been widely used in organic synthesis and especially in natural product synthesis. Padmanabham and Nicholas synthesised dihydrojasmone **216**, in only 6 steps (*Scheme 132*).[120]



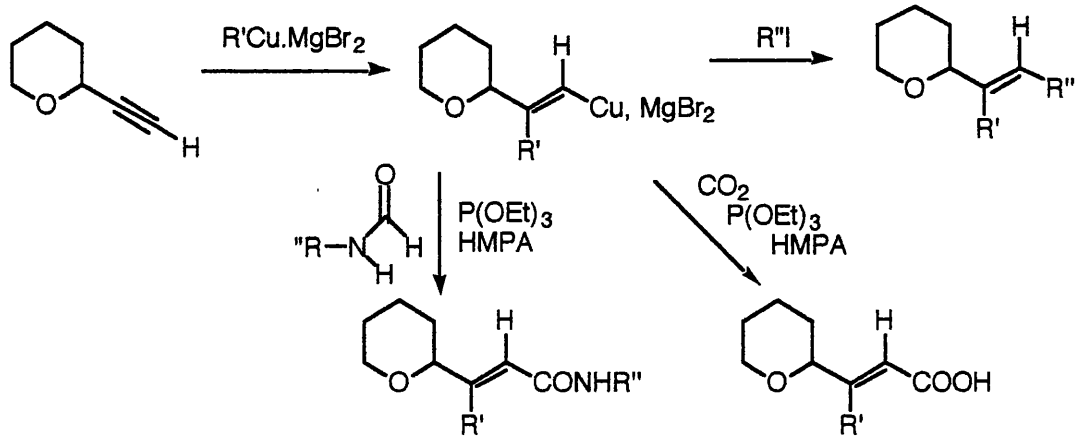
Scheme 132

Schreiber and co-workers have also made excellent use of the cobalt based reactions. In their synthesis of (+)-epoxydictymene **217** they used a Nicholas reaction followed by a PKR to give product **217** in 57 % overall yield from the two key steps (*Scheme 133*).[121]



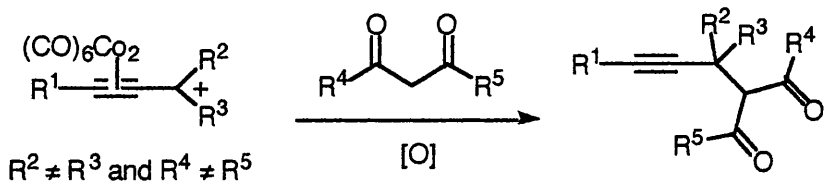
Scheme 133

The attractiveness of the alkyne group was that it could be reacted further to introduce more functionality into the molecule (*Scheme 134*).[122]



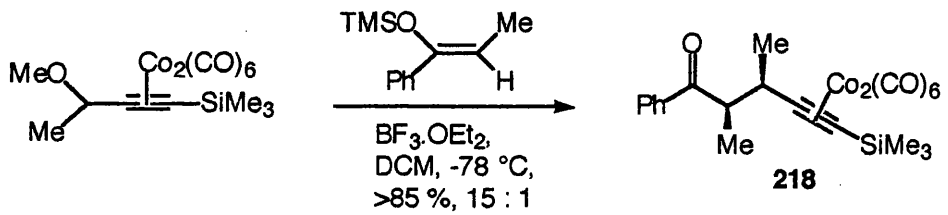
Scheme 134

The major limitation of the Nicholas reaction has been the unpredictabiltity of the stereoselectivity in the reaction. Nicholas found that reactions of chiral complexes with prochiral β-diketones were found to proceed with diastereoselectivities of between 2:1 to 15:1 (*Scheme 135*).[118]



Scheme 135

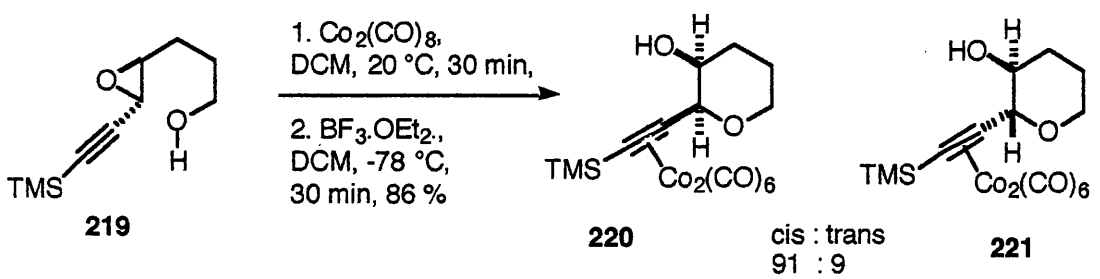
Schreiber and co-workers found that the synthesis of alkylated products made by the Nicholas reaction went predominantly *syn* (*Scheme 136*).[123]



Scheme 136

In most cases the *Z* enol ether provided higher levels of diastereoselectivity than the *E* enol ether. Decomplexation of **218** proceeded in high yields using $TMANO.2H_2O$ or ferric nitrate and with preservation of the diastereoselectivity of the products.[118]

A procedure for the synthesis of tetrahydropyran skeletons had been developed by Hanaoka and co-workers[124] and involved the use of an epoxide **219** to induce stereoselectivity in compounds **220** and **221** (*Scheme 137*).



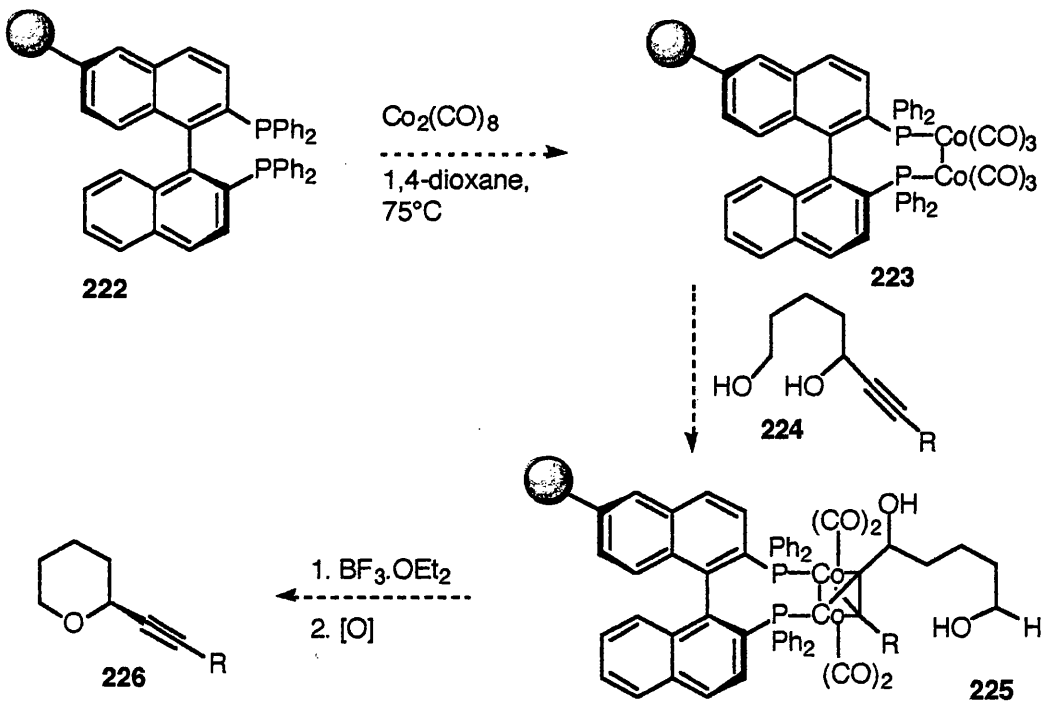
Scheme 137

However, the route of Hanaoka and co-workers relied on the stereochemistry of the epoxide **219**.

Although some stereoselectivity has been observed in the Nicholas reaction it remains unpredictable and relies on the stereoselectivity present in the alkyne component.

6.1.2 Proposed Work

The Nicholas reaction has proven to be very useful in natural product synthesis and particularly for the synthesis of the tetrahydropyran skeleton.[125] We proposed to start with polymer supported BINAP **222** and attach dicobalt octacarbonyl onto it, to form the cobalt complexed precursor **223**. Gibson and her group[102] have shown that dicobalt octacarbonyl could be attached to a non-chiral phosphorus based polymeric support and used in catalytic amounts in the Pauson-Khand reaction. The complex **223** would react with the alkyne **224** to form complex **225** and further reaction with a Lewis acid[123] would lead to the Nicholas reaction product **226** (*Scheme 138*).

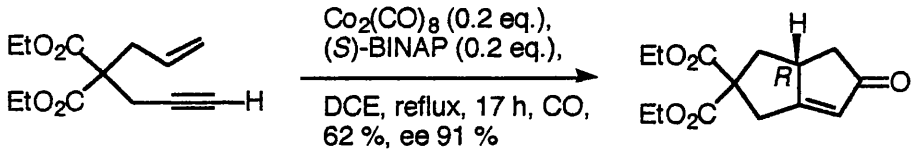


Scheme 138

Our method was only reliant on the chirality of the BINAP ligand **222**. Either the (*R*) or (*S*)-BINAP ligand, or other chiral phosphine ligands could be used to induce the correct stereochemistry in our target compound. It was thought that other functionality

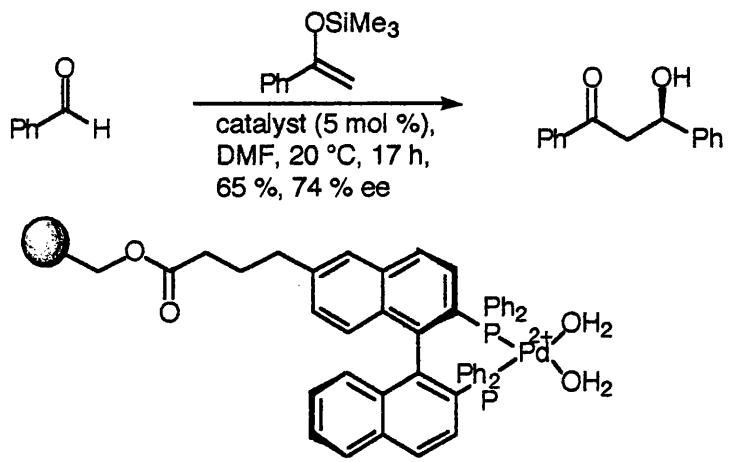
could be built into the acyclic starting material to provide a simple route to functionalised tetrahydropyran ring systems.

The chirality induced by the BINAP ligand could be utilised to synthesise the tetrahydropyran skeleton stereoselectively. Hiroi and his group[126] have used (*S*)-BINAP as a chiral catalyst to induce stereoselectivity in the Pauson-Khand reaction but it has not been used when the BINAP ligand is attached to a solid support (*Scheme 139*).



Scheme 139

There are also examples by Bayston and co-workers[127] using polymer supported BINAP as a hydrogenation catalyst and by Fujii and Sodeoka[128] as a catalyst for asymmetric aldol reactions and Mannich-type reactions (*Scheme 140*).



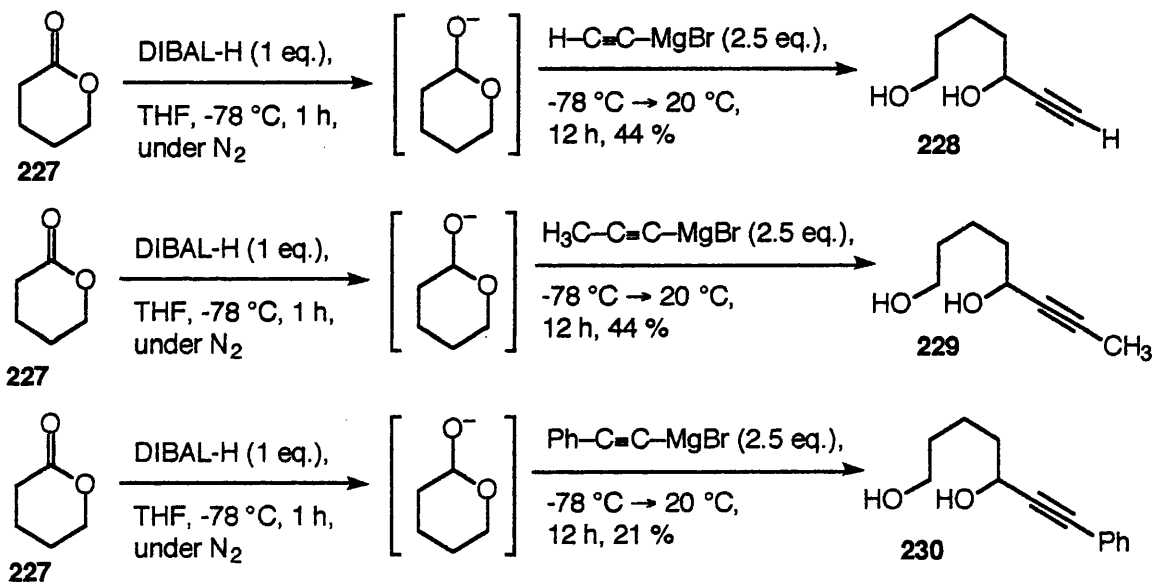
Scheme 140

The major advantages of using the polymer supported BINAP cobalt complex **223** would be that the complex would be relatively air-stable, compared to dicobalt octacarbonyl and the product and ligand **222** could be easily separated and purified. Other advantages would be that further reactions could be carried out utilising the

chirality induced by the BINAP ligand before removal of the metal moiety. After removal of the metal moiety, the ligand **222** could be stored and recycled.

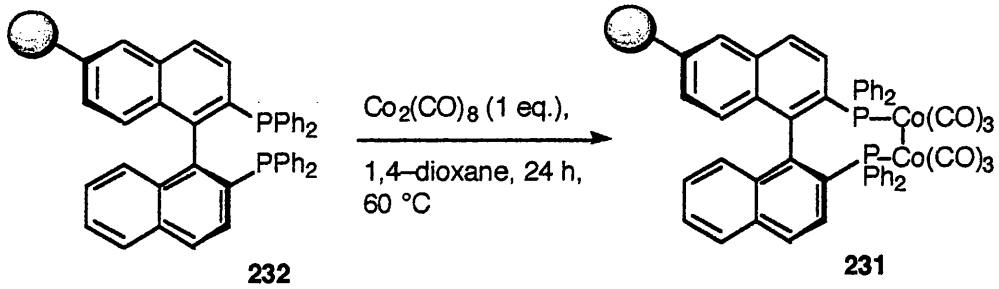
6.2 Results and Discussion

∂-Valerolactone **227** was reduced using DIBAL-H. 2.5 equivalents of the appropriate Grignard reagent were added and the mixture was slowly warmed to room temperature. Following aqueous work-up the reaction mixture was purified using column chromatography on silica gel. The columns had to be run twice to yield products **228, 229** and **230** of the desired purity (*Scheme 141*).



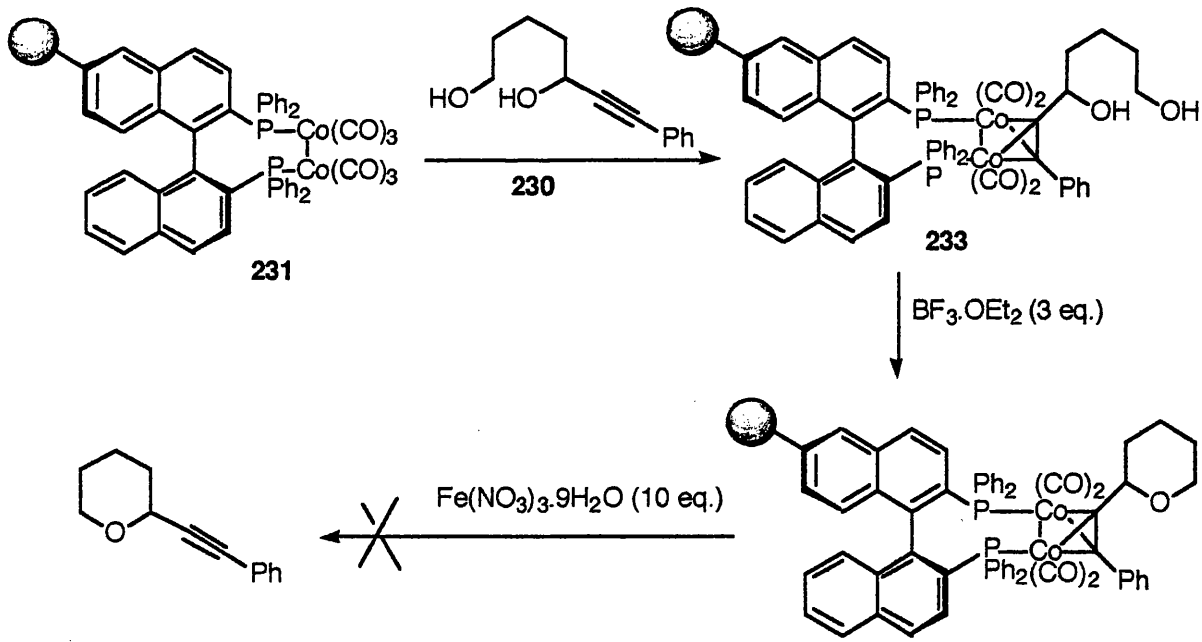
Scheme 141

The procedure of Gibson and co-workers[102] was adapted to synthesise cobalt complexed (-)-BINAP **231**. The resin **232** was swollen in 1,4-dioxane for 30 minutes before dicobalt octacarbonyl was added. The reaction was shaken at room temperature for 30 minutes before being shaken at 60 °C for 24 hours. The solvent was drained off and the mixture washed alternately using THF and Et_2O. The purple beads were washed using DCM and dried under vacuum (*Scheme 142*).



Scheme 142

The beads **231** were swollen in DCM for 30 minutes before cooling to -78 °C for 30 minutes (*Scheme 143*). Substrate **230** was added and the mixture shaken at -78 °C for 30 minutes. Three equivalents of the Lewis acid, $BF_3.OEt_2$ was added and the mixture shaken at -78 °C for a further 30 minutes. After distilled water was added, the reaction mixture was slowly warmed to room temperature and shaken for 2 hours. The solvent was removed and after aqueous work-up ^1H NMR spectroscopy was run.



Scheme 143

6.3 Conclusions

It looked as though there was a mixture of starting material **230** and cobalt complexed material **233** and the solution also looked purple. Ferric nitrate was used to remove the cobalt complex[119] but unfortunately only starting material **230** was isolated (*Scheme 143*). However, we took it as a promising sign that the starting material

appeared to have been attached to the cobalt complex. Unfortunately, owing to time restrictions no further work has been carried out on this project.

Chapter 7

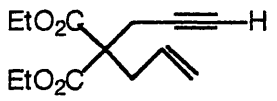
7 Experimental

7.1 General Details

Reagents were purchased from Aldrich Chemical Company (Gillingham, UK), Lancaster Synthesis (Morecambe, UK), Avocado (Heysham, UK) and were used without further purification. Solid phase resin were purchased from CN Biosciences (Nottingham, UK) and dicobalt octacarbonyl was purchased from Strem (Bischheim, France). Organic solvents were obtained from Rhône–Poulenc–Rorer and were dried, where necessary, using the procedures described by Leonard, Lygo and Procter. Bulb to bulb distillations were carried out in a Buchi GKR-50 Kugelrohr oven. Glassware was dried for at least 30 minutes in an oven at approximately 140 °C. Melting points were recorded in open capillaries using a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz respectively, unless otherwise stated. ^{13}C NMR spectra were assigned with the aid of Distortionless Enhancement by Polarisation Transfer (DEPT)–edited spectra. All chemical shifts (δ) are given in ppm relative to residual $CHCl_3$ (δ = 7.26) and (δ = 77.0) in $CDCl_3$ solutions. Figures in brackets in ^{13}C NMR indicate the number of hydrogen attached to the carbon atom. All coupling constants are measured in Hz. Thin layer chromatography was performed using Merck aluminium–backed silica plates of 0.25 mm thickness. Chromatograms were visualised using UV conditions at 254 nm, staining with iodine or using a variety of common stains prepared by the methods described by Leonard, Lygo and Procter. Column chromatography was carried out on silica gel (particle size 70 – 230 mesh) or deactivated neutral alumina (standard grade, ca. 150 mesh). Mass spectra (MS) were recorded on AEI MS12 or MS902 spectrometers using the electron–impact ionisation (EI) mode or, if stated, chemical ionisation (CI) or fast atom bombardment (FAB) modes. Infra–red (IR) spectra were recorded on Nicolet Impact 410 or Jasco FT-IR spectrometers.

7.2 Experimental for Chapter 2

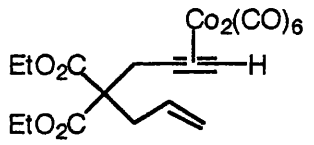
Diethyl 6-hepten-1-yne-4,4-dicarboxylate[129] 107



107

Sodium hydride (0.27 g, 6.75 mmol, 60 wt % in mineral oil) was washed with dry diethyl ether and dried under vacuum before being added portion-wise to a solution of diethylallylmalonate (1.00 g, 4.99 mmol) in THF (25 ml) at room temperature. Propargyl bromide (0.72 ml, 7.00 mmol, 80 wt % in toluene) was added dropwise and the mixture stirred for 18 h. The solution was then subjected to aqueous work-up using saturated aqueous ammonium chloride (1 x 20 ml), DCM (4 x 30 ml), distilled water (3 x 50 ml) and brine (2 x 50 ml). The organic layer was dried over anhydrous magnesium sulfate. Following filtration and removal of the organic solvent under reduced pressure the resultant liquid was purified using bulb-to-bulb distillation. The title compound **107** (1.10 g, 4.62 mmol, 93%) was obtained as a colourless oil. Boiling range 80 – 100 °C @ 0.02 mm Hg ; υ_{max}(thin film)/cm^{-1} 3284, 3081, 2983, 2938, 2908, 2875, 1753, 1642, 1368, 925 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 5.61 (1H, ddt, J = 17, 10, 7.5 Hz, C*H*=CH_2), 5.17 (1H, dd, J = 17, 1.8 Hz, CH=C*H*$_2$), 5.11 (1H, dd, J = 10, 1.9 Hz, CH=C*H*$_2$), 4.19 (4H, q, J = 7.1 Hz, 2(C*H*$_2$–O)), 2.81 – 2.76 (4H, m, 2(C*H*$_2$–CO)), 2.00 (1H, t, J = 2.7 Hz, C≡C*H*), 1.24 (6H, t, J = 7.1 Hz, CH_2–2(C*H*$_3$)) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 169.7 (2C, 0), 131.7 (1), 119.8 (2), 78.9 (0), 71.4 (1), 61.6 (2), 56.8 (0), 36.3 (2), 22.5 (2C, 2), 14.0 (2C, 3) ; *m/z* (CI, isobutane) 239 [(M + H)$^+$, 100 %], 211 (4), 193 (8), 165 (9), 164 (3), 137 (4), 119 (2), 91 (3), 79 (1). Found : (M + H)$^+$, 239.1282. $C_{13}H_{19}O_4$ requires *M*, 239.1283. The ^{1}H and ^{13}C NMR data give good agreement with the published values.[129]

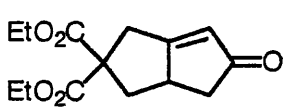
Hexacarbonyl Diethyl 6-hepten-1-yne-4,4-dicarboxylate Dicobalt[11] 29



29

Dicobalt octacarbonyl (3.97 g, 11.6 mmol) was introduced to a two-necked round-bottomed flask under nitrogen. Pet. ether (40 / 60) (20 ml) was added and the mixture stirred at room temperature for 5 min. Diethyl 6-hepten-1-yne-4,4-dicarboxylate **107** (2.27 g, 10.0 mmol) was dissolved in pet. ether (40 / 60) (6 ml) and added dropwise. The mixture was stirred for 3 - 4 h and then filtered through a pad of celite. The crude product was purified by column chromatography on silica gel. (pet. ether (40 / 60) : diethyl ether, 100 : 0 to 80 : 20, gradient elution). The title compound **29** (4.16 g, 7.94 mmol, 83%) was obtained as a dark red viscous gum. It was stored under nitrogen and in the freezer. υ_{max}(thin film)/cm^{-1} 2984, 2093, 2051, 2020, 1734, 1466, 1446, 1367, 1284, 1212, 1189, 1142, 1095, 1070, 923, 857 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 5.98 (1H, s, C≡C*H*), 5.71 (1H, ddt, J = 17, 10, 7.2 Hz, C*H*=CH_2), 5.20 – 5.11 (2H, m, C=CH_2), 4.26 (2H, dq, J = 7.1, 3.7 Hz, O–CH_2), 4.16 (2H, dq, J = 7.1, 3.6 Hz, O–CH_2), 3.63 (2H, s, CH_2), 2.77 (2H, d, J = 7.3 Hz, CH_2), 1.26 (6H, t, J = 7.1 Hz, 2(CH_3)) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 170.0, 131.8, 120.0, 76.7, 65.9, 61.7, 37.6, 36.7, 31.6, 22.6, 15.3, 14.1, 14.0 ; MS (CI, ammonia) 541.5 ((M + NH_4)$^+$, 7 %), 256 (58).

5-Oxo-3,3a,4,5-tetrahydro-1H-pentalene-2,2-dicarboxylic acid diethyl ester 30



30

General Procedure A

Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 equivalent) was dissolved in toluene (25 ml). The appropriate amine (3 equivalents) was

added dropwise. The reaction mixture was stirred under air at room temperature for 4 d. The crude product **30** was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The results are summarised in Table 1.

υ_{max} (thin film)/cm^{-1} 3077, 2982, 2938, 1731, 1637, 1447, 1414, 822 ; δ (^1H) (400 MHz ; $CDCl_3$) 5.92 (1H, broad s, C=C*H*), 4.21 (4H, dq, J = 16, 7.1 Hz, CH_2–O), 3.34 (1H, d, J = 19 Hz, C*H*2–C=O), 3.24 (1H, d, J = 19 Hz, C*H*2–C=O), 3.08 (1H, broad s, CH2–C*H*–CH2), 2.78 (1H, dd, J = 13, 7.7 Hz, CH_2), 2.62 (1H, dd, J = 18, 7.4 Hz, CH_2), 2.11 (1H, dd, J = 18, 3.3 Hz, CH_2), 1.72 (1H, t, J = 13 Hz, C*H*), 1.25 (6H, dt, J = 10, 7.1 Hz, 2(CH_3)) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 209.5 (0), 185.5 (0), 171.4 (0), 170.7 (0), 125.5 (1), 62.1 (2), 62.0 (2), 60.8 (0), 45.0 (1), 42.1 (2), 38.8 (2), 35.1 (2), 14.0 (2C, 3) ; m/z (EI) 266 [(M + H)+, 43 %], 221 (22), 221 (18), 192 (61), 164 (25), 163 (24), 119 (100), 91 (55), 65 (11). ^1H and ^{13}C NMR spectral data of **30** gave good agreement with the literature values.[17]

General Procedure B

Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 equivalent) was dissolved in the appropriate solvent. The appropriate amine (3 equivalents) was added dropwise. The reaction mixture was stirred under air at 20 °C for 4 d. The crude product **30** was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The results are summarised in Table 2.

General Procedure C

Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 equivalent) was dissolved in the appropriate solvent. NMM (3 equivalents) was added dropwise. The reaction mixture was stirred under air at 50 °C for 24 h. The crude product **30** was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The results are summarised in Table 3.

General Procedure D

Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 equivalent) was dissolved in the appropriate solvent. NMM (3 equivalents) was added dropwise. The reaction mixture was stirred under air at 50 °C for 48 h. The crude product **30** was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The results are summarised in Table 4.

General Procedure E

Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 equivalent) was dissolved in the appropriate solvent. NMM (3 equivalents) was added dropwise. The reaction mixture was stirred under air at 20 °C for 4 days. The crude product **30** was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The results are summarised in Table 5.

General Procedure F

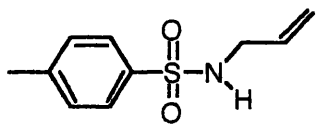
Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 equivalent) was dissolved in the appropriate solvent. The appropriate amine (3 equivalents) was added dropwise. The reaction mixture was stirred under air at the appropriate temperature for the appropriate time. The crude product **30** was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The results are summarised in Table 6.

The cyclopentanone **144** (0.04 g, 0.15 mmol, 31 %) was obtained as a brown oil. δ (^{1}H) (400 MHz ; $CDCl_3$) 4.18 (4H, dq, J = 12, 7.2 Hz, 2(CH_2–O)), 2.82 (2H, m, 2(C*H*)), 2.66 (2H, dd, J = 14, 7.7 Hz, CH_2), 2.48 (2H, dd, J = 19, 9.2 Hz, CH_2), 2.12 (2H, dd, J = 19, 4.1 Hz, CH_2), 1.99 (2H, dd, J = 14, 6.8 Hz, CH_2), 1.24 (6H, q, J = 7.9 Hz, 2(CH_3)) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 218.6 (0), 172.0 (0), 171.8 (0), 137.6 (0), 61.6 (2C, 2), 43.8 (2C, 2), 40.5 (2C, 2), 39.3 (2C, 1), 14.0 (2C, 3). ^{1}H and ^{13}C NMR spectral data of **30** gave good agreement with the literature values.[17]

Deuteriated Reactions

Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 equivalent) was dissolved in toluene (25 ml). Brucine (3 equivalents) was dissolved in the appropriate deuterated alcohol (15 ml) and added. The reaction mixture was stirred at room temperature for 5 d. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The results are summarised in chapter 2, page 54.

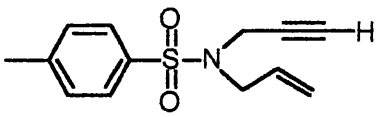
***N*-Allyl-toluene-4-sulfonamide 234**



234

Allylamine (1.31 ml, 17.4 mmol) was dissolved in DCM (50 ml), placed under nitrogen and cooled to 0 °C. Triethylamine (3.20 ml, 15.5 mmol) was added dropwise. DMAP (0.22 g, 1.80 mmol) and tosyl chloride (4.10 g, 21.5 mmol) were dissolved in DCM (15 ml) and added *via* cannula to the reaction mixture. The reaction mixture was slowly warmed to room temperature and stirred for 6 h. The reaction mixture was washed with distilled water (2 x 50 ml), brine (2 x 75 ml) and separated. The organic layer was dried over anhydrous magnesium sulfate, filtered and the organic solvent removed under reduced pressure. The crude product was recrystallised from hot diethyl ether / pet. ether. The white / yellow crystals were filtered and washed with pet. ether to yield the title compound **234** (2.86 g, 13.6 mmol, 77 %). m.p. ; 56 – 58 °C (Lit.[130] 63 – 65 °C) ; υ_{max}(solution)/cm^{-1} 3253, 2890, 2820, 1596, 1425, 1327, 1162, 1093, 1064, 811 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.75 (2H, d, J = 8.3 Hz, Aryl–*H*), 7.31 (2H, d, J = 7.9 Hz, Aryl–*H*), 5.71 (1H, ddt, J = 17, 10, 5.9 Hz, C*H*=CH_2), 5.17 (1H, dd, J = 17, 1.3 Hz, CH=CH_2), 5.10 (1H, dd, J = 10, 1.2 Hz, CH=CH_2), 4.30 (1H, broad s, N*H*), 3.59 (2H, distorted t, J = 6.0 Hz, CH_2), 2.43 (3H, s, CH_3) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 143.5 (0), 136.6 (1), 132.9 (0), 129.7 (2C, 1), 127.1 (2C, 1), 117.7 (2), 45.8 (2), 21.5 (3) ; *m/z* (EI) 211 [(M + H)$^+$, 10%], 155 (38), 147 (20), 120 (8), 91 (100), 89 (6), 56 (34). The ^{1}H NMR spectral data gave good agreement with the literature values.[130]

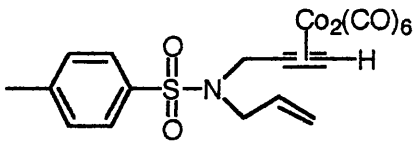
4-Methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide[131] 120



120

N-Allyl-toluene-4-sulfonamide **234** (1.00g, 4.74 mmol) was dissolved in THF (200 ml) at room temperature. Sodium hydride (0.25 g, 10.0 mmol, 60 wt % in mineral oil) was washed with dry diethyl ether and dried under vacuum before being added portion-wise to the solution and stirred for 5 h. Propargyl bromide (0.69 ml, 5.80 mmol, 80 wt % in toluene) was added dropwise and the reaction mixture stirred at room temperature for 7 d. Saturated aqueous ammonium chloride (100 ml) was added to quench the reaction and the organic solvent was removed under reduced pressure. The aqueous residue was washed with diethyl ether (2 x 30 ml). The organic layer was washed with saturated aqueous ammonium chloride (1 x 30 ml), distilled water (2 x 50 ml) and brine (2 x 50 ml) and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent removed under reduced pressure. The compound was purfied using column chromatography on silica gel (pet. ether (40 / 60) : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **120** (0.65 g, 2.6 mmol, 55 %) was obtained as white crystals. m.p. ; 59 – 62 °C (Lit.[131] 62 – 63 °C) ; υ_{max} (solution)/cm^{-1} 3306, 3148, 3085, 2980, 2928, 2245, 1645, 1598, 1420, 1346, 1152, 1088 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.73 (2H, d, J = 8.3 Hz, Aryl-*H*), 7.30 (2H, d, J = 8.0 Hz, Aryl-*H*), 5.73 (1H, ddt, J = 17, 10, 6.5 Hz, C*H*=CH_2), 5.29 (1H, dd, J = 17, 1.4 Hz, C=C*H*$_2$), 5.24 (1H, dd, J = 10, 1.1 Hz, C=C*H*$_2$) 4.09 (2H, d, J = 2.4 Hz, C*H*$_2$), 3.83 (2H, d, J = 6.5 Hz, C*H*$_2$), 2.43 (3H, s, C*H*$_3$), 2.00 (1H, t, J = 2.4 Hz, C≡C*H*) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 143.4 (0), 135.9 (0), 131.8 (1), 129.4 (2C, 1), 127.7 (2C, 1), 119.9 (2), 76.4 (0), 73.7 (1), 48.9 (2), 35.7 (2), 22.0 (3) ; *m/z* (EI) 249 [$(M + H)^+$, 8 %], 222 (7), 184 (12), 155 (37), 91 (100), 65 (29), 63 (5). The ^{1}H and ^{13}C NMR spectral data gave good agreement with the literature values.[131]

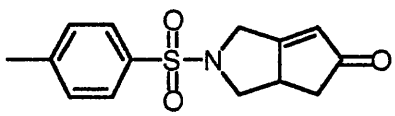
Hexacarbonyl 4-methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide Dicobalt[11] 235



235

Dicobalt octacarbonyl (3.22g, 9.42 mmol) was introduced to a two-necked round-bottomed flask under nitrogen. Pet. ether (40 / 60) (20 ml) was added and the mixture stirred at room temperature for 5 min. 4-Methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide **234** (1.95 g, 7.85 mmol) was dissolved in pet. ether (40 / 60) (15 ml) and diethyl ether (15 ml) and added dropwise. The mixture was stirred for 4 h and then filtered through a pad of Celite. The crude product was purified by column chromatography on silica gel. Pet. ether (40 / 60) eluted the excess starting material and the product was eluted using 5 : 1 pet. ether (40 / 60) : diethyl ether. The title compound **235** (3.96 g, 7.4 mmol, 95%) was obtained as a red liquid. δ (^{1}H) (400 MHz ; $CDCl_3$) 7.73 (2H, d, J = 8.3 Hz, Aryl-*H*), 7.31 (2H, d, J = 8.2 Hz, Aryl-*H*), 6.01 (1H, s, C≡C*H*), 5.54 (1H, ddt, J = 17, 10, 6.7 Hz, C*H*=CH_2), 5.20 (1H, dd, J = 17, 1.2 Hz, C=CH_2), 5.16 (1H, distorted t, C=CH_2), 4.50 (2H, s, CH_2), 3.83 (2H, d, J = 6.6 Hz, CH_2), 2.43 (3H, s, CH_3).

2-(Toluene-4-sulfonyl)-2,3,4a,4-tetrahydro-1H-cyclopenta[c]pyrrol-5-one 122

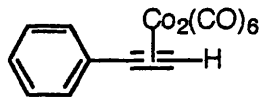


122

Hexacarbonyl 4-methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide dicobalt **235** (0.76 g, 1.42 mmol) was dissolved in toluene (25 ml). *N*-Methyl morpholine (0.47 ml, 4.26 mmol) was added dropwise. Isopropanol (5 ml) was added. The reaction mixture was stirred at 50 °C for 24 h. The crude product was purified

using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title product **122** (0.24 g, 8.66 mmol, 62 %) was obtained as small, white crystals. m.p. : 140 – 143 °C (Lit.[61] 142 – 145 °C) ; υ_{max} (solution cell)/cm^{-1} 3155, 2984, 2902, 1794, 1714, 1650, 1471, 1382, 1351, 1164 ; δ (^1H) (400 MHz ; $CDCl_3$) 7.73 (2H, d, J = 8.2 Hz, Aryl–*H*), 7.35 (2H, d, J = 8.1 Hz, Aryl–*H*), 5.85 (1H, s, C*H*=C), 4.34 (1H, d, 17 Hz, C*H*), 4.08 – 3.90 (2H, m, CH_2), 3.16 (1H, broad s, C*H*), 2.66 – 2.55 (2H, m, CH_2), 2.44 (3H, s, CH_3), 2.06 (1H, dd, J = 18, 3.5 Hz, C*H*) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 208.0 (0), 179.0 (0), 144.2 (0), 133.5 (0), 130.3 (2C, 1), 127.7 (2C, 1), 126.4 (1), 52.7 (2), 47.9 (2), 44.2 (1), 40.0 (2), 22.0 (3) ; *m/z* (EI) 277 [$(M + H)^+$, 100 %], 249 (8), 213 (2), 184 (3), 155 (30), 139 (5), 122 (34), 91 (68), 65 (25), 39 (9). The ^1H NMR spectral data gave good agreement with the literature values.[61]

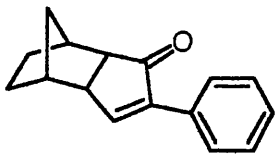
Hexacarbonyl Phenylacetylene Dicobalt[132] 20



20

Dicobalt octacarbonyl (2.00g, 5.85 mmol) was introduced to a two-necked round-bottomed flask under nitrogen. Pet. ether (40 / 60) (25 ml) was added and the mixture stirred at room temperature for 5 min. Phenylacetylene **94** (0.58 ml, 5.32 mmol) was added dropwise. The mixture was stirred for 4 h and then filtered through a pad of Celite. The crude product was purified by column chromatography on silica gel using pet. ether as the eluent. The title compound **20** (2.09 g, 5.38 mmol, 100%) was obtained as small red crystals. δ (^1H) (400 MHz ; $CDCl_3$) 7.55 – 7.50 (2H, m, Aryl–*H*), 7.37 – 7.30 (3H, m, Aryl–*H*), 6.38 (1H, s, C≡C*H*). The ^1H NMR spectral data gave good agreement with the literature values.[132]

2-Phenyl-3a,4,5,6,7,7a-hexahydro-4,7-methano-inden-1-one 41

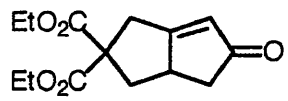


41

Hexacarbonyl phenylacetylene dicobalt **20** (1.03 g, 2.65 mmol) was dissolved in toluene (15 ml). Norbornene **39** (0.25 g, 2.65 mmol) was dissolved in toluene (10 ml) and added to the mixture. *N*-Methylmorpholine (0.87 ml, 7.95 mmol) was added dropwise. Isopropanol (5 ml) was added. The reaction mixture was stirred at 50 °C for 24 h. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title product **41** (0.54 g, 2.41 mmol, 90%) was obtained as pink crystals. m.p. ; 86 – 88 °C (Lit.[24] 95 °C) ; υ_{max} (solution cell)/cm^{-1} 3155, 3037, 2961, 2912, 2875, 1794, 1696, 1561, 1473, 1382, 774 ; δ (^1H) (400 MHz ; $CDCl_3$) 7.72 – 7.68 (2H, m, Aryl–*H*), 7.64 (1H, d, J = 2.9 Hz, C=C*H*), 7.40 – 7.30 (3H, m, Aryl–*H*), 2.71 (1H, distorted t, C*H*), 2.51 (1H, d, 3.9 Hz, C*H*), 2.38 (1H, d, J = 5.2 Hz, C*H*), 2.28 (1H, d, J = 4.1 Hz, CH), 1.76 – 1.57 (2H, m, CH_2), 1.42 – 1.29 (2H, m, CH_2), 1.13 (1H, dt, J = 11, 1.8 Hz, C*H*), 1.01 (1H, dt, J = 11, 1.3 Hz, C*H*) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 208.0 (0), 159.2 (1), 145.1 (0), 140.0 (0), 130.5 (1), 127.4 (2C, 1), 126.1 (2C, 1), 54.0 (1), 46.8 (1), 38.5 (1), 37.4 (1), 30.3 (2), 28.2 (2), 27.4 (2) ; *m/z* (EI) 224 [$(M + H)^+$, 100 %], 196 (18), 167 (13), 158 (55), 128 (22), 115 (12), 102 (10), 67 (7). The ^1H and ^{13}C NMR gave good agreement with the literature values.[24]

7.3 Experimental for Chapter 3

Synthesis of 5-Oxo-3,3a,4,5-tetrahydro-1H-pentalene-2,2-dicarboxylic acid diethyl ester 30



30

General Procedure G

The appropriate number of equivalents of morpholinomethyl resin **156** were swollen in THF (15 ml) for approximately 15 minutes. Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 eq.) was dissolved in THF (5 ml) and added to the resin. The reaction mixture was shaken at 40 °C for 6 hours. The mixture was washed using 50 ml of DCM, 50 ml of diethyl ether and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 7.

General Procedure H

Three equivalents of morpholinomethyl resin **156** were swollen in THF (15 ml) for approximately 15 minutes. Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 eq.) was dissolved in THF (5 ml) and added to the resin. The reaction mixture was shaken at 40 °C for 18 hours. The mixture was washed using 50 ml of DCM, 50 ml of diethyl ether and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 8.

General Procedure I

The appropriate number of equivalents of morpholinomethyl resin **156** were swollen in THF (15 ml) for approximately 15 minutes. Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 eq.) was dissolved in THF (5 ml) and added to

the resin. The reaction mixture was shaken at 40 °C for 24 hours. The mixture was washed using 50 ml of DCM, 50 ml of diethyl ether and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 9.

General Procedure J

The appropriate number of equivalents of morpholinomethyl resin **156** were swollen in the appropriate solvent (15 ml) for approximately 15 minutes. Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 eq.) was dissolved in the appropriate solvent (5 ml) and added to the resin. The reaction mixture was shaken at 40 °C for 18 hours. The mixture was washed using 50 ml of DCM, 50 ml of diethyl ether and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 10.

General Procedure K

The appropriate number of equivalents of morpholinomethyl resin **156** were swollen in the appropriate solvent (15 ml) for approximately 15 minutes. Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** (1 eq.) was dissolved in the appropriate solvent (5 ml) and added to the resin. The reaction mixture was shaken at 50 °C for 18 hours. The mixture was washed using 50 ml of DCM, 50 ml of diethyl diethyl ether and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 11.

General Procedure L

The appropriate number of equivalents of polyamine resin **163** were swollen in THF (15 ml) for approximately 15 minutes. Hexacarbonyl diethyl 6-hepten-1-yne-4,4-

dicarboxylate dicobalt **29** (1 eq.) was dissolved in THF (5 ml) and added to the resin. The reaction mixture was shaken at 40 °C for the appropriate length of time. The mixture was washed using 50 ml of DCM, 50 ml of diethyl ether and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 12.

General Procedure M

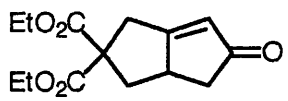
Three equivalents of polyamine resin **163** were swollen in DCM (15 ml) for approximately 15 minutes. Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** was dissolved in DCM (5 ml) and added to the resin. The reaction mixture was shaken at 20 °C for the appropriate length of time. The mixture was washed using 50 ml of DCM, 50 ml of diethyl ether and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 13.

General Procedure N

Three equivalents of Wang resin **164** were swollen in DCM (15 ml) for approximately 15 minutes. Hexacarbonyl diethyl 6-hepten-1-yne-4,4-dicarboxylate dicobalt **29** was dissolved in DCM (5 ml) and added to the resin. The reaction mixture was shaken at 20 °C for the appropriate length of time. The mixture was washed using 50 ml of DCM, 50 ml of diethyl ether and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 14.

7.4 Experimental for Chapter 4

Synthesis of 5-Oxo-3,3a,4,5-tetrahydro-1H-pentalene-2,2-dicarboxylic acid diethyl ester 30



30

General Procedure O

The appropriate number of equivalents of morpholinomethyl resin **156** (3.50 mmol/g) were swollen in THF (5 ml) for approximately 15 minutes. Diethyl 6-hepten-1-yne-4,4-dicarboxylate**107**(1 eq.) was dissolved in THF (2 ml) and added to the resin **156**. The appropriate number of equivalents of freshly sublimed dicobalt octacarbonyl were added, followed by THF (1 ml). The reaction mixture was shaken at 40 °C for 18 h. The mixture was washed using DCM (30 ml), diethyl ether (30 ml) and repeated. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 50 : 50, gradient elution). The title compound **30** was obtained as a brown oil. The results are summarised in Table 15.

General Procedure P

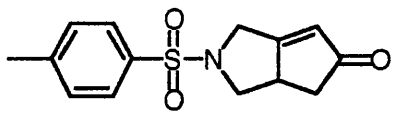
Morpholinomethyl resin **156** (50 mol %) was swollen in THF (20 ml) for approximately 15 minutes. The appropriate alkene (1 eq.) was dissolved in THF (4 ml) and added to the resin. The appropriate alkyne (1 eq.) was dissolved in THF (4 ml) and added to the resin. Freshly sublimed dicobalt octacarbonyl (35 mol %) was added, followed by THF (4 ml). The reaction mixture was shaken at 40 °C for 18 h. The mixture was washed using DCM (30 ml), diethyl ether (30 ml) and repeated.

General Procedure Q

Morpholinomethyl resin **156** (50 mol %) was swollen in DME (20 ml) for approximately 15 minutes. The appropriate alkene (1 eq.) was dissolved in DME (4 ml) and added to the resin. The appropriate alkyne (1 eq.) was dissolved in DME (4 ml) and added to the resin. Freshly sublimed dicobalt octacarbonyl (35 mol %) was

added, followed by DME (4 ml). The reaction mixture was shaken at 40 °C for 18 h. The mixture was washed using DCM (30 ml), diethyl ether (30 ml) and repeated.

2-(Toluene-4-sulfonyl)-2,3,4a,4-tetrahydro-1H-cyclopenta[c]pyrrol-5-one 122



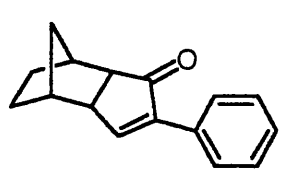
122

Following general procedure P, 4-methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide **120** (0.40 g, 1.64 mmol), morpholinomethyl resin **156** (0.26 g) and dicobalt octacarbonyl (0.21 g, 0.60 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title product **122** (0.08 g, 0.29 mmol, 17 %) was obtained as small, white crystals with a melting range of 140 - 143 °C (Lit.[61] 142 - 145 °C). ^{1}H NMR spectral data gave good agreement with the literature values.[61]

Following general procedure Q*, 4-methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide **120** (0.10 g, 0.41 mmol), morpholinomethyl resin **156** (0.07 g) and dicobalt octacarbonyl (0.05 g, 0.15 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title product **122** (0.054 g, 0.19 mmol, 49 %) was obtained as small, white crystals with a melting range of 140 - 143 °C (Lit.[61] 142 - 145 °C). ^{1}H NMR spectral data gave good agreement with the literature values.[61]

*except that 8 ml of DME were used instead of 32 ml

2-Phenyl-3,3a,4,5,6,7,7a-hexahydro-4,7-methano-inden-1-one 41



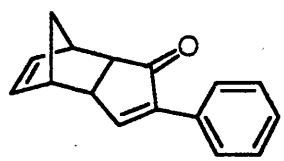
41

Following general procedure P, norbornene **39** (0.17 g, 2.02 mmol), phenylacetylene **94** (0.20 ml, 1.76 mmol), morpholinomethyl resin **156** (0.25 g) and dicobalt octacarbonyl (0.213 g, 0.63 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **41** (0.31 g, 1.38 mmol, 78 %) was obtained as a pale yellow solid with a melting range of 86 - 88 °C (Lit.[24] 95 °C). ^{1}H NMR spectral data gave good agreement with the literature values.[24]

Following general procedure Q*, norbornene **39** (0.04 g, 0.44 mmol), phenylacetylene **94** (0.05 ml, 0.39 mmol), morpholinomethyl resin **156** (0.07 g) and dicobalt octacarbonyl (0.051 g, 0.15 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **41** (0.06 g, 0.27 mmol, 69 %) was obtained as a pale yellow solid with a melting range of 86 - 88 °C (Lit. 95 °C). ^{1}H NMR sprectral data gave good agreement with the literature values[15].

*except that 8 ml of DME was used instead of 32 ml

2-Phenyl-3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one 22



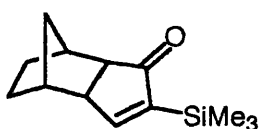
22

Following general procedure P, norbornadiene **21** (0.20 ml, 1.74 mmol), phenylacetylene **94** (0.20 ml, 1.76 mmol), morpholinomethyl resin **156** (0.26 g) and dicobalt octacarbonyl (0.202 g, 0.59 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **22** (0.25 g, 1.13 mmol, 58 %) was obtained as a pale yellow solid. m.p. ; 66 - 68 °C (Lit.[61] 67 - 69 °C) ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.71 (2H, dd, J = 6.9, 1.6 Hz, Aryl-*H*), 7.69 (1H, s, C=C*H*), 7.42 - 7.25 (3H, m Aryl-*H*), 6.34 (1H, dd, J = 5.5, 3.1 Hz, C=C*H*), 6.26 (1H, dd, J = 5.5, 2.9 Hz, C=C*H*), 3.03 (1H, br. s, C*H*), 2.85 (1H, distorted. t, C*H*), 2.79 (1H, br. s, C*H*), 2.48

(1H, dt, J = 5.1, 1.2 Hz, C*H*), 1.43 (1H, dt, J = 9.4, 1.2 Hz, C*H*), 1.34 (1H, br. d, J = 9.4 Hz, C*H*). ^{1}H NMR spectral data gave good agreement with the literature values.[61]

Following general procedure Q, norbornadiene **21** (0.20 ml, 1.74 mmol), phenylacetylene **94** (0.20 ml, 1.76 mmol), morpholinomethyl resin **156** (0.25 g) and dicobalt octacarbonyl (0.220 g, 0.64 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **22** (0.33 g, 1.49 mmol, 85 %) was obtained as a pale yellow solid. m.p. ; 66 - 68 °C (Lit.[61] 67 - 69 °C). The ^{1}H NMR spectral data was identical to the previous experiment.[61]

2-Trimethylsilanyl-3,3a,4,5,6,7,7a-hexahydro-4,7-methano-inden-1-one 166

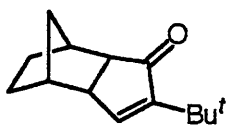


166

Following general procedure P, norbornene **39** (0.17 g, 1.81 mmol), (trimethylsilyl)acetylene **165** (0.24 ml, 1.73 mmol), morpholinomethyl resin **156** (0.25 g) and dicobalt octacarbonyl (0.202 g, 0.61 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **166** (0.049 g, 0.22 mmol, 13 %) was obtained as a yellow oil. υ_{max} (KBr)/cm^{-1} 3033, 2950, 2907, 2873, 1682, 1571, 1279, 1249, 1177 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.56 (1H, d, J = 2.5 Hz, C=C*H*), 2.65 (1H, dd, J = 5.3, 2.5 Hz, C*H*), 2.49 (1H, d, J = 3.6 Hz, C*H*), 2.18 (1H, br. s, C*H*), 2.12 (1H, d, J = 5.2 Hz, C*H*), 1.70 - 1.52 (2H, m, CH_2), 1.35 - 1.22 (2H, m, CH_2), 0.93 (2H, s, CH_2), 0.17 (9H, s, 3(CH_3)) ; δ (^{13}C) (100MHz ; $CDCl_3$) 215.0 (0), 173.0 (1), 54.4 (1), 51.9 (1), 39.1 (1), 38.0 (1), 31.1 (2), 29.1 (2), 28.3 (2), -1.8 (3C, 3) ; *m/z* (EI) 220 [(M + H)$^+$, 8 %], 205 (100), 177 (3), 151 (3), 137 (3), 131 (3), 84 (78), 73 (8), 49 (70), 47 (11) ; Found : (M + H)$^+$, 220.1281. $C_{12}H_{20}OSi$ requires *M*, 220.1283.

Following general procedure Q, norbornene **39** (0.17 g, 1.81 mmol), (trimethylsilyl)acetylene **165** (0.24 ml, 1.73 mmol), morpholinomethyl resin **156** (0.25 g) and dicobalt octacarbonyl (0.220 g, 0.61 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **166** (0.09 g, 0.41 mmol, 23 %) was obtained as a yellow oil. The ^{1}H NMR spectral data were identical to the previous experiment.

2-*tert*-Butyl-3,3a,4,5,6,7,7a-hexahydro-4,7-methano-inden-1-one 168



168

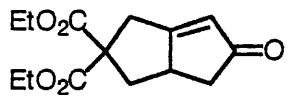
Following general procedure P, norbornene **39** (0.17 g, 1.81 mmol), 3,3-dimethyl-1-butyne **167** (0.21 ml, 1.70 mmol), morpholinomethyl resin **156** (0.25 g) and dicobalt octacarbonyl (0.212 g, 0.61 mmol) were combined. The crude product was purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **168** (0.28 g, 1.20 mmol, 75 %) was obtained as a yellow oil. υ_{max} (thin film)/cm^{-1} 2952, 2867, 1694, 1612, 1475, 1454, 1360, 1319, 1230, 1198, 1059 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.05 (1H, d, J = 2.8 Hz, C=C*H*), 2.48 (1H, dd, J = 5.0, 2.8 Hz, C*H*), 2.36 (1H, d, J = 4.0 Hz, C*H*), 2.13 (2H, d, J = 4.8 Hz, CH_2), 1.70 - 1.52 (2H, m, CH_2), 1.33 - 1.23 (2H, m, CH_2), 1.17 (9H, s, 3(CH_3)), 0.99 – 0.88 (2H, m, CH_2) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 209.6 (0), 156.6 (0), 155.7 (1), 53.9 (1), 46.0 (1), 38.2 (1), 37.2 (1), 30.8 (0), 29.8 (2), 28.2 (2), 27.4 (3C, 3), 27.9 (1) ; *m/z* (EI) 204 [(M + H)$^+$, 100 %], 189 (58), 162 (62), 161 (22), 105 (15), 83 (32), 59 (32), 31 (23) ; Found : (M + H)$^+$, 204.1516. $C_{14}H_{20}O$ requires *M*, 204.1514 ^{13}C NMR and I.R. spectral data gave good agreement with the literature values.[53]

Following general procedure Q, norbornene **39** (0.17 g, 1.81 mmol), 3,3-dimethyl-1-butyne **167** (0.21 ml, 1.70 mmol), morpholinomethyl resin **156** (0.25 g) and dicobalt octacarbonyl (0213 g, 0.61 mmol) were combined. The crude product was

purified using column chromatography on silica gel (hexane : diethyl ether, 100 : 0 to 0 : 100, gradient elution). The title compound **168** (0.19 g, 0.93 mmol, 52 %) was obtained as a yellow oil. ^{1}H NMR spectral data gave good agreement with the previous experiment.[53]

RECYCLING OF RESIN

5-Oxo-3,3a,4,5-tetrahydro-1H-pentalene-2,2-dicarboxylic acid diethyl ester 30



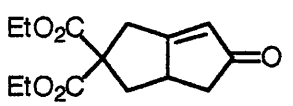
30

Morpholinomethyl resin **156** (50 mol %) was swollen in THF (5 ml) for approximately 15 minutes. Diethyl 6-hepten-1-yne-4,4-dicarboxylate **107** (1 eq.) was dissolved in THF (2 ml) and added to the resin. Dicobalt octacarbonyl (35 mol %) was dissolved in THF (1 ml) and added to the resin. The reaction mixture was shaken at 40 °C for 18 h. The title compound **30** was obtained as a brown oil. ^{1}H NMR spectral data gave good agreement with the literature values.[17]

Resin was washed with a 2 : 1 mixture of THF : HCl (1M) (3 x 25 ml), followed by treatment of the resin with 10 % *N*-ethyl-di-iso-propylamine in DMF (3 x 25 ml) and rinsed with DCM (5 x 10 ml) and dried under nitrogen.

Amounts of acid, amine and DCM washes were increased by 2 with the number of runs.

5-Oxo-3,3a,4,5-tetrahydro-1H-pentalene-2,2-dicarboxylic acid diethyl ester 30



30

Morpholinomethyl resin **156** (50 mol %) was swollen in DME (5 ml) for approximately 15 minutes. Diethyl 6-hepten-1-yne-4,4-dicarboxylate **107** (1 eq.) was dissolved in DME (2 ml) and added to the resin. Dicobalt octacarbonyl (35 mol %) was dissolved in DME (1 ml) and added to the resin. The reaction mixture was shaken

at 40 °C for 18 h. The title compound **30** was obtained as a brown oil. ^{1}H NMR spectral data gave good agreement with the literature values.[17]

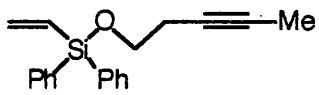
Resin was washed with a 2 : 1 mixture of THF : HCl (1M) (3 x 25 ml), followed by treatment of the resin with 10 % *N*-ethyl-di-iso-propylamine in DMF (3 x 25 ml) and rinsed with DCM (5 x 10 ml) and dried under nitrogen.

7.5 Experimental for Chapter 5

General Procedure for the synthesis of the alkoxydiphenylvinylsilanes[116]

The appropriate alkynol (0.9 eq.) was dissolved in THF (125 ml). Triethylamine (1.1 eq.) and chlorodimethylvinylsilane **194** (1 eq.) were added. The mixture was stirred at room temperature for 24 h under a nitrogen balloon. The compound was washed twice using saturated aqueous ammonium chloride, dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. Purification was by distillation.

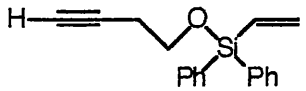
3,3-Diphenyl-4-oxa-3-sila-1-nonen-7-yne 196



196

Following the general procedure, 3-pentyn-1-ol (1.7 ml, 18.6 mmol), triethylamine (3.1 ml, 22.3 mmol) and chlorodiphenylvinylsilane **194** (4.5 ml, 20.4 mmol) were combined. Distillation yielded the title compound **196** (4.51 g, 15.4 mmol, 83 %) as a yellow oil. Boiling range 150 – 155 °C @ 0.2 mm Hg ; υ_{max} (thin film)/cm^{-1} 3069, 3050, 3022, 3010, 2943, 2875, 2234, 1591, 1387, 1265, 1057, 738 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.66 - 7.62 (4H, m, Aryl-*H*), 7.47 - 7.36 (6H, m, Aryl-*H*), 6.51 (1H, dd, J = 20, 15 Hz, C=C*H*$_2$), 6.30 (1H, dd, J = 15, 3.8 Hz, C=C*H*$_2$), 5.94 (1H, dd, J = 20, 3.8 Hz, C*H*=C), 3.85 (2H, t, J = 7.3 Hz, C*H*$_2$), 2.44 (2H, tq, J = 7.4, 2.5 Hz, C*H*$_2$), 1.77 (3H, t, J = 2.5 Hz, C*H*$_3$) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 137.1 (2), 135.0 (4C, 1), 134.0 (1), 133.0 (2C, 0), 130.0 (2C, 1), 127.8 (4C, 1), 76.9 (0), 75.8 (0), 62.7 (2), 22.9 (2), 3.4 (3). *m/z* (EI) 292 [(M + H)$^+$, 14 %], 265 (12), 226 (22), 209 (100), 199 (35), 183 (34), 149 (13), 105 (20), 91 (4), 77 (10). Found : (M + H)$^+$, 292.1280. $C_{19}H_{20}OSi$ requires *M*, 292.1283. The ^{1}H and ^{13}C NMR spectral data gave good agreement with the literature values.[116]

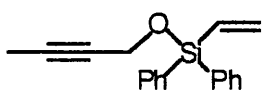
3,3-Diphenyl-4-oxa-3-sila-1-octen-7-yne 195



195

Following the general procedure, but-3-ynol (0.56 ml, 7.43 mmol), triethylamine (1.2 ml, 8.17 mmol) and chlorodiphenylvinylsilane **194** (1.8 ml, 8.17 mmol) were combined. Distillation yielded the title compound **195** (1.51 g, 5.42 mmol, 67 %) as a colourless oil. Boiling range 110 – 130 °C @ 0.05 mm Hg ; υ_{max} (thin film)/cm^{-1} 3301, 3069, 3051, 3011, 2945, 2920, 2878, 1591, 1429, 1120 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.70 - 7.59 (4H, m, Aryl-*H*), 7.50 - 7.46 (6H, m, Aryl-*H*) 6.51 (1H, dd, J = 20, 15 Hz, CH=C*H*$_2$), 6.32 (1H, dd, J = 15, 3.8 Hz, CH=C*H*$_2$), 5.95 (1H, dd, J = 20, 3.8 Hz, CH=C*H*$_2$), 3.90 (2H, t, J = 7.2 Hz, C*H*$_2$-O), 2.49 (2H, dt, J = 7.1, 2.7 Hz, C*H*$_2$), 1.97 (1H, t, J = 2.7 Hz, C≡C*H*) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 137.4 (2), 135.0 (4C, 1), 133.8 (2C, 0), 133.1 (1), 130.1 (2C, 1), 127.9 (4C, 1), 81.2 (0), 69.5 (1), 62.1 (2), 22.5 (2) ; *m/z* (EI) 279 [(M + H)$^+$, 100 %], 278 (5), 239 (23), 227 (38), 201 (35), 199 (5), 174 (5), 149 (18), 130 (3), 105 (2), 91 (1), 79 (3), 78 (1). Found : (M + H)$^+$, 279.1207. $C_{18}H_{19}OSi$ requires *M*, 279.1205. The ^{1}H and ^{13}C NMR spectral data gave good agreement with the literature values.[116]

3,3-Diphenyl-4-oxa-3-sila-1-octen-6-yne 193

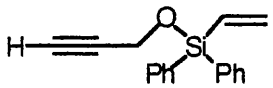


193

Following the general procedure, but-2-ynol (0.55 ml, 7.43 mmol), triethylamine (1.2 ml, 8.17 mmol) and chlorodiphenylvinylsilane **194** (1.8 ml, 8.17 mmol) were combined. Distillation yielded the title compound **193** (1.41 g, 5.06 mmol, 62 %) as a clear, yellow oil. Boiling range 130 - 140 °C @ 0.05 mm Hg ; υ_{max} (thin film)/cm^{-1} 3069, 3050, 2945, 2918, 2864, 2237, 1591, 1429, 1120, 996, 778 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.69 - 7.65 (4H, m, Aryl-*H*), 7.48 - 7.38 (6H, m, Aryl-*H*), 6.55

(1H, dd, J = 20, 15 Hz, CH=C*H*$_2$), 6.32 (1H, dd, J = 15, 3.7 Hz, CH=C*H*$_2$), 5.96 (1H, dd, J = 20, 3.7 Hz, C*H*=CH$_2$), 4.41 (2H, q, J = 2.3 Hz, C*H*$_2$-O), 1.80 (3H, t, J = 2.4 Hz, C*H*$_3$) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 137.3 (2), 135.1 (4C, 1), 133.7 (2C, 0), 133.1 (1), 130.0 (2C, 1), 127.9 (4C, 1), 81.9 (0), 77.2 (0), 52.5 (2), 3.6 (3) ; *m/z* (EI) 278 [(M + H)$^+$, 72 %], 263 (100), 251 (32), 221 (92), 199 (28), 171 (33), 145 (20), 123 (17), 105 (27), 77 (18). Found : (M + H)$^+$, 278.1125. $C_{18}H_{18}OSi$ requires *M*, 278.1127.

3,3-Diphenyl-4-oxa-3-sila-1-hepten-6-yne 192



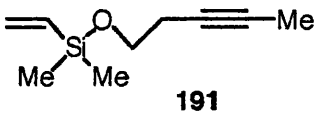
192

Following the general procedure, propargyl alcohol (1.3 ml, 21.9 mmol), triethylamine (3.1 ml, 21.9 mmol) and chlorodiphenylvinylsilane **194** (4.5 ml, 20.4 mmol) were combined. Distillation yielded the title compound **192** (4.76 g, 18.0 mmol, 88 %) as a clear, yellow oil. Boiling range 150 - 200 °C @ 0.4 mm Hg ; υ_{max} (thin film)/cm^{-1} 3294, 3096, 3051, 1591, 1429, 1405, 1372, 1120, 1085, 999, 967 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.67 - 7.63 (4H, m, Aryl-*H*), 7.48 - 7.37 (6H, m, Aryl-*H*), 6.54 (1H, dd, J = 20, 15 Hz, CH=C*H*$_2$), 6.32 (1H, dd, J = 15, 3.7 Hz, CH=C*H*$_2$), 5.97 (1H, dd, J = 20, 3.7 Hz, C*H*=CH$_2$), 4.41 (2H, d, J = 2.4 Hz, C*H*$_2$-O), 2.41 (1H, t, J = 2.4 Hz, C≡C*H*) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 137.6 (2), 135.0 (4C, 1), 133.3 (2C, 0), 132.8 (1), 130.2 (2C, 1), 127.9 (4C, 1), 81.7 (0), 77.2 (1), 52.5 (1) ; m/z (EI) 264 [(M + H)+, 21 %], 234 (55), 207 (100), 181 (20), 160 (97), 157 (30), 131 (23), 105 (22), 77 (14), 53 (5).

General procedure for the synthesis of the alkoxydimethylvinylsilanes[115]

The appropriate alkynol (0.9 eq.) was dissolved in THF (125 ml). Triethylamine (1.1 eq.) and chlorodimethylvinylsilane **187** (1 eq.) were added. The mixture was stirred at room temperature for 18 h under a nitrogen balloon. The compound was filtered twice through Celite and the solvent removed under reduced pressure. Purification was by distillation.

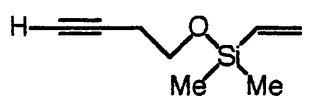
3,3-Dimethyl-4-oxa-3-sila-1-nonen-7-yne 191



191

Following the general procedure, 3-pentyn-1-ol (1.4 ml, 15.10 mmol), triethylamine (2.5 ml, 18.1 mmol) and chlorodimethylvinylsilane **187** (2.3 ml, 16.6 mmol) were combined. Distillation yielded the title compound **191** (1.79 g, 10.7 mmol, 71 %) as a clear, yellow oil. Boiling range 70 - 90 °C @ 30 mm Hg ; υ_{max} (thin film)/cm^{-1} 3050, 2958, 2922, 2872, 2738, 1594, 1475, 1098, 1009, 837 ; δ (^1H) (400 MHz ; $CDCl_3$) 6.11 (1H, dd, J = 20, 15 Hz, C=CH_2), 6.00 (1H, dd, J = 15, 4.3 Hz, C=CH_2), 5.77 (1H, dd, J = 20, 4.3 Hz, CH=C), 3.64 (2H, t, J = 7.3 Hz, CH_2), 2.32 (2H, tq, J = 7.5, 2.5 Hz, CH_2), 1.76 (3H, t, J = 2.5 Hz, C≡C–CH_3), 0.17 (6H, s, Si(CH_3)$_2$) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 138.1 (1), 133.3 (2), 76.7 (0), 75.80 (0), 61.9 (2C, 2), 22.9 (2), 3.4 (3), -2.2 (2C, 3) ; m/z (EI) 153 [$(M - CH_3)^+$, 74 %], 141 (15), 115 (52), 85 (93), 74 (64), 59 (100), 54 (51). Found : $(M - CH_3)^+$, 153.0734. $C_8H_{13}OSi$ requires $(M - CH_3)^+$, 153.0736.

3,3-Dimethyl-4-oxa-3-sila-1-octen-7-yne 190

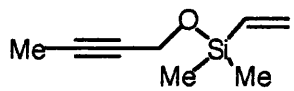


190

Following the general procedure, 3-butyn-1-ol (1.1 ml, 15.09 mmol), triethylamine (2.5 ml, 18.1 mmol) and chlorodimethylvinylsilane **187** (2.3 ml, 16.6 mmol) were combined. Distillation yielded the title compound **190** (1.94 g, 12.6 mmol, 85 %) as a colourless oil. Boiling range 40 – 60 °C @ 30 mm Hg ; υ_{max} 3051, 3012, 2959, 2920, 2875, 2122, 1387, 1101, 959, 839 cm^{-1} ; δ (^1H) (400 MHz ; $CDCl_3$) 6.13 (1H, dd, J = 20, 15 Hz, C=CH_2), 6.02 (1H, dd, J = 15, 4.4 Hz, C=CH_2), 5.79 (1H, dd, J = 20, 4.4 Hz, CH=C), 3.71 (2H, t, J = 7.1 Hz, CH_2), 2.40 (2H, dt, J = 7.1, 2.7 Hz, CH_2), 1.96 (1H, t, J = 2.7 Hz, C≡CH), 0.19 (6H, s, Si(CH_3)$_2$) ; δ (^{13}C) (100 MHz ;

$CDCl_3$) 137.1 (1), 133.5 (2), 81.3 (1), 69.4 (0), 61.3 (2), 22.6 (2), –2.2 (2C, 3) ; *m/z* (EI) 139 [$(M - CH_3)^+$, 88 %], 127 (18), 115 (100), 109 (74), 85 (86), 74 (45), 59 (76), 45 (28), 31 (61). Found : $(M - CH_3)+$, 139.0578. $C_7H_{11}OSi$ requires $(M - CH_3)^+$, 139.0579.

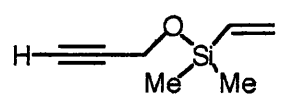
3,3-Dimethyl-4-oxa-3-sila-1-octen-6-yne189



189

Following the general procedure, 2-butyn-1-ol (1.1 ml, 15.09 mmol) triethylamine (2.5 ml, 18.1 mmol) and chlorodimethylvinylsilane **187** (2.3 ml, 16.6 mmol) were combined. Distillation yielded 2-butynyloxydimethylvinylsilane **189** (1.87 g, 12.1 mmol, 73 %) as a colourless oil. Boiling range 60 – 70 °C @ 30 mm Hg ; υ_{max}(thin film)/cm^{-1} 3180, 3051, 3011, 2961, 2922, 2862, 1371, 1146, 1075, 1008, 958, 834 ; δ (^1H) (400 MHz ; $CDCl_3$) 6.14 (1H, dd, J = 20, 15 Hz, CH=CH_2), 6.03 (1H, dd, J = 15, 4.3 Hz, CH=CH_2), 5.80 (1H, dd, J = 20, 4.3 Hz, CH=CH_2), 4.23 (2H, q, J = 2.4 Hz, CH_2), 1.82 (3H, t, J = 2.4 Hz, CH_3), 0.22 (6H, s, Si(CH_3)$_2$) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 136.8 (1), 133.6 (2), 81.3 (0), 67.9 (0), 51.4 (2), 3.6 (3), –2.0 (2C, 3) ; *m/z* (EI) 139 [$(M - CH_3)^+$, 100 %], 127 (4), 109 (88), 97 (32), 83 (15), 75 (18), 59 (12). Found : $(M - CH_3)^+$, 139.0580. $C_7H_{11}OSi$ requires $(M - CH_3)^+$, 139.0579.

3,3-Diphenyl-4-oxa-3-sila-1-hepten-6-yne 188



188

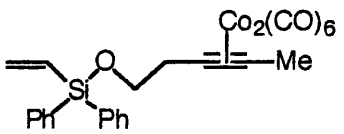
Following the general procedure, propargyl alcohol (2.6 ml, 45.0 mmol), 2,6-lutidine (5.3 ml, 45.0 mmol) and chlorodimethylvinylsilane **187** (5.7 ml, 41.4 mmol) were combined. Distillation yielded the title compound **188** (3.73 g, 26.6 mmol, 64 %) as a colourless oil. Boiling range 100 - 110 °C @ 760 mmHg ; δ (^1H) (400 MHz ; $CDCl_3$) 6.15 (1 H, dd, J = 20, 15 Hz, C=CH_2), 6.05 (1 H, dd, J = 15, 4.5 Hz, C=CH_2),

5.83 (1 H, dd, J = 20, 4.5 Hz, C*H*=C), 4.27 (2 H, d, J = 2.4 Hz, CH_2), 2.40 (1 H, t, J = 2.4 Hz, C≡C*H*), 0.24 (6 H, s, Si(CH_3)$_2$) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 136.5 (1), 134.0 (2), 82.0 (1), 73.2 (0), 51.0 (2), –2.1 (2C, 3).

General Method for Synthesis of Cobalt Complexes[11]

Dicobalt octacarbonyl (1.1 equivalents) was placed in a two-necked round-bottomed flask under nitrogen. Pet. ether (40 / 60) (15 ml) was added and the solution stirred at room temperature for 5 minutes. The silyl compound **190, 191, 192,** or **195** (1 equivalent) was dissolved in pet. ether (40 / 60) (2 - 3 ml), added dropwise and the mixture stirred for 3 - 4 hours. The crude product was purified using column chromatography on deactivated alumina (pet. ether (40 / 60) : diethyl ether, 100 : 0 to 80 : 20, gradient elution) The solvent was removed under reduced pressure. The products **198, 199, 200, 201, 202, 203, 204** and **205** were stored under nitrogen and in the freezer.

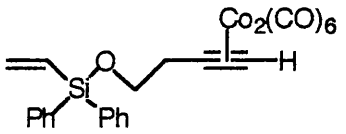
Hexacarbonyl 3,3-Diphenyl-4-oxa-3-sila-1-nonen-7-yne dicobalt 205



205

Following the general procedure, dicobalt octacarbonyl (0.91 g, 3.11 mmol) and 3,3-diphenyl-4-oxa-3-sila-1-nonen-7-yne **196** (0.76 g, 2.59 mmol) were combined. The title compound **203** (1.27 g, 2.20 mmol, 85 %) was obtained as a dark red solid. δ (^{1}H) (400 MHz ; $CDCl_3$) 7.63 (4H, m, Aryl-*H*), 7.49 - 7.37 (6H, m, Aryl-*H*), 6.49 (1H, dd, J = 20, 15 Hz, CH=CH_2), 6.27 (1H, dd, J = 15, 3.6 Hz, CH=CH_2), 5.92 (1H, dd, J = 20, 3.6 Hz, C*H*=CH_2), 3.97 (2H, t, J = 6.7 Hz, CH_2-O), 3.07 (2H, t, J = 6.6 Hz, CH_2–C≡C), 2.58 (3H, s, C≡C*H*).

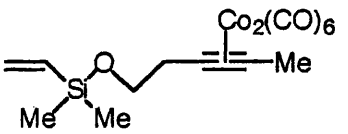
Hexacarbonyl 3,3-Diphenyl-4-oxa-3-sila-1-octen-7-yne Dicobalt 204



204

Following the general procedure, dicobalt octacarbonyl (1.26 g, 3.68 mmol) and 3,3-diphenyl-4-oxa-3-sila-1-octen-7-yne **195** (0.90 g, 3.24 mmol) were combined. The title compound **204** (0.99 g, 1.76 mmol, 54 %) was obtained as a dark red solid. δ (^{1}H) (400 MHz ; $CDCl_3$) 7.66 - 7.58 (4H, m, Aryl-*H*), 7.49 - 7.46 (6H, m, Aryl-*H*) 6.50 (1H, dd, J = 20, 15 Hz, CH=C*H*$_2$), 6.29 (1H, dd, J = 15, 3.8 Hz, CH=C*H*$_2$), 5.99 (1H, s, C≡C*H*), 5.93 (1H, dd, J = 20, 3.8 Hz, CH=C*H*$_2$), 3.97 (2H, t, J = 6.9 Hz, C*H*$_2$-O), 3.07 (2H, dt, J = 7.0, 1.0 Hz, C*H*$_2$).

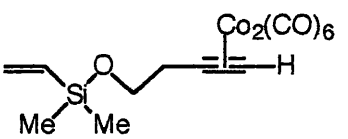
Hexacarbonyl 3,3-Dimethyl-4-oxa-3-sila-1-nonen-7-yne dicobalt 201



201

Following the general procedure, dicobalt octacarbonyl (5.22 g, 15.3 mmol) and 3,3-dimethyl-4-oxa-3-sila-1-nonen-7-yne **196** (2.20 g, 13.1 mmol) were combined. The title compound **201** (5.86 g, 12.9 mmol, 99 %) was obtained as a dark red solid. δ (^{1}H) (400 MHz ; $CDCl_3$) 6.14 (1H, dd, J = 20, 15 Hz, C=C*H*$_2$), 6.03 (1H, dd, J = 15, 4.4 Hz, C=C*H*$_2$), 5.80 (1H, dd, J = 20, 4.4 Hz, C*H*=C), 3.82 (2H, t, J = 6.5 Hz, C*H*$_2$), 3.03 (2H, t, J = 6.5 Hz, C*H*$_2$), 2.64 (3H, s, C≡C–C*H*$_3$), 0.20 (6H, s, Si(C*H*$_3$)$_2$).

Hexacarbonyl 3,3-Dimethyl-4-oxa-3-sila-1-octen-7-yne Dicobalt 200

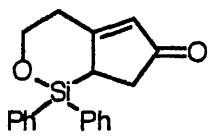


200

Following the general procedure, dicobalt octacarbonyl (2.49 g, 7.28 mmol) and 3,3-dimethyl-4-oxa-3-sila-1-octen-7-yne **190** (0.86 g, 5.60 mmol) were combined. The title compound **200** (1.29 g, 2.93 mmol, 54 %) was obtained as a dark red solid. δ (^{1}H) (400 MHz ; $CDCl_3$) 6.17 (1H, dd, J = 20, 15 Hz, C=C*H*$_2$), 6.04 (1H, dd, J = 15, 4.4 Hz, C=C*H*$_2$), 6.03 (1H, s, C≡C*H*) 5.81 (1H, dd, J = 20, 4.4 Hz, C*H*=C), 3.80 (2H, t, J = 6.8 Hz, C*H*$_2$), 2.40 (2H, dt, J = 6.0, 1.9 Hz, C*H*$_2$), 0.21 (6H, s, Si(C*H*$_3$)$_2$)

Examples of Experimental Procedures for the Cyclisation of Compounds 200, 201 and 204 to form 206, 208 and 207

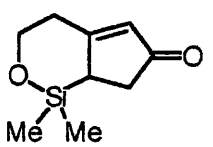
2,3-(*Z*)-6-oxa-7-sila-7,7-diphenyl-bicyclo[3.4.0]pent-2-en-1-one 207



207

Hexacarbonyl 3,3-diphenyl-4-oxa-3-sila-1-octen-7-yne dicobalt **204** (0.89 g, 1.58 mmol) was dissolved in toluene (27 ml). *N*-Methylmorpholine (0.52 ml, 4.74 mmol) was added dropwise. The mixture was placed under an atmosphere of nitrogen and stirred for 4 days at room temperature. The solvent was removed under reduced pressure and the red residue was analysed by ^{1}H NMR spectrometry. Only starting material was returned.

2,3-(*Z*)-6-oxa-7-sila-7,7-dimethyl-bicyclo[3.4.0]pent-2-en-1-one 206

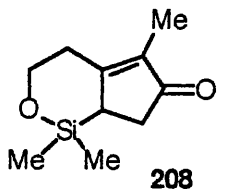


206

Hexacarbonyl 3,3-dimethyl-4-oxa-3-sila-1-octen-7-yne dicobalt **200** (0.85 g, 1.93 mmol) was dissolved in DCM (25 ml). *N*-Methyl morpholine (0.64 ml, 5.79 mmol) was added drop wise. Isopropanol (5 ml) was added. The mixture was stirred

for 2 days at 28 °C. The solvent was removed under reduced pressure and the red residue was analysed by ^{1}H NMR spectrometry. Only starting material was returned.

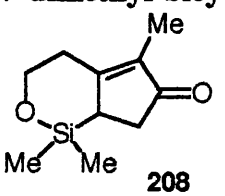
2,3-(Z)-2-methyl-6-oxa-7-sila-7,7-dimethyl-bicyclo[3.4.0]pent-2-en-1-one 208



208

Hexacarbonyl 3,3-dimethyl-4-oxa-3-sila-1-nonen-7-yne dicobalt **201** (0.89 g, 1.96 mmol) was dissolved in methanol (50 ml). TMANO.2H_2O (2.18 g, 19.6 mmol) was added. The mixture was stirred for 17 h at room temperature. The solvent was removed under reduced pressure. Hexane : ether (4 : 1, 100 ml) was added, followed by 50 ml of sat. aq. $NaHCO_3$. The two layers were separated and the aqueous layer was washed using hexane : ether (4 : 1, 2 x 40 ml). The organic extracts were combined and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The residue was distilled using bulb to bulb distillation (50 – 80 °C @ 50 mmHg). The yellow oil was analysed by ^{1}H NMR spectrometry. Only starting material was returned.

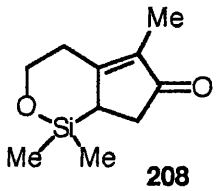
2,3-(Z)-2-methyl-6-oxa-7-sila-7,7-dimethyl-bicyclo[3.4.0]pent-2-en-1-one 208



208

Morpholinomethyl resin **156** (0.38 g) was swollen in THF (15 ml) for approximately 30 minutes. Hexacarbonyl 3,3-dimethyl-4-oxa-3-sila-1-nonen-7-yne dicobalt **201** (0.22 g, 0.44 mmol) was added, followed by THF (5 ml). The mixture was shaken at room temperature for 4 days. The resin was washed alternately using DCM and diethyl ether (4 x 50 ml). The solvent was removed under reduced pressure and the red residue was analysed by ^{1}H NMR spectrometry. Only starting material was returned.

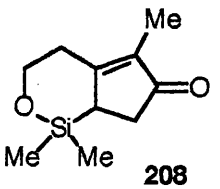
2,3-(Z)-2-methyl-6-oxa-7-sila-7,7-dimethyl-bicyclo[3.4.0]pent-2-en-1-one 208



208

Polyamine resin **163** (0.38 g) was swollen in THF (15 ml) for approximately 30 minutes under an atmosphere of nitrogen. Hexacarbonyl 3,3-dimethyl-4-oxa-3-sila-1-nonen-7-yne dicobalt **201** (0.20 g, 0.44 mmol) was added, followed by THF (5 ml). The mixture was shaken at room temperature for 4 days. The resin was washed alternately using DCM and diethyl ether (4 x 50 ml). The solvent was removed under reduced pressure and the red residue was analysed by ^{1}H NMR. Only starting material was returned.

2,3-(Z)-2-methyl-6-oxa-7-sila-7,7-dimethyl-bicyclo[3.4.0]pent-2-en-1-one 208



208

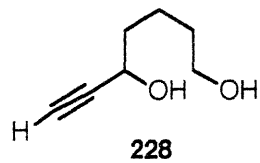
Aminomethylated resin **211** (0.38 g) was swollen in DCM (1 ml) for approximately 30 minutes. Hexacarbonyl 3,3-dimethyl-4-oxa-3-sila-1-nonen-7-yne dicobalt **201** (0.11 g, 0.22 mmol) was added, followed by isopropanol (3 ml). The mixture was shaken at room temperature for 7 days. The resin was washed alternately using DCM and diethyl ether (4 x 50 ml). The solvent was removed under reduced pressure and the red residue was analysed by ^{1}H NMR. Only starting material was returned.

7.6 Experimental for Chapter 6

General Procedure for the Synthesis of the Diols

δ-Valerolactone (1 eq.) was added to a solution of THF (20 ml) cooled to -78 °C and purged with nitrogen. DIBAL-H (1.0 M in hexanes) (1 eq.) was added and the reaction mixture stirred for 1.5 hours. The appropriate Grignard reagent (2.5 eq.) was added and the mixture stirred for 30 minutes at -78 °C. The mixture was slowly warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched using saturated ammonium chloride (30 ml) and the organic solvent removed under vacuum. Ethyl acetate (30 ml) was added and the aqueous layer was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed using brine (1 x 200 ml). The organic layer was dried using anhydrous magnesium sulfate, filtered and the solvent removed under vacuum. The compound was purified using column chromatography on deactivated alumina (5 % water) (hexane : ethyl acetate 100 : 0 to 0 : 100, gradient elution followed by chloroform, methanol).

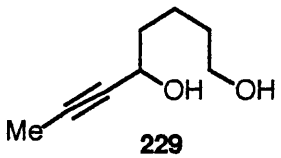
Hept-6-yne-1,5-diol 228



228

Following the general procedure, DIBAL-H (10.0 ml, 9.99 mmol), δ-valerolactone **227** (0.93 ml, 9.99 mmol) and ethynyl magnesium bromide (0.5 M in THF) (50.0 ml, 25.0 mmol) were combined. The title compound **228** (0.42 g, 3.28 mmol, 33 %) was isolated as a yellow oil. υ_{max}(thin film)/cm^{-1} 3446, 2936, 2865, 2113, 1717, 1458, 1335, 1028, 904 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 4.39 (1H, dq, J = 6.5, 2.0 Hz, C*H*), 3.67 (2H, q, J = 3.8 Hz, CH_2), 2.47 (1H, d, J = 2.0 Hz, C≡C*H*), 2.10 – 2.04 (3H, m, CH_2, CO*H*), 1.80 – 1.73 (2H, m, CH_2), 1.67 (2H, m CH_2), 1.45 (1H, s, CO*H*) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 83.9 (1), 71.9 (0), 61.6 (1), 61.0 (2), 36.2 (2), 31.1 (2), 20.2 (2) ; *m/z* (CI, ammonia) 146 [(M + NH_4)$^+$, 100 %], 129 (6), 118 (1), 102 (2), 91 (1), 71 (1), 69 (1).

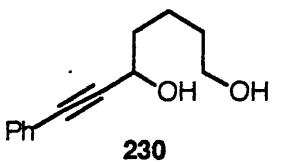
Oct-6-yne-1,5-diol 229



229

Following the general procedure, DIBAL-H (10.0 ml, 9.99 mmol), δ-valerolactone **227** (0.93 ml, 9.99 mmol) and propynyl magnesium bromide (0.5 M in THF) (50.0 ml, 25.0 mmol) were combined. The title compound **229** (0.63 g, 4.44 mmol, 44 %) was isolated as a yellow oil. υ_{max}(thin film)/cm^{-1} 3423, 2938, 2863, 2239, 1722, 1662, 1437, 1340, 1142, 1026 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 4.35 (1H, broad s, CO*H*), 3.65 (2H, t, J = 5.9 Hz, CH_2), 2.07 (1H, broad s, C≡C*H*), 1.84 (3H, d, J = 2.1 Hz, CH_3), 1.75 – 1.48 (7H, m, C*H*,3(CH_2)) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 80.0 (0), 79.3 (0), 61.7 (1), 61.5 (2), 36.7 (2), 31.2 (2), 20.4 (2), 2.5 (3) ; *m/z* (EI) 141 [(M + H)$^+$, 1 %], 123 (7), 109 (6), 99 (12), 84 (15), 69 (100), 67 (26), 41 (24), 39 (14).

7-Phenyl-hept-6-yne-1,5-diol 230

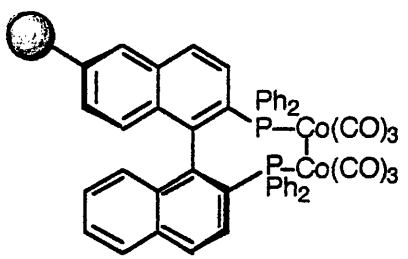


230

Following the general procedure, DIBAL-H (10.0 ml, 9.99 mmol), δ-valerolactone **227** (0.93 ml, 9.99 mmol) and phenylethynyl magnesium bromide (1.0 M in THF) (25.0 ml, 25.0 mmol) were combined. The title compound **230** (0.42 g, 2.06 mmol, 21 %) was isolated as a yellow oil. υ_{max}(thin film)/cm^{-1} 3386, 2938, 2864, 2228, 1720, 1598, 1572, 1490, 1442, 1335, 1255, 1027 ; δ (^{1}H) (400 MHz ; $CDCl_3$) 7.44 (1H, d, J = 2.2 Hz, Aryl–*H*), 7.42 (1H, d, J = 4.1 Hz, Aryl–*H*), 7.31 (3H, dd, J = 5.3, 2.2 Hz, Aryl–*H*), 4.62 (1H, q, J = 6.3 Hz, CO*H*), 3.69 (2H, distorted t, CH_2), 2.05 (1H, broad s, C≡CH), 1.88 – 1.84 (2H, m, CH_2), 1.70 – 1.60 (4H, m, 2(CH_2)), 1.40 (1H, broad s, CO*H*) ; δ (^{13}C) (100 MHz ; $CDCl_3$) 132.1 (2C, 1), 128.8 (1), 128.7 (2C, 1), 123.0 (0), 90.4 (0), 85.4 (0), 63.21 (2), 63.15 (1), 37.9 (2), 32.7 (2), 21.9 (2) ; *m/z* (EI) 204 [(M + H)$^+$, 2 %], 185 (4), 158 (6), 146 (18), 131 (100), 103 (27), 102 (12), 77 (20), 59 (15), 31 (15) ; Found : (M + H)$^+$, 204.1149. $C_{13}H_{16}O_2$ requires *M*,

204.1150. The ^{1}H and ^{13}C NMR spectral data gave reasonable agreement with the published data.[133]

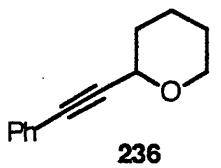
Synthesis of Cobalt Complexed Solid Supported (-)-BINAP[102] 231



231

Polymer supported (-)-BINAP **222** (0.33 g) was placed in a solid phase reactor and 1,4-dioxane (5 ml) was added. The mixture was agitated under nitrogen for 30 minutes at room temperature. Freshly sublimed dicobalt octacarbonyl (0.061 g, 0.18 mmol) was dissolved in 1,4–dioxane (2 ml) and added. The mixture was agitated under nitrogen for 30 minutes. The mixture was shaken at 60 °C for 24 hours. The solvent was drained off and the purple beads **231** were washed using THF (25 ml), diethyl ether (4 x 25 ml) and DCM (4 x 25 ml) before being dried under nitrogen.

2-Phenylethynyl-tetrahydro-pyran 236



236

The cobalt complexed resin **231** (0.5 g, 0.32 – 0.45 mmol / g) was swollen for 30 minutes in DCM (30 ml) and purged with nitrogen at room temperature. 7-Phenyl-hept-6-yne-1,5-diol **230** (0.05 g, 0.23 mmol) was added, followed by DCM (5 ml). The mixture was shaken at room temperature for 45 minutes before cooling to -78 °C for 20 minutes. $BF_3.OEt_2$ (0.1 ml, 0.68 mmol) was added and the mixture shaken at -78 °C for 45 minutes. Distilled water (20 ml) was added and the mixture slowly warmed to room temperature. The organic solvent was removed under vacuum. Ethyl acetate (35 ml) was added and the two layers separated. The aqueous layer was extracted using

ethyl acetate (2 x 50 ml) and the organic layer and extracts were combined and washed using distilled water (2 x 150 ml) and brine (1 x 150 ml). The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The complex was dissolved in 95 : 5 EtOH : H_2O (120 ml). $Fe(NO_3)_3.9(H_2O)$ (0.92 g, 2.30 mmol) was added and the mixture stirred for 4.5 hours. The solvent was removed under vacuum. Ethyl acetate (30 ml) and distilled water (30 ml) were added and the two layers separated. The aqueous layer was extracted using ethyl acetate (2 x 30 ml). The organic extracts were combined and washed using distilled water (150 ml) and brine (150 ml). The mixture was dried over anhydrous magnesium sulfate, filtered and the solvent removed under vacuum. The residue had turned green so cobalt was assumed to be still present. The previous step using $Fe(NO_3)_3.9H_2O$ was repeated and the residue purified using column chromatography on silica gel (hexane : ethyl acetate 100 : 0 to 0 : 100, gradient elution). ^1H NMR spectral analysis showed that only starting materials were recovered.

References

1 For a review see: N. E. Schore, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, Oxford, 1995, Vol. 12, p. 703 – 739.

2 I. U. Khand, G. R. Knox, P. L. Pauson and W. E. Watts, *J. Chem. Soc., Perkin Trans. 1*, 1973, 975 – 977.

3 For a review see: O. Geis and H. Schmalz, *Angew. Chem. Int. Ed. Engl.*, 1998, **37**, 911 – 914.

4 For a review see: K. M. Brummond and J. L. Kent, *Tetrahedron*, 2000, **56**, 3263 – 3283.

5 For a review see: A. J. Fletcher and S. D. R. Christie, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1 – 13.

6 R. F. Newton, P. L. Pauson and R. G. Taylor, *J. Chem. Research (S).*, 1980, 277.

7 J. G. Donkervoort, A. R. Gordon, C. Johnstone, W. J. Kerr and U. Lange, *Tetrahedron*, 1996, **52**, 7391 – 7420.

8 D. C. Billington, W. J. Kerr and P. L. Pauson, *J. Organomet. Chem.*, 1987, **328**, 223 – 227.

9 S. P. Chavan, S. S. Patil and T. Raindranathan, *Tetrahedron*, 1999, **55**, 13417 – 13422.

10 M. Yamanaka and E. Nakamura, *J. Am. Chem. Soc.*, 2001, **123**, 1703 – 1708.

11 P. L. Pauson, *Tetrahedron*, 1985, **41**, 5855 – 5860.

12 N. E. Schore and M. C. Croudace, *J. Org. Chem.*, 1981, **46**, 5436 – 5438.

13 D. C. Billington, W. J. Kerr, P. L. Pauson and C. F. Farnocchi, *J. Organomet. Chem.*, 1988, **356**, 213 – 219.

14 D. C. Billington, I. M. Helps, P. L. Pauson, W. Thomson and D. Willison, *J. Organomet. Chem.*, 1988, **354**, 233 – 242.

15 P. Magnus, L. M. Principe and M. J. Slater, *J. Org. Chem.*, 1987, **52**, 1483 – 1486.

16 S. Shambayati, W. E. Crowe and S. L. Schreiber, *Tetrahedron Lett.*, 1990, **31**, 5289 – 5292.

17 Y. K. Chung, B. Y. Lee, N. Jeong, M. Hudecek and P. L. Pauson, *Organometallics*, 1993, **12**, 220 – 223.

18 N. Jeong, Y. K. Chung, B. Y. Lee, S. H. Lee and S. Yoo, *Synlett*, 1991, 204 – 206.

19 M. Ahmar, F. Antras and B. Cazes, *Tetrahedron Lett.*, 1999, **40**, 5503 – 5506.

20 A. R. Gordon, C. Johnstone and W. J. Kerr, *Synlett*, 1995, **10**, 1083 – 1084.

21 W. J. Kerr, M. McLaughlin, P. L. Pauson and S. M. Robertson, *Chem. Commun.*, 1999, 2171 – 2172.

22 W. A. Smit, S. O. Simonyan, V. A. Tarasov, G. S. Mikaelian, A. S. Gybin, I. I. Ibragimov, R. Caple, D. Froen and A. Kreager, *Synthesis*, 1989, 472 – 475.

23 S. W. Brown and P. L. Pauson, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1205 – 1209.

24 T. Sugihara, M. Yamada, H. Ban, M. Yamaguchi and C. Kaneko, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2801 – 2804.

25 C. M. Lukehart, *Fundamental Transition Metal Organometallic Chemistry*, Brooks/Cole, Monterey, 1985.

26 T. Rajesh and M. Periasamy, *Tetrahedron Lett.*, 1999, **40**, 817 – 818.

27 T. Sugihara, M. Yamada, M. Yamaguchi and M. Nishizawa, *Synlett*, 1999, 771 – 773.

28 M. E. Krafft, I. L. Scott, R. H. Romero, S. Fiebelmann and C. E. V. Pelt, *J. Am. Chem. Soc.*, 1993, **115**, 7199.

29 J. G. Ford, W. J. Kerr, G. G. Kirk, D. M. Lindsay and D. Middlemiss, *Synlett*, 2000, 1415 – 1418.

30 M. S. Balakrishna, V. S. Reddy, S. S. Krishnamurthy, J. F. Nixon and J. C. T. R. B. S. Laurent, *Coordination Chem. Rev.*, 1994, **129**, 1 – 90.

31 X. Verdaguer, A. Moyano, M. A. Pericás, A. Riera, A. E. Greene, J. F. Piniella and A. Alvarez-Larena, *J. Organomet. Chem.*, 1992, **433**, 305 – 310.

32 A. M. Hay, W. J. Kerr, G. G. Kirk and D. Middlemiss, *Organometallics*, 1995, **14**, 4986 – 4988.

33 D. T. Rutherford and S. D. R. Christie, *Tetrahedron Lett.*, 1998, **39**, 9805 – 9808.

34 J. Castro, H. Sorensen, A. Riera, C. Morin, A. Moyano, M. A. Pericás and A. E. Greene, *J. Am. Chem. Soc.*, 1990, **112**, 9388 – 9389.

35 V. Bernardes, X. Verdaguer, N. Kardos, A. Riera, A. Moyano, M. A. Pericás and A. E. Greene, *Tetrahedron Lett.*, 1994, **35**, 575 – 578.

36 S. Fonquerna, R. Rios, A. Moyano, M. A. Pericás and A. Riera, *Eur. J. Org. Chem.*, 1999, 3459 – 3478.

37 X. Verdaguer, J. Vazquez, G. Fuster, V. Bernardes-Genisson, A. E. Greene, A. Moyano, M. A. Pericás and A. Riera, *J. Org. Chem.*, 1998, **63**, 7037 – 7052.

38 J. Balsells, J. Vazquez, A. Moyano, M. A. Pericás and A. Riera, *J. Org. Chem.*, 2000, **65**, 7291 – 7302.

39 M. Isobe and S. Takai, *J. Organomet. Chem.*, 1999, **589**, 122 – 125.

40 C. Mukai, H. Sonobe, J. S. Kim and M. Hanaoka, *J. Org. Chem.*, 2000, **65**, 6654 – 6659.

41 S. E. MacWhorter, V. Sampath, M. M. Olmstead and N. E. Schore, *J. Org. Chem.*, 1988, **53**, 203 – 205.

42 P. Mayo and W. Tam, *Tetrahedron*, 2001, **57**, 5943 – 5952.

43 P. Bladon, P. L. Pauson, H. Brunner and R. Eder, *J. Organomet. Chem.*, 1988, **355**, 449.

44 Y. Gimbert, F. Robert, A. Durif, M. Averbuch, N. Kann and A. E. Greene, *J. Org. Chem.*, 1999, **64**, 3492 – 3497.

45 S. Chia, W. R. Cullen, M. Franklin and A. R. Manning, *Inorg. Chem.*, 1975, 2521 – 2526.

46 R. P. Hughes, S. J. Doig, R. C. Hemond, W. L. Smith, R. E. Davis, S. M. Gadol and K. D. Holland, *Organometallics*, 1990, **9**, 2745 – 2753.

47 J. Castro, A. Moyano, M. A. Pericás, A. Riera, A. Alvarez-Larena and J. F. Piniella, *J. Am. Chem. Soc.*, 2000, **122**, 7944 – 7952.

48 J. Adrio and J. C. Carretero, *J. Am. Chem. Soc.*, 1999, **121**, 7411 – 7412.

49 J. C. Carretero and J. Adrio, *Synthesis*, 2001, 1888 – 1896.

50 X. Verdaguer, A. Moyano, M. A. Pericás, A. Riera, M. A. Maestro and J. Mahia, *J. Am. Chem. Soc.*, 2000, **122**, 10242 – 10243.

51 J. Castro, A. Moyano, M. A. Pericás and A. Riera, *J. Org. Chem.*, 1998, **63**, 3346 – 3351.

52 J. Vazquez, S. Fonquerna, A. Moyano, M. A. Pericás and A. Riera, *Tetrahedron: Asymmetry*, 2001, **12**, 1837 – 1850.

53 V. Derdau, S. Laschat and P. G. Jones, *Heterocycles*, 1998, **48**, 1445 – 1453.

54 W. J. Kerr, D. M. Lindsay, E. M. Rankin, J. S. Scott and S. P. Watson, *Tetrahedron Lett.*, 2000, **41**, 3229 – 3233.

55 A. J. Fletcher, D. T. Rutherford and S. D. R. Christie, *Synlett*, 2000, 1040 – 1042.

56 V. Rautenstrauch, P. Megand, J. Coneas and W. Kuster, *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 1413 – 1416.

57 N. Jeong, S. H. Hwang and Y. Lee, *J. Am. Chem. Soc.*, 1994, **116**, 3159 – 3160.

58 N. Y. Lee and Y. K. Chung, *Tetrahedron Lett.*, 1996, **37**, 3145 – 3148.

59 B. L. Pagenkopf and T. Livinghouse, *J. Am. Chem. Soc.*, 1996, **118**, 2285 – 2286.

60 B. L. Pagenkopf, D. B. Belanger, D. J. R. O'Mahony and T. Livinghouse, *Synthesis*, 2000, 1009 – 1019.

61 J. W. Kim and Y. K. Chung, *Synthesis*, 1998, 142 – 144.

62 T. Sugihara and M. Yamaguchi, *J. Am. Chem. Soc.*, 1998, **120**, 10782 – 10783.

63 D. B. Belanger, D. J. R. O'Mahony and T. Livinghouse, *Tetrahedron Lett.*, 1998, **39**, 7637 – 7640.

64 D. B. Belanger and T. Livinghouse, *Tetrahedron Lett.*, 1998, **39**, 7641 – 7644.

65 S. Hosokawa and M. Isobe, *Tetrahedron Lett.*, 1998, **39**, 2609.

66 T. Sugihara and M. Yamaguchi, *Synlett*, 1998, 1384 – 1386.

67 S. U. Son, D. S. Choi and Y. K. Chung, *Organic Lett.*, 2000, **2**, 2097 – 2100.

68 N. Jeong and S. H. Hwang, *Angew. Chem. Int. Ed. Engl.*, 2000, **39**, 636 – 638.

69 M. Hayashi, Y. Hashimoto, Y. Yamamoto, J. Usuki and K. Saigo, *Angew. Chem. Int. Ed. Engl.*, 2000, **39**, 631 – 633.

70 B. Y. Lee and Y. K. Chung, *J. Am. Chem. Soc.*, 1994, **116**, 8793 – 8794.

71 K. Hiroi, T. Watanabe, R. Kawagishi and I. Abe, *Tetrahedron: Asymmetry*, 2000, **11**, 797 – 808.

72 M. E. Krafft, L. V. R. Bonaga and C. Hirosawa, *Tetrahedron Lett.*, 1999, **40**, 9171 – 9175.

73 A. C. Comely, S. E. Gibson, A. Stevenazzi and N. J. Hales, *Tetrahedron Lett.*, 2001, **42**, 1183 – 1185.

74 F. A. Hicks and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 11688 – 11689.

75 F. A. Hicks and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 7026 – 7033.

76 T. Morimoto, N. Chatani, Y. Fukumoto and S. Murai, *J. Org. Chem.*, 1997, **62**, 3762 – 3765.

77 Y. Morisaki, T. Kondo and T. Mitsudo, *Organic Lett.*, 2000, **2**, 949 – 952.

78 N. Jeong, S. Lee and B. K. Sung, *Organometallics*, 1998, **17**, 3642 – 3644.

79 Y. Koga, T. Kobayashi and K. Narasaka, *Chemistry Lett.*, 1998, 249 – 250.

80 N. Jeong, B. K. Sung and Y. K. Choi, *J. Am. Chem. Soc.*, 2000, **122**, 6771 – 6772.

81 N. Jeong, S. D. Seo and J. Y. Shin, *J. Am. Chem. Soc.*, 2000, **122**, 10220 – 10221.

82 P. A. Evans and J. E. Robinson, *J. Am. Chem. Soc.*, 2001, **123**, 4609 – 4610.

83 T. Shibata and K. Takagi, *J. Am. Chem. Soc.*, 2000, **122**, 9852 – 9853.

84 S. Tanimori, K. Fukubayashi and M. Kirihata, *Tetrahedron Lett.*, 2001, **42**, 4013 – 4016.

85 W. Heiber and H. Schulten, *ibid*, 1937, **232**.

86 I. Wender, H. W. Sternberg and M. Orchin, *J. Am. Chem. Soc.*, 1952, **74**, 1216 – 1219.

87 S. C. Berk, R. B. Grossman and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 8593 – 8601.

88 M. E. Krafft and L. V. R. Bonaga, *Synlett*, 2000, 959 – 962.

89 M. E. Krafft, L. V. R. Bonaga and C. Hirosawa, *J. Org. Chem.*, 2001, **66**, 3004 – 3020.

90 U. V. Mallavadhani, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, John Wiley and Sons, Chichester, 1995, Vol. 7, p. 1494 - 1497.

91 R. K. Haynes and S. C. Vonwiller, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, John Wiley and Sons, Chichester, 1995, Vol. 7, p. 4811 - 4815.

92 M. Costa and A. Mor, *Tetrahedron Lett.*, 1995, **36**, 2867 – 2870.

93 D. Hoppe and T. Hense, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2282 – 2316.

94 S. O. Simonian, W. A. Smit, A. S. Gybin, A. S. Shashkov, G. S. Mikaelian, V. A. Tarasov, I. I. Ibragimov, R. Caple and D. E. Froen, *Tetrahedron Lett.*, 1986, **27**, 1245 – 1248.

95 M. E. Krafft and L. V. R. Bonaga, *Angew. Chem. Int. Ed. Engl.*, 2000, **39**, 3676 – 3680.

96 G. L. Bolton, J. C. Hodges and J. R. Rubin, *Tetrahedron*, 1997, **53**, 6611 – 6634.

97 J. L. Spitzer, M. J. Kurth, N. E. Schore and S. D. Najdi, *Tetrahedron*, 1997, **53**, 6791 – 6808.

98 G. L. Bolton, *Tetrahedron Lett.*, 1996, **37**, 3433 – 3436.

99 W. J. Kerr, D. M. Lindsay and S. P. Watson, *Chem. Commun.*, 1999, 2551 – 2552.

100 D. S. Brown, E. Campbell, W. J. Kerr, D. M. Lindsay, A. J. Morrison, K. G. Pike and S. P. Watson, *Synlett*, 2000, 1573 – 1576.

101 W. J. Kerr, D. M. Lindsay, M. McLaughlin and P. L. Pauson, *Chem. Commun.*, 2000, 1467 – 1468.

102 A. C. Comely, S. E. Gibson and N. J. Hales, *Chem. Commun.*, 2000, 305 – 306.

103 N. E. Schore, *Synth. Commun.*, 1979, **9**, 41.

104 M. E. Krafft, C. Hirosawa and L. V. R. Bonaga, *Tetrahedron Lett.*, 1999, **40**, 9177 – 9181.

105 K. J. Shea, J. D. R. Gauthier and K. S. Zandi, *Tetrahedron*, 1998, **54**, 2289.

106 K. Tamao, K. Kobayashi and Y. Ito, *J. Am. Chem. Soc.*, 1989, **111**, 6478 – 6480.

107 T. W. Greene and P. G. M. Wuts, in *Protective Groups In Organic Synthesis*, 2nd, ed. Wiley Interscience, New York, 1991, p. 68 – 87.

108 E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, 1972, **94**, 2549.

109 G. A. Tolstikov, M. S. Vostrikov, N. S. Komissarova, M. E. Adler and O. M. Kuznetsov, *Zh. Org. Khim.*, 1988, **24**, 224.

110 F. P. Cossio, J. M. Aizpurua and C. Palomo, *Can. J. Chem.*, 1986, **64**, 225 – 231.

111 S. Kim and J. H. Park, *J. Org. Chem.*, 1988, **53**, 3111 – 3113.

112 S. J. Danishfesky and N. Mantlo, *J. Am. Chem. Soc.*, 1988, **110**, 8129 – 8133.

113 D. G. Saunders, *Synthesis*, 1988, 377 – 379.

114 J. Wachtmeister, A. Muhlman, B. Classon and B. Samuelsson, *Tetrahedron*, 1999, **55**, 10761 – 10770.

115 G. D. Probert, R. Harding, R. J. Whitby and S. J. Coote, *Synlett*, 1997, 1371 – 1374.

116 H. Kagoshima, M. Hayashi, Y. Hashimoto and K. Saigo, *Organometallics*, 1996, **15**, 5439 – 5441.

117 D. J. S. Guthrie, I. U. Khand, G. R. Knox, J. Kollmeier, P. L. Pauson and W. E. Watts, *J. Organomet. Chem.*, 1975, **90**, 93.

118 K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207 – 214.

119 K. M. Nicholas and R. Petit, *Tetrahedron Lett.*, 1971, 3475 – 3478.

120 S. Padmanabham and K. M. Nicholas, *Synthetic Commun.*, 1980, **10**, 503 – 507.

121 T. F. Jamison, S. Shambayati, W. E. Crowe and S. L. Schreiber, *J. Am. Chem. Soc.*, 1997, **119**, 5353.

122 Alexakis, Normant and Villieras, *Tetrahedron Lett.*, 1976, 3461.

123 S. L. Schreiber, T. Sammakia and W. E. Crowe, *J. Am. Chem. Soc.*, 1986, **108**, 3128 – 3130.

124 C. Mukai, Y. Ikeda, Y. Sugimoto and M. Hanaoka, *Tetrahedron Lett.*, 1994, **35**, 2179 – 2182.

125 C. Mukai, Y. Sugimoto, Y. Ikeda and M. Hanaoka, *Tetrahedron Lett.*, 1994, **35**, 2183 – 2186.

126 K. Hiroi, T. Watanabe, R. Kawagishi and I. Abe, *Tetrahedron Lett.*, 2000, **41**, 891 – 895.

127 D. J. Bayston, J. L. Fraser, M. R. Ashton, A. D. Baxter, M. E. C. Polywka and E. Moses, *J. Org. Chem.*, 1998, **63**, 3137 – 3140.

128 A. Fujii and M. Sodeoka, *Tetrahedron Lett.*, 1999, **40**, 8011 – 8014.

129 T. Kobayashi, Y. Koga and K. Narasaka, *J. Organomet. Chem.*, 2001, **624**, 73 – 87.

130 H. Dang and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1493 – 1497.

131 W. Opplozer, A. Pimm, B. Stammen and W. E. Hume, *Helv. Chim. Acta*, 1997, **80**, 623 – 639.

132 R. Giordano, E. Sappa and G. Predieri, *Inorg. Chim. Acta*, 1995, **228**, 139 – 146.

133 A. R. Katritzky, S. Rachwal and B. Rachwal, *J. Chem. Soc., Perkin Trans. 1*, 1990, 171 - 1725.