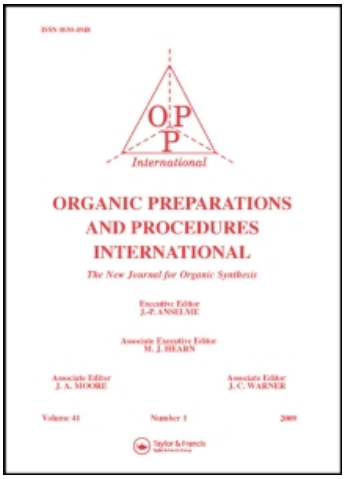

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THE ASYMMETRIC PAUSON-KHAND REACTION. A REVIEW

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INTRODUCTION

The Pauson-Khand reaction is a formal [2+2+1] cycloaddition involving an alkyne, an alkene and carbon monoxide mediated by a hexacarbonyldicobaltalkyne complex to yield cyclopentenones in a single step. Since its discovery in the early seventies,[1] this versatile reaction has become the synthesis of choice of cyclopentenones and their derivatives.

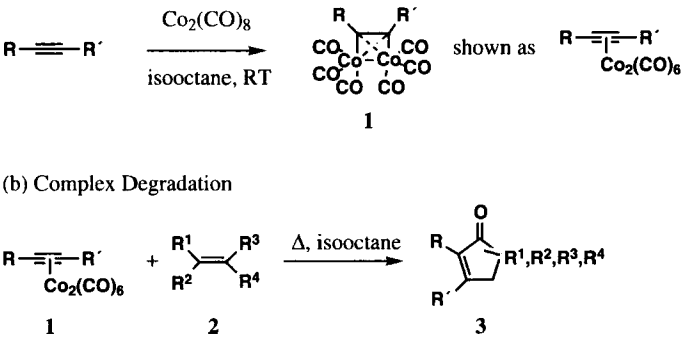


Fig. 1 The Pauson-Khand Reaction

The reaction involves two distinct stages, namely (i) formation of the hexacarbonyldicobalt-alkyne complex (**1**) and (ii) the subsequent decomposition of the complex in the presence of an alkene (**2**). Formation of the hexacarbonyldicobalt alkyne complex is accomplished by stirring the alkyne with $Co_2(CO)_8$ for several hours at ambient temperature in an ethereal or hydrocarbon solvent. The complexes formed RC≡CR´$Co_2(CO)_6$ (**1**) are usually quite stable (*Fig. 1*).

Of the various methodologies published, the most common procedures involve the use of stoichiometric amounts of the alkyne and the dicobalt complex. In the classical procedure, the second step is performed by heating the complex (**1**) and an alkene (**2**) in an inert solvent such as toluene either under an atmosphere of CO, or an inert gas, for several hours to generate cyclopentenones (**3**) in

yields ranging between 30 and 60%.[1-7] Over the years, many excellent reviews[8-14] have detailed the many aspects of this reaction, *i.e.*, mechanism, applications and improvements in procedures which will be summarized briefly. The main purpose of this review is to describe the more recent results of the exploitation of the Pauson-Khand reaction in asymmetric synthesis. The first part provides a brief description of some of the milestones in the development of this reaction since its discovery until the present. The second part focuses on the use of the Pauson-Khand reaction in asymmetric synthesis with particular emphasis on the publications that have appeared between the years 1992-1996.

The structural variations of the alkene and alkyne are practically limitless; with newer techniques, this reaction may be carried out in the presence of a range of functional groups only with few exceptions. Schore[11-14] has summarized the scope of the reaction in his reviews. The mechanism of complexation and subsequent reactions has also been covered by Schore and others[11-16] and shall not be dealt with here.

I. DEVELOPMENT OF REACTION METHODOLOGY

During its development, many improvements to the classical thermal Pauson-Khand reaction have been reported. Since complex formation proceeds readily, the modifications have focussed on the decomposition step. Induction either by ultraviolet[17,18] or ultrasound[17] radiation have been reported with some success. The observation that silica gel can catalyze the decomposition of the hexacarbonyldicobalt complex[19] led to the development of the commonly used dry-state adsorption conditions (DSAC).[17,19-27] In a general procedure,[20] the red cobalt alkyne complex containing both the alkyne and alkene moieties within the same molecule in hexane is mixed with silica gel (or other solid supports such as alumina or zeolites) and the solvent is removed by evaporation *in vacuo* without heating. The system is flushed with oxygen and the pink powder is heated (45-60°) for periods

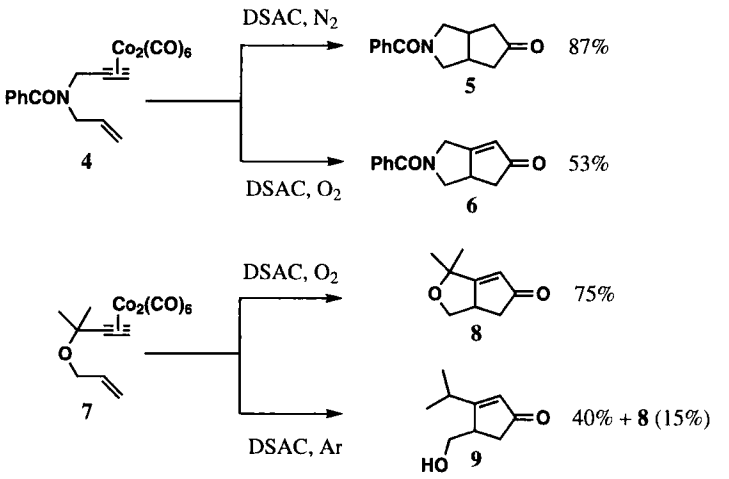
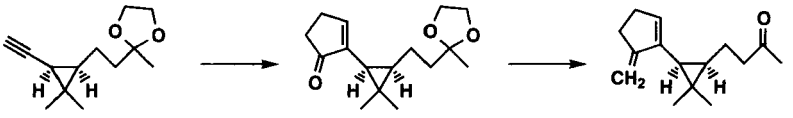


Fig. 2 Effect of Oxygen in DSAC Reactions

ranging from as little as 30 min. to several hours under a stream of oxygen until the color fades or changes to pale grey indicating the formation of metallic cobalt. The yields of these DSAC catalyzed reactions are generally high.[20-22] This method can be applied to systems in which the classical procedure has failed[19] although normally the substrates that react well require a polar group within the molecule in order to bind to the solid support. The importance of the use of oxygen rather than inert atmospheres is illustrated in *Fig. 2*. When compound **4** is heated with silica gel[26] under nitrogen the reduced compound **5** is produced in high yields whereas if air is present the expected product **6** is formed. Reduction does not always occur in the cyclopentenone ring. Compound **7**, when subjected to DSAC under oxygen gives **8** in high yield while under an inert atmosphere, the monocyclic enone **9** becomes the major product.[20] The catalytic effect of SiO_2 and other solid supports has been suggested to be due to (i) stabilization of a pre-transition state conformation imposed by the anchoring of polar centers in the enyne complexes with the surface OH groups on silica and (ii) *via* promotion of ligand exchange catalyzed once more by the OH groups.[20] An alternative explanation[28] is that SiO_2 promotes decarbonylation of the dicobalthexacarbonyl complex to provide a free complexation site for the alkene.

Solution phase reactions may be promoted by reagents that catalyze decomposition of the hexacarbonyldicobalt-alkyne complexes *via* oxidative decarbonylation.[9,28-35] Alkylphosphine and *n*-alkylphosphine oxides were first examined as reaction promoters by Pauson.[29] Use of a stoichiometric amount of phosphine oxides in the presence of either stoichiometric or catalytic amounts of preformed complex, led to an improved yields with respect to the earlier method although elevated temperatures were still necessary. An observation that transition metal carbonyl complexes release carbon dioxide in the presence of tertiary amine N-oxides[30] led to the use of such compounds as promoters of the Pauson-Khand reaction.[9,28,31-36] When simple trialkylamine-N-oxides such as N-methylmorpholine-N-oxide (NMO) and trimethylamine N-oxide (TMANO) are used, the reaction may be carried out at ambient temperature leading to good to excellent yields.[28,31-36] Oxygen once again is important in order to prevent reduction of the carbon-carbon double bond, although it is less critical than under DSAC conditions.[20,26] In some cases, improved yields have been obtained using NMO as an additive compared to DSAC conditions although sometimes at the expense of diastereoselectivities.[32] Electron-deficient substrates originally believed to be unreactive[9] have been cyclized easily in the presence of NMO.[33] It was noted that only the particularly unreactive methyl propynate had been studied previously. Recently, a modified procedure using nine equiv. TMANO•$2H_2O$ under an atmosphere of ethylene (25-30 atm) was developed for the key Pauson-Khand cyclization of **10** to give **11** in 81% yield.[34-36] This compound was further converted to obtain the natural product

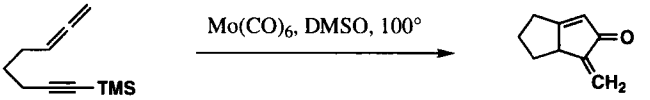


10 **11** (+)-taylorinone **12**

Fig. 3 Total Synthesis of Taylorinone

taylorinone (**12**) (*Fig. 3*). The use of other promoters such as DMSO and CH_3CN has been reported with varying results.[37] When they are used either as additives to inert solvents or used as the solvent, saturated ketones have been isolated, particularly in acetonitrile.

Although the Pauson-Khand reaction is extremely versatile, it is at present limited to fairly small-scale synthesis due to the relatively high cost of dicobaltoctacarbonyl. Some processes using substoichiometric (although not catalytic) amounts of either $Co_2(CO)_8$ or pre-formed alkyne complexes have been described.[29,38] The earliest of these used 0.2 equivalents of an alkyne complex in the presence of alkene, alkyne and CO promoted by tri-(n-butyl)phosphine oxide. Initial turn-over numbers were disappointingly low; the relative amounts of gaseous reactants and the overall pressure was found to be crucial and high pressures of CO are required in order to generate new $Co_2(CO)_6$-alkyne complex. In one case,[39] 0.22 mol % of $Co_2(CO)_8$ was used as the catalyst for the reaction between n-heptyne and ethylene, giving 98% conversion of starting material and yields of product between 47 and 49% with an average catalyst turn-over number of 220. The limitation of the catalytic process appears to be the formation of oxidized metal cluster compounds.[1,8,40,41] Additives have been used to prevent this process, triphenyl phosphate[42] and sodium borohydride[43] have been studied in this respect with some useful results. In one report, the $Co_2(CO)_8$ catalyzed (3 mol %) reaction of various enyne substrates in the presence of $(PhO)_3P$ (10 mol %) gave cyclopentenones in good to excellent yields (58-94%).[42] When $Co(acac)_2$ was used as a catalyst (0.01-0.05 mol %) in the presence of $NaBH_4$ (0.02-0.2 mol %), similar results were obtained; in one case, an alkynedicobalthexacarbonyl intermediate was isolated from the reaction medium.[43]



13 14

Fig. 4 Use of Alternative Carbonyl Complexes

An alternative to the catalytic methods is the use of other transition metal carbonyls, *e.g.*, iron[44], tungsten[45,46] and molybdenum[47] carbonyl complexes have been investigated. The reaction of the allenic substrate **13** mediated by $Co_2(CO)_8$ proved unsuccessful. However, when $Mo(CO)_6$ was utilized the bicyclic product (**14**)[47], *Fig.4*, was isolated in 68% yield *via* the loss of the TMS group.

II. THE INTERMOLECULAR PAUSON-KHAND REACTION

The regioselectivity of the intermolecular Pauson-Khand reaction has been studied extensively.[8-14] To illustrate some general trends, some simple examples are illustrated in *Fig. 5*. The reaction between ethylene and monosubstituted alkynes **15** gives the C-2 substituted regioisomers **16** exclusively[48-54] whereas disubstituted alkynes afford predominantly the same isomer,[52] i. e., the more bulky ethyl group of **17** ends up at at C-2 of **18**, although small amounts of the C-3 substituted regioisomer **19** is formed. The new C-C single bond is formed at the less substituted alkyne carbon atom.

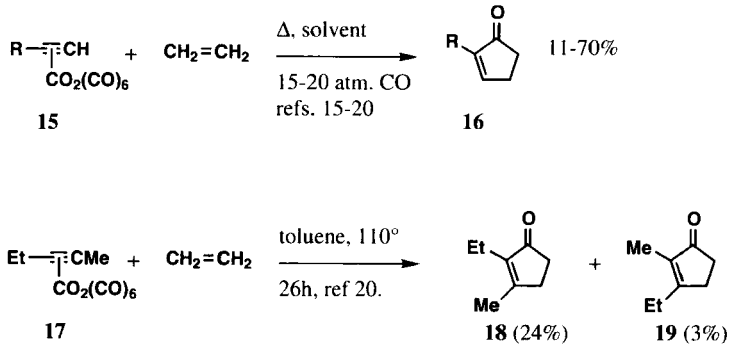


Fig. 5 Regioselectivity of the Intermolecular Pauson-Khand Reaction

The C-3 substituted cyclopentenones may be synthesized using alkyltrimethylsilyl alkyne complexes, leading to 2-trimethylsilyl-3-alkylcyclopentenones, which upon acid hydrolysis loose the TMS group.[3] A similar approach was used to control the regiochemistry of the key annulation step in the total synthesis of the natural product (13Z)-spata-13(15),17-diene (**22**) (*Fig. 6*).[55] The Pauson-Khand coupling between **20** and the cobalt complex derived from TMS-acetylene afforded **21** which upon further manipulation, yielded **22**.

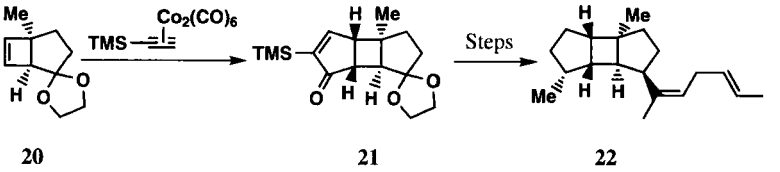


Fig. 6 Total Synthesis of (13Z)-Spata-13,(15),17-diene (22)

The use of aliphatic alkenes does not lead to good regioselectivity in reactions with either acetylene or simple monosubstituted alkynes[56] although interestingly tetrahydropyranyl allyl ether shows solvent dependent formation of the C-4 or C-5 regioisomers.[10] Important secondary products formed when simple alkenes are used are 1,3-dienes; in some cases they can become the major or sole reaction products.[48,56,57] Other useful substrates are cyclic alkenes and strained alkenes react particularly well. Thus, cyclopentene and norbornene react rapidly whereas cyclohexene is a poor substrate.[1,3,57] Similarly, heterocyclic alkenes such as 2,5-dihydrofuran react to give bicyclic systems,[4] 2,3-dihydrofuran (**23**) gives the 6-oxa derivative (**24**)[9] in which the heterocyclic oxygen and the ketone group are adjacent to each other (*Fig. 7*).

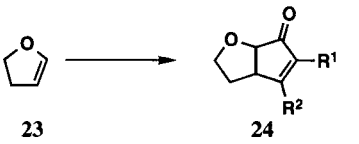
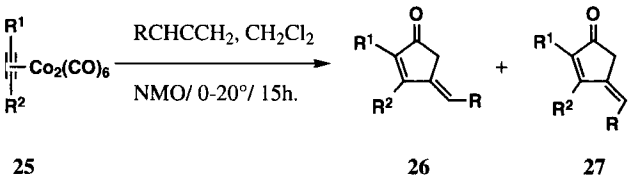


Fig. 7 Cyclization of 2,3-Dihydrofuran

As mentioned previously, allenic substrates may be used instead of alkenes;[47,59] the intermolecular cycloaddition between mono or disubstituted alkyne cobalt complexes (*Fig. 8*), and substi-

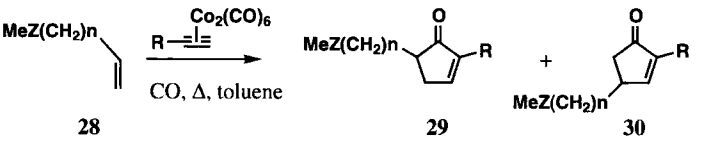
tuted allenes **25** mediated by NMO[59] gave the cyclopentenones **26** and **27**. The exocyclic double bond was formed at the C-4 position and the E/Z ratios ranged from 3:1 to 100:0.



25 **26** **27**

Fig. 8 Cyclization of Allenes

The control of the regiochemistry with respect to alkene substrates has been demonstrated by Krafft and coworkers[60] where heteroatom-containing terminal olefins were investigated (*Fig. 9*). When the olefins containing either sulfur or nitrogen (**28**) were examined, C-5 substituted products **29** were obtained preferentially to the alternative C-4 substituted derivatives **30**. The optimal number of methylene groups between the heteroatom and the double bond was investigated subsequently. The



28 **29** **30**

Group Z	n	Yield(%)	29:30	R
S	1	29	2:1	Ph
S	2	61	18:1	Ph
S	3	50	3:1	Bu
NMe	2	60	20:1	Bu
NMe	2	72	5:1	Ph
NMe	3	69	3:1	Ph

Fig. 9 Control of Regiochemistry by Soft Ligand Containing Substrates

regioselectivity increased dramatically for substrates containing two methylene groups whereas compounds with either more or less gave mixtures of regioisomers. Oxygen containing olefins, however, gave poor regioselectivities. These results suggested that both nitrogen and sulfur act as soft ligands to the cobalt complex giving a conformation that favors the formation of the C-5 diastereomers while oxygen being a hard ligand, gave poor results. The stereochemical outcome of this "directed" Pauson-Khand reaction was also investigated; the reaction between either *cis*- or *trans*-3-pentenylsulphides gave in each case the major product having the *trans* relative stereochemistry between the C-4 and C-5. This methodology was later applied to the preparation of a key intermediate, previously used by Corey, for the total synthesis of PGA_2.[61]

III. THE INTRAMOLECULAR PAUSON-KHAND REACTION

The intramolecular Pauson-Khand reaction has been particularly well studied in cases where the products formed contain a fused bicyclic system.[17-24,26,27,32,42,44,47] One of the advantages of this methodology is that the regiochemistry is predetermined by the position of the substituents in the enyne starting material, since the carbonyl group is inserted at the terminal carbon atoms of the alkene and alkyne which in the transition state are located close to the cobalt atoms. The bridge between the two unsaturated centers must contain at least three atoms. Hex-1-ene-5-yne with two methylene groups undergoes alkyne trimerization rather than form the cyclobutane fused Pauson-Khand product.[62] The bridge separating the alkyne and alkene moieties, however, may contain substituents and heteroatoms. With the use of promoters (N-oxides etc.) or under DSAC conditions, these types of substrates cyclize readily, often with good stereoselectivity.

The stereochemical outcome of these reactions is of importance and some general trends shall be discussed here. For more detail, the reviews of Schore *et al.*[8-14] are recommended. Normally, cyclization gives products in which the bulkier substituents lie on the *exo* face of the newly formed bicyclic compounds (*Fig. 10*). Thus ring-closure of **31** gave **32** and **33** with an *exo/endo* ratio of 4:1.

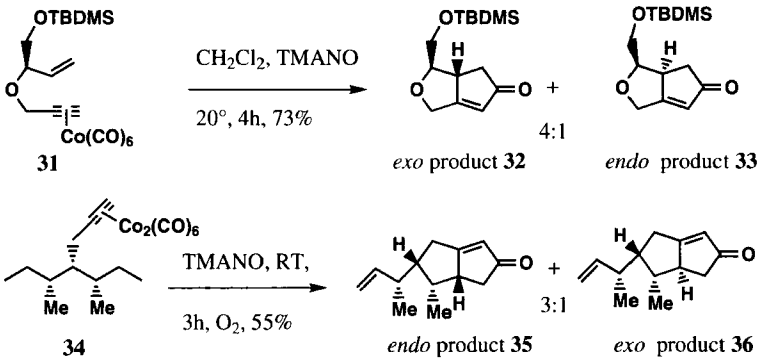


Fig. 10 Formation of endo Fused Bicyclic Systems as Major Products and an Exception

In an unique case a reversal of the normal stereochemistry was demonstrated[65] in which the *endo* fused isomer **35** was obtained as the major product from **34**. These results were explained by the conformational preferences of the enyne substrate **34** and the interactions associated with the transition state of the complex formation step making the formation of **36** more difficult. The position of substitutions in the bridge is important as far as the stereoselectivity of the reaction is concerned. In general, groups flanking the newly formed C-C single bond prefer to be on the convex face of the molecule whereas there appears to be a less strict configurational preference for the more distant groups. Bridgehead groups other than hydrogen may influence the configurations at the neighboring positions.

Following their work on soft ligand containing substrates[60] in the intermolecular reaction, Krafft *et al.* subsequently showed that sulfur bearing enyne precursors also exhibit accelerated reactions.[64] The rate was most enhanced when two methylene groups separated to alkyne moiety from the

sulfur atom. Hoye and Suriano demonstrated that the reaction of electron-deficient alkynones proceed in good to high yields.[65]

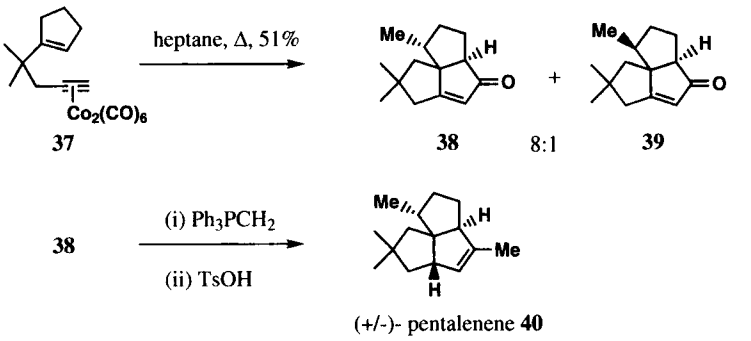


Fig. 11 The Synthesis of the Natural Product Pentalenene

More complex structures have been constructed using the intramolecular Pauson-Khand reaction.[66,67] The cyclic alkene **37** was used in the synthesis of the natural product (+/-)-pentalenene (**40**).[66] Thermal decomposition of **37** gave the isomers **38** and **39** with good stereoselectivity, the major isomer **38** was further modified to yield **40** (*Fig. 11*).

The DSAC conditions were used for the conversion of **41, 45** and **46** to the precursors of the bicyclic fenestrane derivatives **42, 43, 47a, 47b, 48a** and **48b**[23] which upon ultraviolet irradiation gave the fenestranes **44** and **49** (*Fig. 12*). The regioselectivity in these systems is of interest, compound **41** containing a 1,6-enyne and a 1,7-enyne system reacted exclusively to give the bicyclic compounds **42** and **43** derived form the 1,6-enyne. Compounds **45** and **46**, however, each containing two 1,6-enyne systems gave the heterocycles **47a, 47b** and **48a, 48b** possibly due to the anchoring of the polar allyloxy moiety to the surface of the silica gel used as an accelerator.

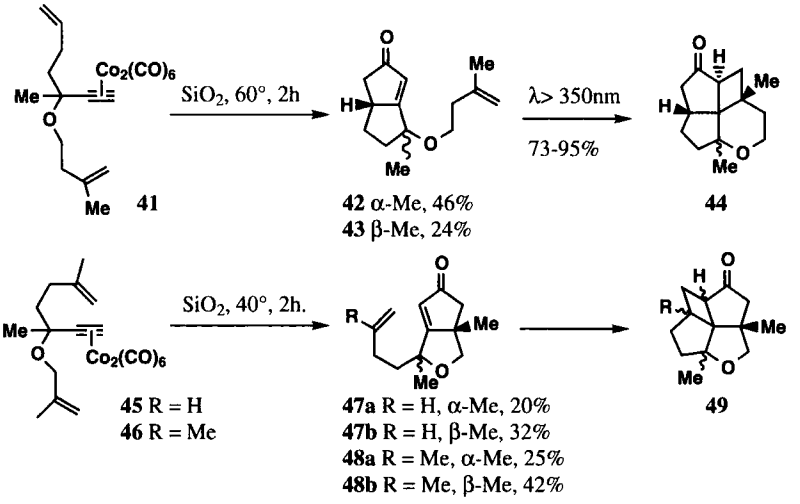


Fig 12. Synthesis of Fenestrane Derivatives and Regioselectivity of Substrates

IV. THE ASYMMETRIC PAUSON-KHAND REACTION

The careful choice of substrates or reaction conditions can make the Pauson-Khand reaction enantiospecific. Asymmetric synthesis using either chiral auxiliaries or chiral substrates are most often reported although the use of chiral cobalt complexes and N-oxides have also been investigated.

1. The Use Of Chiral Substrates (Chiral Pool Techniques)

The chiral pool approach to the asymmetric Pauson-Khand reactions has perhaps been the most popular methodology used to date. The earliest use of such methodology was published by Mulzer *et al.*[68] when they used (S)-2,3-*O*-isopropylidene-glyceraldehyde (**50**) as the source of chirality in the synthesis of carbocyclin, a synthetic platelet aggregation inhibitor.

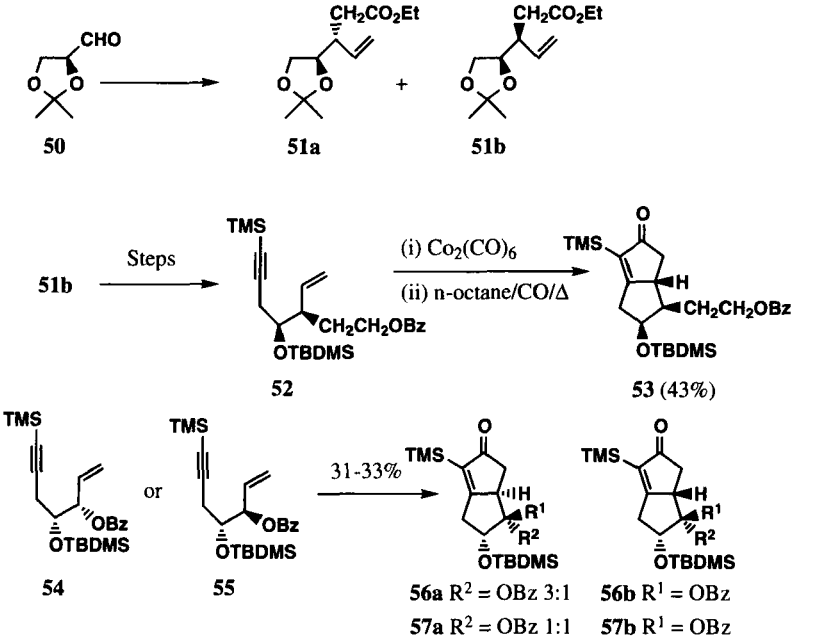


Fig. 13 Use of Chiral Substrates in the Asymmetric Pauson-Khand Reaction

The treatment of **52**, derived from **51b**, with octacarbonyldicobalt and subsequent thermal decomposition gave the enantiomerically pure compound **53** in 48% yield. The separated isomers **54** and **55** when treated similarly each gave mixtures of diastereoisomers **56** and **57** in (3:1) and (1:1) ratios respectively (*Fig. 13*). The stereoselectivities of these last two reactions depend upon the relative position of the benzoyl protecting group in the precursors **54** and **55**, the major product in the case of **54** being **56a** in which this group is on the exocyclic face. The influence of the configuration at the more distant C-7 is less important. The bulky *tert*-butyldimethylsilyl protecting group at C-7 becomes located on the convex face of the molecule in **56a** and **57a** and on the concave face in **56b** and **57b**.

Due to their interesting biological activity, (-)-α-kainic acid **68** and its derivatives (*Fig. 14*) have been the target of enantiospecific syntheses, some of which utilize the Pauson-Khand

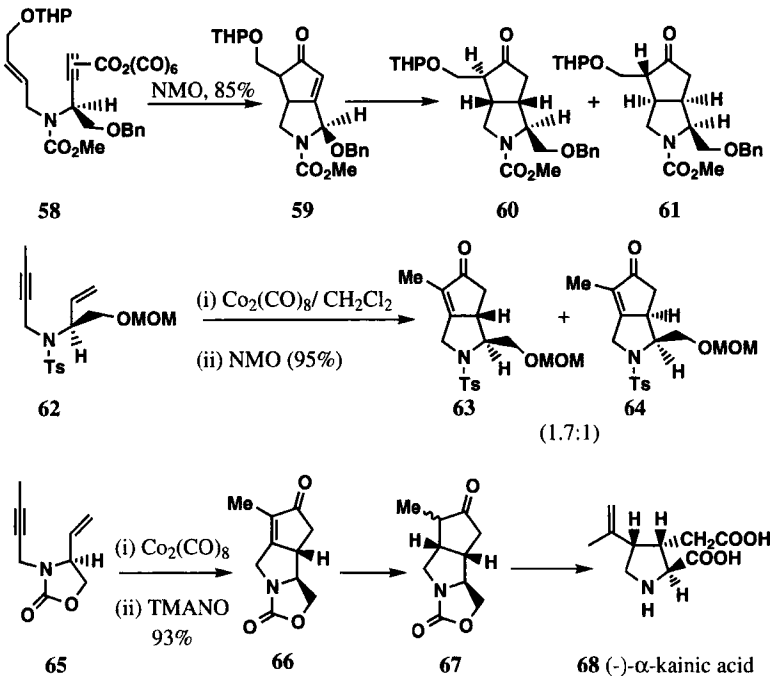
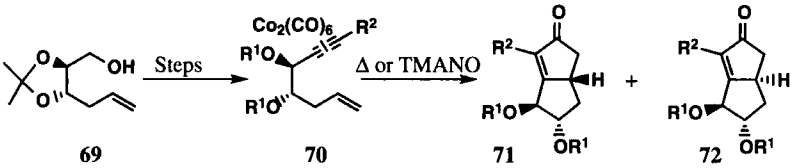
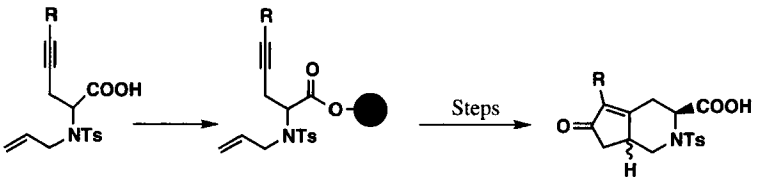


Fig. 14 Synthesis of α-Kainic acid Utilizing the Pauson-Khand Reaction

reaction.[69,70,71] The source of chirality in each case was derived by the use of (R)-4-benzyloxy-1-butyn-3-ol,[69] an optically active vinylglycine derivative,[70] and L-glutamic acid[71] respectively. The cyclization of the chiral complex **58**[69] with NMO lead to an inseparable mixture of isomers **59** which were reduced by hydrogenation to give the separable isomers **60** and **61**. The major product **60** has the same stereochemistry as **68**. An inseparable mixture of isomers **63** and **64** resulted from the Pauson-Khand reaction of **62**[70] mediated by NMO although with poor diatereoselectivity. As above the reduced systems were easily separated, the major isomer was then used to synthesize **68**. In a third approach,[71] the chiral oxazolidinone derivative **65** was used to control the stereoselectivity of the cyclization step giving **66** in 93% yield. Reduction gave a mixture of isomers **67** of which one isomer was used to synthesize **68** .



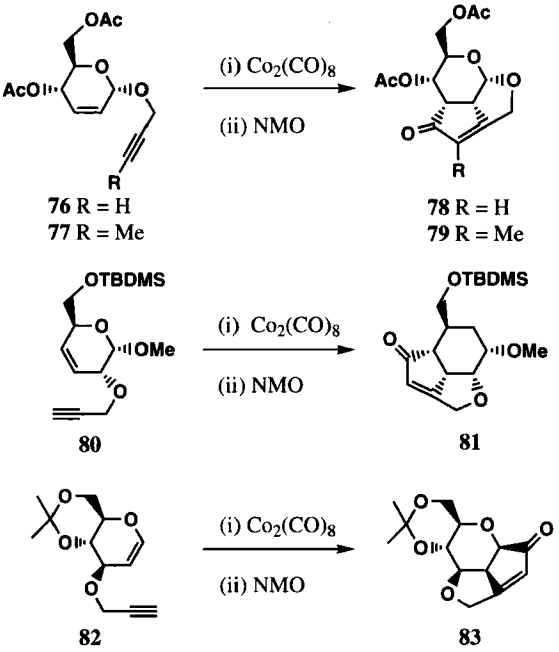
The chiral complexes **70**[72] synthesized from **69**, which can be derived from either L-ascorbic acid or dimethyl-L-tartrate, upon cyclization gave the bicyclic compounds **71** and **72** in high yields and good to excellent diastereomeric ratios. These ratios ranged from 45:55 when the R^2 group was a proton to 100:0 for bulkier R^2 substituents, regardless of the size of the oxygen bound groups.



73 74 (+/-) 75

Amino acid derivatives were used in one report[73] for the synthesis on a solid support of the bicyclic compounds **75**. The amino acid derivative **73**, derived from racemic propargyl glycine methyl ester when loaded onto a resin support, gave **74** in excellent yield. The stereoselectivity of this reaction was comparable to that found under solution phase conditions with the advantage that the purification steps were much simplified.

Carbohydrates have attracted attention as chiral substrates for the Pauson-Khand reaction. The first successful cyclization of sugar derived enynes was reported by Marco-Contelles in 1994.[74] Oxidation of the hexacarbonyldicobalt complexes **76** and **77** by NMO proved to be the key for the synthesis of the tricyclic compounds **78** and **79** in good yields (66 and 61% respectively) as single diastereoisomers (*Fig. 15*). One of the substrates **76** had been characterized previously[75] but proved reluctant to cyclization under the thermal DSAC conditions tried. An in-depth study of various substrates[76] showed that the products formed depend upon the configuration at the position to which the alkyne containing substituent is connected. Thus, the Pauson-Khand reaction applied to **80** and **82** gave **81** and **83** respectively. Two related papers[77,78] described the same phenomenon in other sugar



76 R = H
77 R = Me

78 R = H
79 R = Me

80

81

82

83

Fig. 15 Asymmetric Pauson-Khand Reactions in Sugar Based Substrates.

based substrates. In these reports, catalytic amounts of DMSO were used rather than N-oxides for the complex decomposition step.

The Pauson-Khand reaction has been applied successfully in the synthesis of fused tricyclic β-lactams with interesting structures.[79] The enantiometrically pure 2-azetidinones **84**, **86** and **88** afforded the β-lactams **85**, **87** and **89** as single isomers in good to excellent yields. NMR analysis of **89** did not allow its exact stereochemistry to be determined (*Fig. 16*).

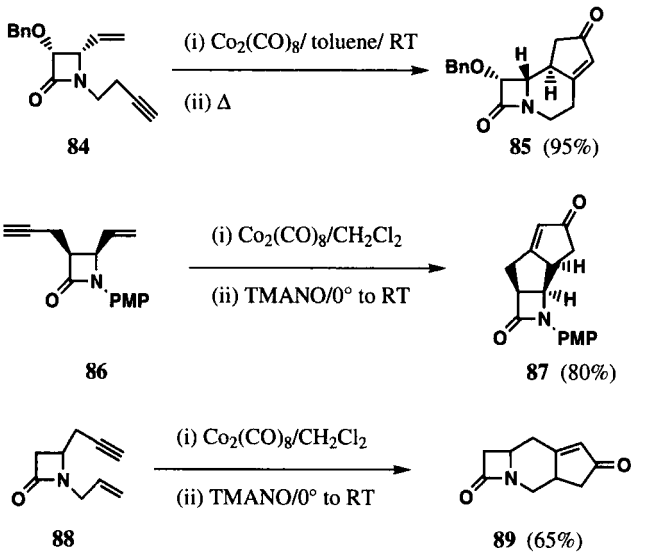


Fig. 16 Novel β-lactams via the Chiral Pool Approach to the Pauson-Khand Reaction

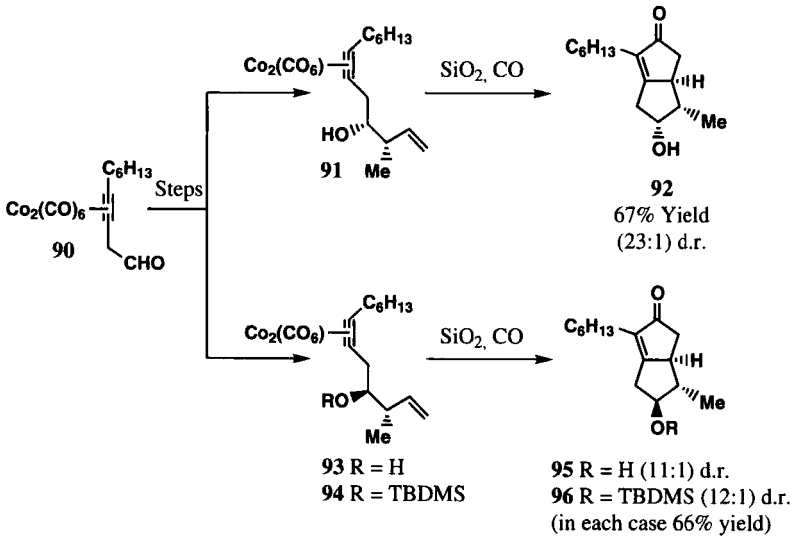


Fig. 17 Chiral Enynes via Enantioselective Allylborations and Their Cyclization Using DSAC Conditions

Asymmetric chemical modification may also be performed on achiral substrates. Thus, the

reaction of 3-decynalhexacarbonyldicobalt complex **90** with chiral allylboration reagents resulted in the enantioselective formation of enyne complexes **91**, **93** and **94** with enantiomeric excesses ranging from 31-88%.[80] When these enynes were heated with silica gel the bicyclic enones **92**, **95** and **96** were produced with high diastereoselectivities, the isomers having the C-6 substituent on the *exo* face of the molecule were formed preferentially (*Fig. 17*).

2. Chiral Auxiliaries

Asymmetric Pauson-Khand reactions have been carried out using the chiral auxiliary approach where a removable chiral substituent is used to influence the stereochemistry of the reaction. The majority of this work has been described by Moyano *et al.* who have based their investigations on menthol,[81] camphor[82] and particularly chiral 2-phenylcyclohexanol derivatives.[81-89] In their earliest publication,[81] the cyclization of 7-alkoxy-1-hepten-6-ynes was reported with initially disappointing diastereoselectivities (1.1:1) in the case of (-)-menthol acetylenic ethers. More promising results (3.2:1) were achieved when *trans*-2-phenylcyclohexanol was used as the chiral auxiliary. Further

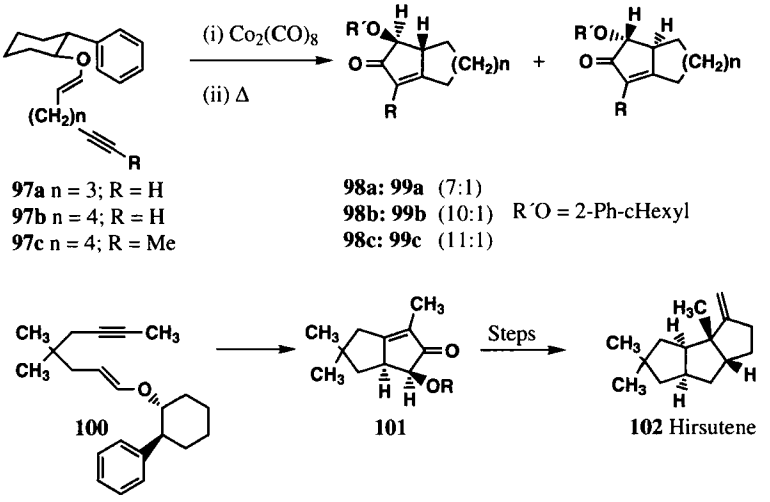


Fig. 18 Use of 2-Phenylcyclohexanol as a Chiral Auxiliary

investigation into enol ethers derived from (1S, 2R)-(+)-2-phenylcyclohexanol showed that although other more expensive or less readily available chiral auxiliaries often gave higher diastereoselectivities, the ease of separation of the phenylcyclohexanol derivatives and their crystalline nature made their use favorable.

The ring closure of derivatives **97a-97c** gave mixtures of the isomers **98a-98c** and **99a-99c** in which the former, containing exocyclic ether groups predominated, with good diastereomeric ratios ranging from (7:1) to (11:1).[83,84]

The chiral auxiliary tethered 1,6-enyne **100** was used to prepare **101** a key precursor in the formal

synthesis of the natural product hirsutene (**102**) (*Fig. 18*).[83]

This methodology is not limited to intramolecular reactions. The intermolecular Pauson-Khand reaction, between (1R,2S)-2-phenylcyclohexyloxyethynehexacarbonyl-dicobalt (**103**) and norbornadiene yielded a 2.5:1 mixture of diastereomers (*Fig. 19*).[85] The major isomer **104** was isolated by column chromatography in 58% yield. Other chiral auxiliaries were investigated, the best being 2-(9-phenanthryl)-cyclohexanol (>10:1 d.r.) but the 2-phenyl derivatives were used due to their easy separation. Thus compound **104** was subjected to copper mediated conjugate addition reactions to give *exo* face alkylated adducts (**105a-105d**) in 52-80% yields. Reductive cleavage of the chiral auxiliary was achieved with SmI_2 allowing the unchanged 2-phenylcyclohexanol to be recovered. A Lewis acid catalyzed *retro* Diels-Alder reaction applied to one derivative **105c** gave (S)-(-)-4-heptyl-2-cyclopentenone (**106**) with 95% ee.

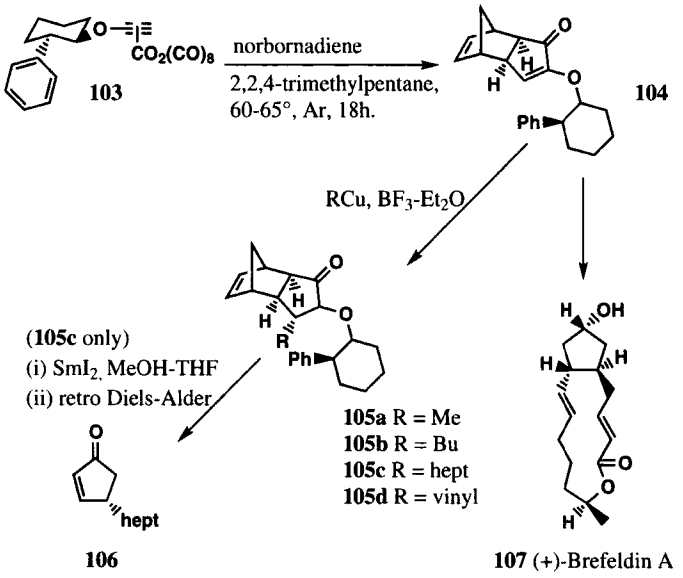
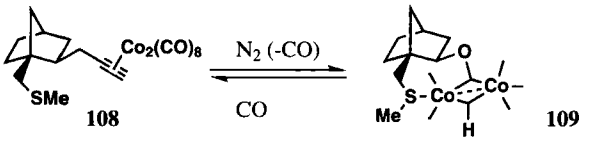


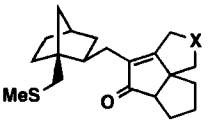
Fig. 19 Chiral Auxiliary Mediated Intermolecular Pauson-Khand Reactions

A more sophisticated application of the conjugate addition/retro Diels-Alder procedure was reported by the same group for the enantioselective formal synthesis of the fungal metabolite (+)-brefeldin A (**107**).[86] Similarly (+)-β-cuparenone[87] was synthesised using a derivative of (1R,2S)-2-phenylcyclohexanol to control the stereochemistry of the reaction.

The cobalt complex **108** derived from 10-methylthioisoborneol when placed under a stream of nitrogen was found to reversibly lose CO to form the cyclic complex **109** (*Fig. 20*).[88] Reaction of this complex with norbornene or norbornadiene gave mixtures of isomers with high diastereomeric ratios. Compound **108** was subsequently utilized in the asymmetric synthesis of the angular triquinane derivatives **110** and **111** with 9.5:1 and 12:1 selectivities respectively.[89] The sulfur atom was proposed

to act as a soft ligand, chelating at a vacant co-ordination site on cobalt, thus explaining the excellent diastereoselectivities observed.





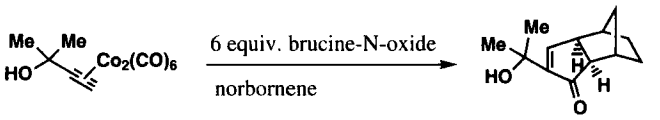
110 X = O, d.r. (9.5:1)

111 X = CH_2, d.r. (12:1)

Fig. 20 Use of Soft Ligand Containing Chiral Auxiliaries: Synthesis of Angular Quinanes (NB for clarity the carbonyl groups have been left out)

3. Chiral Promoters

Although tertiary N-oxides have proved to be valuable reaction promoters, only one example of the use of a chiral N-oxide has been recorded.[90] In this report, brucine-N-oxide catalyzed the reaction between the complex **112** and norbornene under varying temperature and solvent conditions (*Fig. 21*). Better stereoselectivities were observed at lower temperatures while the presence of THF as a coordinating solvent was found to accelerate the reaction without affecting the product ratios.



112 **113a + 113b**

Solvent	Reaction Conditions	Yield (%)	Enantionmeric Ratio (**113a:113b**)
CH_2Cl_2	RT. 5 min.	91	50:50
CH_2Cl_2	-10°, 12h.	61	45:55
THF	-17°, 1.5h.	97	35:65
THF	-37°, 6h.	88	32:68
THF	-55°, 48h.	69	30:70
CH_2Cl_2:THF	-20°, 48h.	78	32:68

Fig. 21 Product Ratios vs. Reaction Conditions: Use of a Chiral-N-oxide

The prochiral complex $Co_2(CO)_6$(phenylacetylene) **114** when treated with the optically active phosphine glyphos (**115**) gave a mixture of the diastereomers **116** and **117** which could be separated by preparative liquid chromatography (*Fig. 20*);[91] heating these complexes in toluene lead to their epimerisation. Reaction of the enantiomerically pure complexes with norbornene at low temperatures gave pure diastereomers of **118** in low yields (22-33%, 90-100% ee) while at higher

temperatures mixtures of enantiomers resulted. The same glyphos complexes were reacted with 2,5-dihydrofuran under DSAC conditions in order to circumvent the epimerization problem.[92] The reaction rate and optical purities were found to be temperature dependent; although slightly higher yields

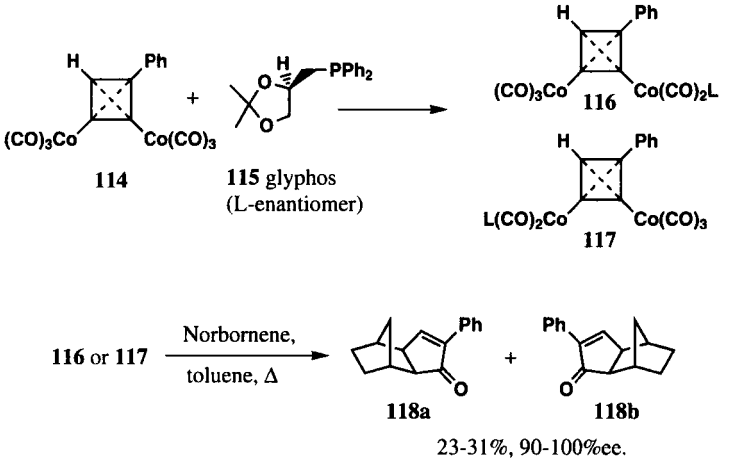
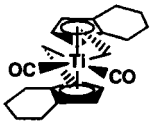


Fig. 22 High Diastereoselectivity Obtained with Glyphos Modified Complexes

were achieved under these conditions (41%), the enantiomeric excesses were much lower (76-79%). Decomposition of either **116** or **117** with NMO gave optically pure products **118** (ee >99%) in good yields (80-92%).[93]

In another report, chiral phosphine or phosphate pentacarbonyldicobalt complexes, derived from (-)-menthyl propargyl ether, decomposed in the presence of TMANO in THF/CH_2Cl_2 (1:1) gave *exo* substituted products in high yields (85-98%) with excellent optical purities (80-100% ee).[94]

Finally, although not a "classic" Pauson-Khand reaction, the recent contribution of Hicks and Buchwald[95] is of interest. Using (S,S)-(EBTHI)Ti(CO)$_2$ (**119**) as a catalyst, they performed highly enantioselective Pauson-Khand type reactions with both high yields (70-94%) and good to excellent diastereoselectivities (72-96% ee). This paper is remarkable since not only are the reactions asymmetric but also less than stoichiometric amounts of the titanium complex (5-20 mol%) were used.



119 (S,S)-(EBTHI)Ti(CO)$_2$

V. CONCLUSIONS

The versatility of the Pauson-Khand reaction as far as substrates and products are concerned makes it the reaction of choice for the synthesis of cyclopentenones. The possibility of the use of asymmetric synthetic methodology now makes the production of single enantiomers feasible. Chiral auxiliary and chiral pool techniques are as yet the most popular methods used and will most likely continue to be of great importance although the continued study of chiral carbonyl complexes and N-oxides is desirable. The investigation into metal carbonyls other than $Co_2(CO)_8$ as catalysts, particu-

larly those resistant to the formation of metal clusters, is important since this would allow the Pauson-Khand reaction to be carried out on an industrial scale.

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