1

The Pauson-Khand Reaction – an Introduction

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1.1 The Discovery and Early Evolution of the Khand Reaction

Over the period from the 1950s, metal-mediated methods have changed the profile and escalated the preparative potential of organic synthesis well beyond that which was previously possible or imaginable. New organic cyclisation techniques have been at the heart

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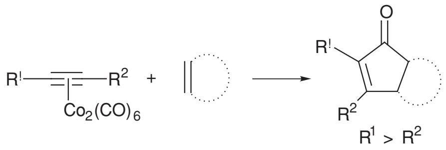
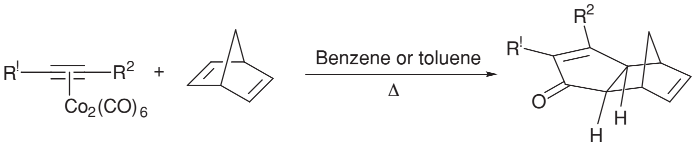
of the developments in this domain. In relation to this, the preparative interconversion now known as the Pauson-Khand reaction is a cyclopentenone-forming [2+2+1] annulation process involving an alkyne, an alkene, and a unit of carbon monoxide, originally supplied as a ligand in the starting hexacarbonylalkynedicobalt complex, as illustrated in Scheme 1.1. Despite many citations to this process having been divulged initially in 1973, the first account of this cobalt-mediated cyclisation was noted within a very short *Chemical Communications* article from Pauson's laboratory, submitted in November, 1970 and appearing in press in 1971, with the following line, "... the reaction of norbornadiene with complexes (I) [hexacarbonylalkynedicobalt complexes] yields hydrocarbon and ketonic products derived from norbornadiene, acetylene, and carbon monoxide."[1] Pauson and co-workers went on to describe this process in appreciably more detail in 1973.[2]



Scheme 1.1

As detailed by Pauson and Khand, the formation of cyclopentenones in a single step was a serendipitous discovery.[3] Within Pauson's laboratories at the University of Strathclyde, a programme of work had been aiming to establish the preparation of a series of cobalt-containing compounds from accessible cobalt complexes and alkynes, as a method by which to probe, for example, the reaction pathway involved in alkyne trimerisation processes. Believing that sufficiently reactive alkenes could be employed in a similar fashion to alkynes, norbornadiene was reacted with hexacarbonylalkynedicobalt complexes. Surprisingly, the main organic products from these reactions were ketonic in nature and, more specifically, possessed the general cyclopentenone structure, as shown in Scheme 1.2.[2a] This seminal discovery established the foundations for the study and enhancement of the synthetic transformation that is the subject of this monograph.



$R^1 = R^2 = H$: 43%
$R^1 = Me$; $R^2 = H$: 33%
$R^1 = Ph$; $R^2 = H$: 45%
$R^1 = R^2 = Ph$: 28%
$R^1 = R^2 = Et$: 23%

Scheme 1.2

Throughout the remainder of the 1970s, the initial scope and generality of this cyclopentannulation process was established through an extensive series of studies by Pauson and his co-workers. In relation to this, these reactions were conveniently performed by typically heating a mixture of the alkyne Co-complex and the alkene in hydrocarbon (or ethereal) solvents. Additionally, even from the initial series of reactions, for example those shown in Scheme 1.2, good levels of regio- and stereoselectivity were achievable within these cyclisation processes, with the larger alkyne substituent being installed in the position α to the cyclopentenone carbonyl unit and the *exo*-product predominating in all instances. Despite this, it is worth noting that other workers did not engage in research incorporating this preparative process, in any appreciable sense, until into the 1980s. The reasons for this somewhat delayed engagement by the preparative community may well have their foundations in the only low to moderate cyclopentenone yields delivered in many of the preliminary transformations, coupled with the variety of organometallic by-products formed within a typical reaction process and from which the desired organic compound had to be removed and purified. Having stated all of this and following a series of subsequent enhancements to this general preparative method (*vide infra*), the development and use of the Pauson-Khand reaction escalated considerably. By way of illustration, a simple Web of Science^{SM} search (using "Khand" as the topic keyword), conducted during the production of this manuscript,[4] delivered some 1,339 publications with this cyclopentenone forming technique cited in the paper abstract or keywords. Notably, over 1,300 of these publications have appeared since 1991 and, to illustrate the level of active and on-going employment of this cyclisation process, almost 6% of all these cited publications appeared in the year 2010 alone. In addition, this key annulation reaction has been the subject of a number of review articles.[3,5]

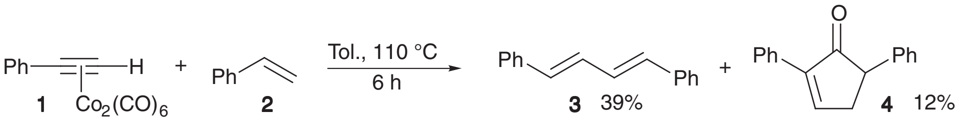
In relation to the use of the term "Khand" in the search process mentioned above and in a more general sense, it is worth discussing the name of this now widely employed transformation. As noted above, the cyclopentenone-forming transformation was discovered by Peter L. Pauson and co-workers at the University of Strathclyde in Glasgow. One of these researchers was Ihsan U. Khand, at this stage a postdoctoral research associate in Pauson's laboratory. Khand was born in India in 1935 and had moved to Glasgow in 1965, before initiating PhD studies in the Pauson laboratory in 1966. Khand's PhD thesis described the preparation and use of cationic iron sandwich complexes, and was completed in 1969, with the degree of PhD award being made in 1970. Thereafter and following a short period undergoing secondary school teacher training in Glasgow, Khand convinced Pauson to allow him to return to the laboratory for a one year period as a postdoctoral associate. It was during this period that the reaction of alkyne-cobalt complexes with alkenes to form cyclopentenones was discovered. Typical of his generosity and remarkable modesty, Peter Pauson only ever referred to this annulation process in spoken or written word as "The Khand Reaction". This can be seen quite clearly in Pauson's 1985 *Tetrahedron* review of this annulation protocol,[5a] as well as within all of his publications describing the development and use of this process. Indeed, it was quite a frustration to Pauson that other workers had amended the name of this, now world-renowned, transformation to include his own name. This was most vividly highlighted during the reviewing and acceptance of Pauson's final paper, in collaboration with our own laboratory; during this process the reviewers and editors had stipulated that the name of the reaction be changed to that which was more universally accepted. Accordingly, Pauson insisted that, if we were to do this, a footnote be inserted. This was duly done and read, "Hitherto one of us has preferred to use the initially designated name of 'Khand' reaction for this synthetic process; in light of what has now become common usage and following comments from the referees, we have subsequently employed the more widely accepted term 'Pauson-Khand' throughout this paper."[6] Based on all of this and returning to the search term initially utilised, if one was to employ "Pauson-Khand", almost one hundred papers would be missed.

Following on from the establishment of ferrocene preparation and reactivity, throughout the 1950s, 1960s, and 1970s Pauson became an internationally-leading contributor to preparative organometallic chemistry and the discovery of the "Khand Reaction" further enhanced his impact on the world stage, which continued well beyond his formal retirement. As for Dr Khand, despite returning to secondary school and college teaching employment from 1971, on an entirely voluntary basis he would appear in the Pauson laboratory most evenings, as well as at weekends and during school holidays, and throughout these periods established much of the original scope of this cycloaddition reaction. Based on this level of drive and dedication, perhaps one can see some of the reasons behind Peter Pauson's desire to have the reaction named as he did. Sadly, at the age of 44, Ihsan Khand passed away in January 1980.

1.2 The Intermolecular Pauson-Khand Reaction

The intermolecular Pauson-Khand (P–K) process has an appreciably wide tolerance in relation to substrate structure and functionality. In relation to the alkyne component, acetylene and terminal alkynes operate most effectively, whilst internal alkynes tend to deliver generally lower yields.[5c] With regards to the alkene partner, strained cyclic species tend to give good yields of cyclopentenone products, whereas increasing the sterics around the olefin reduces annulation effectiveness. In relation to these points relating to alkene reactivity, it is noteworthy that ethylene has been shown to be an effective and widely used PK cyclisation component, although elevated temperatures (80–160 °C) and pressures of ethylene (50-120 atm) were traditionally required.[7] Associated with the alkene strain considerations, a theoretical study by Milet, Gimbert, and co-workers has rationalised that the reactivity of the alkene component within P–K reactions is correlated to the back-donation of electrons from the metal centre to the π^* orbital (LUMO) of the olefin.[8] Furthermore, these authors have noted that a relationship exists between the C=C–C bond angle and the energy of the LUMO: the smaller the angle, the lower the LUMO energy. This is in direct accord with the reactivity pattern previously displayed across an olefin series: norbornene (107 °) $>$ cyclopentene (112 °) $\gg$ cyclohexene (128 °).[2,9]

One distinct limitation in relation to alkene applicability relates to olefins with conjugated electron-withdrawing units, which react to deliver conjugated dienes, where the new C–C bond has formed between the two most accessible carbon atoms of both the alkyne and alkene components. In relation to this, styrene substrates display intermediate behaviour. In the example shown in Scheme 1.3, following reflux in toluene, the phenylacetylene complex **1** couples with styrene **2** to give the conjugated diene **3** as the predominant product (39%), along with the cyclopentenone **4** in a more moderate 12% yield.[9] This outcome is in contrast with the more recent developments from Wender and co-workers,

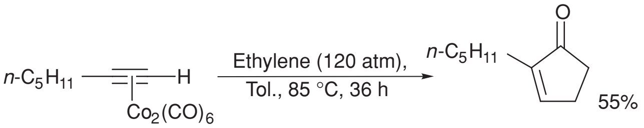


Scheme 1.3

where remarkable increases in efficiency and, indeed, selectivity for the cyclopentenone products have been achieved using rhodium-catalysed techniques.[10]

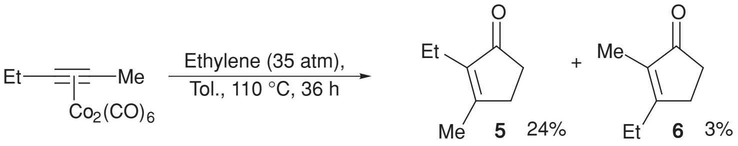
1.2.1 Regioselectivity of Alkyne Insertion

As detailed previously in relation to Pauson's original findings, alkyne regiochemistry is most often based on substituent sterics, with the larger of the C≡C triple bond components residing ultimately in the 2-position of the PK cyclopentenone product. The reasons for this appear to be embedded in key steps within the perceived reaction pathway (as will be detailed in Chapter 2). In most instances, the regioselectivity of alkyne insertion is complete;[5c] that shown in Scheme 1.4 effectively illustrates this point, as well as providing an example of the typical conditions traditionally employed for the use of a gaseous olefin such as ethylene (*vide supra*).[7d]



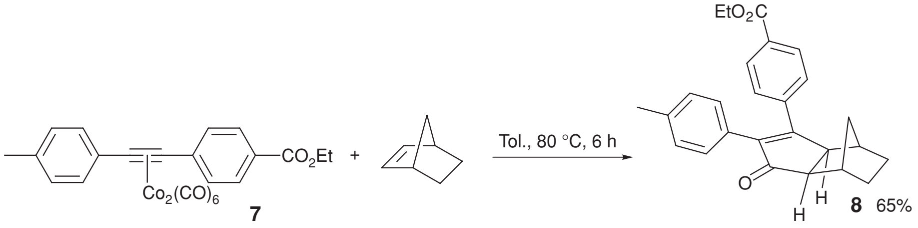
Scheme 1.4

In relation to internal alkynes where the substituents are similar in size, mixtures of products can result. One such example from Billington and Pauson, where both alkyne insertion regioisomers are observed, is provided in Scheme 1.5;[11] despite a mixture of products resulting, an 8:1 ratio of cyclopentenones (**5**:**6**) is obtained, with the less prevalent regioisomer **6** being formed in only 3% yield.



Scheme 1.5

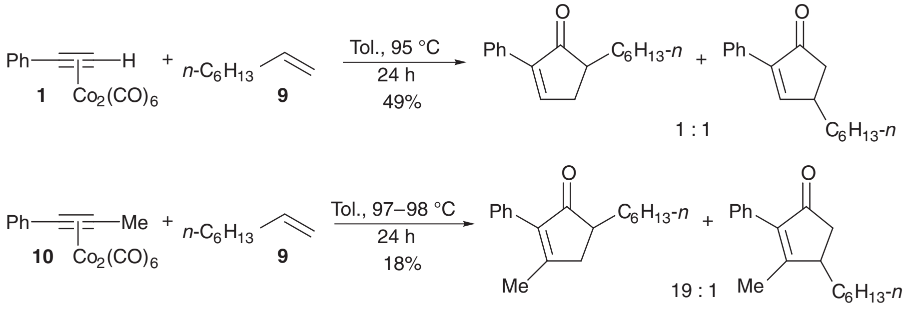
Further examples have appeared in the literature where the mode of alkyne insertion cannot be explained by steric factors. In this regard, it has been shown by Krafft that, in the case of internal alkynes bearing electron-withdrawing components, electronic considerations are required to be invoked in attempts to explain the regiochemical outcome of the P–K process. More specifically, with alkynes conjugated with an electron-withdrawing group (EWG), the cyclisation product formed is that with the EWG installed at the cyclopentenone 3-position.[12] This alkyne polarisation effect is further illustrated by Gimbert and Greene, with the example of an internal alkyne such as **7** possessing electronically distinct yet sterically rather similar substituents. In this instance, the sole cyclopentenone product **8** is that with the more electron-deficient arene positioned in the β-position (Scheme 1.6).[13] In attempts to explain these observations, in relation to the anticipated cyclisation mechanism, Krafft has proposed an argument based on preferential alkene insertion into one Co–C bond within a polarised alkyne complex intermediate. In contrast, following theoretical studies, Gimbert and Greene have used electronic differences between the alkyne termini in order to support the loss of a specific CO ligand (via a *trans*-effect exerted by the alkyne), in turn, leading to selective olefin insertion and, ultimately, delivering the cyclopentenone regiochemistry observed.



Scheme 1.6

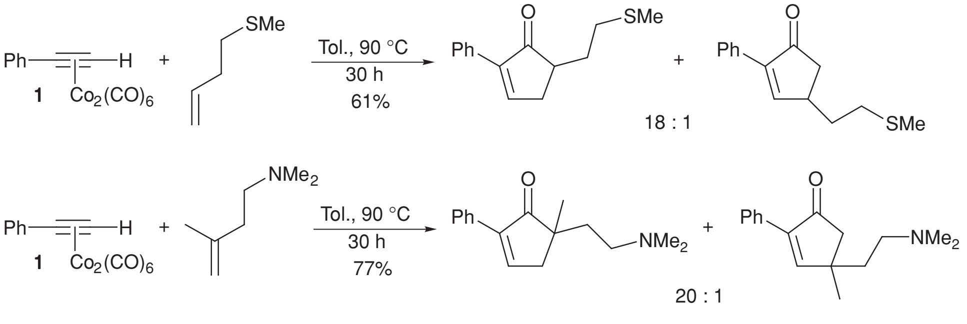
1.2.2 Regioselectivity of Alkene Insertion

From the broad array of examples performed as the scope of the PK annulation process was being established, it became clear that the selectivity associated with the alkene reaction partner was significantly less predictable.[5c,9] In particular, as well as delivering only modest yields of cyclopentenones, simple acyclic alkene substrates are incorporated with no regioselection when reacted with terminal alkynes (although the elevated levels of selectivity associated with the alkyne component are retained). This is illustrated in Scheme 1.7 by the reaction of 1-octene **9** with the phenylacetylene complex **1** to give a 1:1 mixture of the PK cyclisation products.[14] In contrast, when internal alkynes (e.g. **10**) were employed with the same class of aliphatic alkene substrates (e.g. **9**) significantly enhanced regioselectivity in relation to alkene insertion is achieved, albeit at the cost of appreciably lowered chemical yields in most instances.[14]



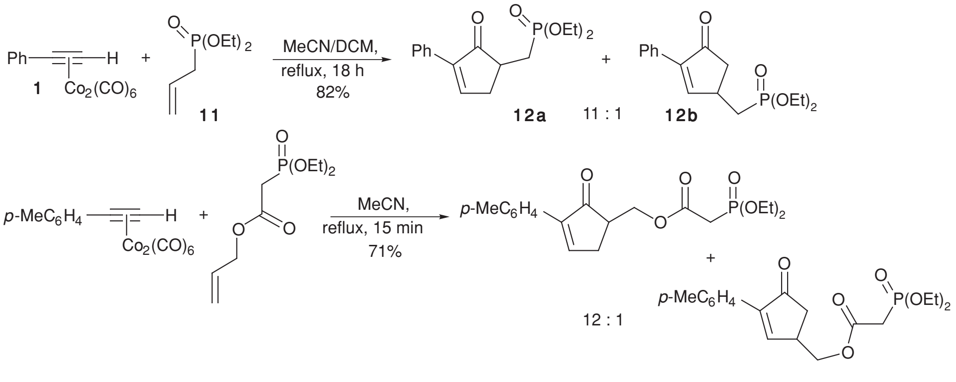
Scheme 1.7

It is worth noting that incorporation of aryl-substituted and heteroatom-containing alkenes can offer good to excellent levels of regioselectivity with terminal alkyne partners.[5c] Indeed, the same can be said, in a general sense, for unsymmetrically-substituted cyclic alkenes. Returning to the issue of employing more simple alkenes with terminal alkynes and in a drive to enhance the selectivity of the alkene incorporation, Krafft turned to the use of heteroatoms tethered to the olefin in attempts to control annulation regiochemistry. Using homallylic (or bishomoallylic) sulfides and amines, as functional units capable of acting as soft donor ligands, both the efficiency and regioselectivity of these PK processes were shown to be appreciable, and certainly when compared to the previously established and normally much less effective intermolecular reactions (Scheme 1.8).[15] These outcomes are believed to result from the tethered heteroatom acting as a ligand for cobalt along the reaction pathway, in turn acting to restrict the conformational flexibility of the complexed alkene, and leading to the more favourable formation of the 5-substituted products.



Scheme 1.8

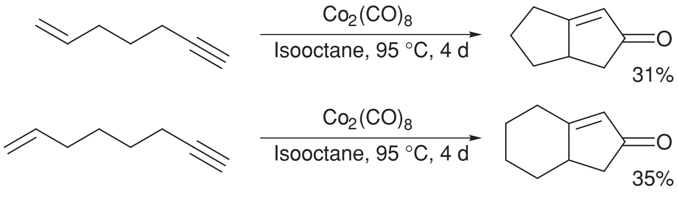
Following on from this pioneering work by Krafft and co-workers in the area of directed intermolecular PK reactions, studies within our own laboratory have led to the development of an analogous system with allylphosphonates. Optimised conditions with phenylacetylene complex **1** and diethyl allylphosphonate **11** led to the formation of cyclopentenones **12** in high yield and good levels of regioselectivity.[16] In due course, it was demonstrated that an extended class of alkenes possessing a tethered phosphonate ester unit could also be employed within P–K processes, again with good levels of olefin regiocontrol (Scheme 1.9), to deliver an additional class of phosphorus-containing cyclopentenones of further synthetic potential.[17]



Scheme 1.9

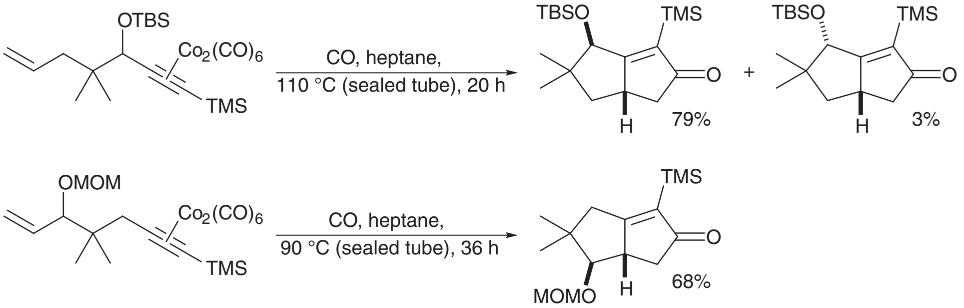
1.3 The Intramolecular Pauson-Khand Reaction

The establishment of the intramolecular variant of the PK reaction by Schore in 1981 provided a crucial advance associated with this methodology, which has allowed this metal-mediated cyclisation technique to grow considerably in importance and utility within preparative organic chemistry.[18] As illustrated in Scheme 1.10, it was shown within the original landmark publication that both hept-6-en-1-ynes and oct-7-en-1-ynes perform in the intramolecular PK process to deliver the bicyclic enones shown. In addition to this and by extension, others went on to show that similar oxygen- and nitrogen-tethered enynes could also take part in similar cyclisations to deliver the equivalent bicyclopentenone products.[19]



Scheme 1.10

A short period after Schore's initial publications in this area, Magnus further enhanced the efficacy of this method by showing that appreciable stereoselectivity could be embedded within intramolecular processes, a feature that was to prove key to the application of the PK reaction in natural product synthesis. As illustrated in Scheme 1.11, substituents at the propargylic (C3) and allylic (C5) positions have a preference to become situated on the *exo*-face of the resulting bicyclic PK products, and *syn* to the ring fusion hydrogen.[20] Furthermore, the level of stereoselectivity achieved is enhanced by bulky substitution at the terminal alkyne carbon. With the stereochemical reaction outcomes established for a number of substrate substitution patterns, Magnus and co-workers went on to utilise these methods within the synthesis of precursors to the linearly-fused triquinane natural products, coriolin and hirsutic acid.[20a,c] In addition, the employment of a similar stereoselective



Scheme 1.11

intramolecular PK strategy allowed the same research group to deliver an elegant approach to the cytotoxic sesquiterpene, quadrone, as well as the related biologically-active natural product, terrecyclic acid.[21]

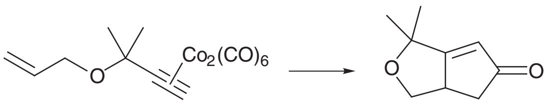
Following on from these seminal examples produced during the early- to mid-1980s, the intramolecular version of the PK annulation has continued to expand in terms of substrate scope and reaction selectivity, as well as general utility and effectiveness. In particular, this growth in PK potential has been driven by a range of emerging procedures and techniques, which have appreciably enhanced the overall efficiency of the cyclisation method, and which will be discussed through the following sections of this introductory chapter.

1.4 Enhancing the Pauson-Khand Annulation by Reaction Promotion

Traditionally, and as detailed in many of the examples cited to this stage, PK reactions were performed at elevated temperatures (and pressures) in aromatic or hydrocarbon solvents.[2,3,5a–d] Moreover, isolation and purification of the cyclopentenone products in the face of a plethora of organometallic by-products often presented further practical difficulties. Additionally and at least as importantly, the PK cyclisation product yields were more usually low to moderate. Accordingly, from the mid-1980s considerable efforts were applied to the enhancement of PK techniques by a number of researchers worldwide.

1.4.1 Dry State Adsorption

In 1985–86, Smit and co-workers reported on an appreciable practical advance in PK methodology.[22] By adsorbing the complexed alkyne onto a support such as silica or alumina and by gently heating in the dry state, reaction times were markedly reduced and yields dramatically enhanced. To illustrate this, an example that compares a more traditional thermal process with the dry state adsorption technique is shown in Scheme 1.12. These authors proposed that the donor sites on the solid surface were acting to enhance decarbonylative ligand exchange. Additionally, the adsorption of the substrate onto the (silica) support may well also act to limit conformational movement of the substrate, akin to the Restricted Rotamer Effect, and promote cyclisation. Through the remainder of the 1980s, Smit, Caple, and co-workers, as well as others, went on expanding the range of substrates utilised in both intra-[19b,23] and intermolecular[24] processes with this dry state method.

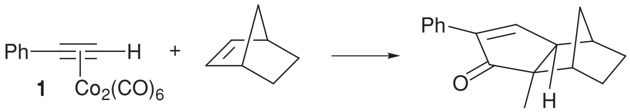


Conditions
Thermal: isooctane, CO, 60 °C, 24 h: 29%[19a]
Dry State Adsorption: SiO_2, O_2, 45 °C, 30 min: 75%[22]

Scheme 1.12

1.4.2 Ultrasound Techniques

Metal-carbonyl bond cleavage, which is believed to be the requisite first step in the P–K annulation, is promoted by ultrasonication.[25] In relation to this, the use of low powered sonication (e.g. an ultrasound cleaning bath) has been applied to both inter-[7d] and intramolecular[26] PK processes. Other than notably decreasing the required reaction times, these methods have had, at best, little general effect on the product yields. In contrast, studies from our own laboratory have shown that the use of high intensity ultrasound, in combination with other reaction promoters, can appreciably improve cyclisation efficiencies.[27] As shown in Scheme 1.13, the use of a titanium ultrasonic horn (Vibracell VC 50) alone reduces the reaction time for the reaction of complex **1** and norbornene from 4 h to 10 min, along with an uplift in reaction yield. When this sonication method is combined with an amine *N*-oxide promoter (*vide infra*) the intermolecular cyclisation is further enhanced in terms of both reaction time and cyclopentenone yield.

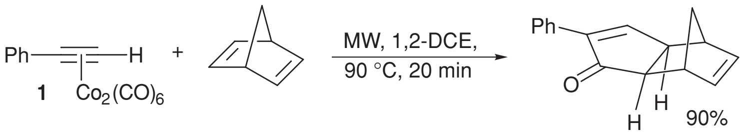


Conditions
Thermal: toluene, 60–70 °C, 4 h: 75%
Ultrasonication: high intensity))), 10 min: 84%
Ultrasonication and *N*-oxide promoter:
high intensity))), $Me_3NO.2H_2O$, 6 min: 95%

Scheme 1.13

1.4.3 Microwave Promotion

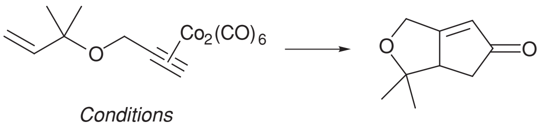
Over recent years and as an alternative to thermal heating, organic transformations have been subjected to irradiation within tuned microwave reactors, which has delivered generally elevated reaction efficiencies, particularly in relation to appreciably reduced reaction times.[28] In 2002, Evans reported the application of microwave (MW) techniques to a series of PK reactions, with the cyclopentenone products being delivered in good to excellent yields, as illustrated in Scheme 1.14.[29] In the same year, Groth *et al*. reported on a MW-promoted catalytic protocol, with cyclohexylamine as a reaction additive;[30] in general and despite the introduction of no additional CO gas being required, when compared to other methods this technique provided relatively moderate efficiencies with a series of normally reactive substrates.



Scheme 1.14

1.4.4 Amine *N*-Oxide Additives

Perhaps the most significant of all advances in the promotion of PK cyclisations, and in turn the elevation of this method as a widely utilisable tool in organic synthesis, came with the application of amine *N*-oxide additives, as first described by Schreiber *et al.* in 1990.[31] It had been well-known that amine *N*-oxides could be employed to remove carbon monoxide ligands from transition metal complexes by oxidation to carbon dioxide.[32] By extension and when applied within the PK manifold, this would render the first step of this process irreversible *and* potentially allow the use of significantly more mild reaction conditions. As shown in Scheme 1.15, the use of *N*-methylmorpholine *N*-oxide (NMO) as the reaction promoter allowed cyclisations to be performed under the remarkably mild conditions of stirring at room temperature;[31] by way of further illustration of the effectiveness of this *N*-oxide method, the outcome of the annulation with the same substrate using the previously optimal dry state absorption method is provided for comparison.[22] Following this publication by Schreiber, Jeong *et al.* divulged similarly mild and effective techniques with the equivalent trimethylamine *N*-oxide (TMANO).[33]



Conditions

Dry state adsorption: SiO_2, O_2, 55 °C, 1.5 h: 59%[22]

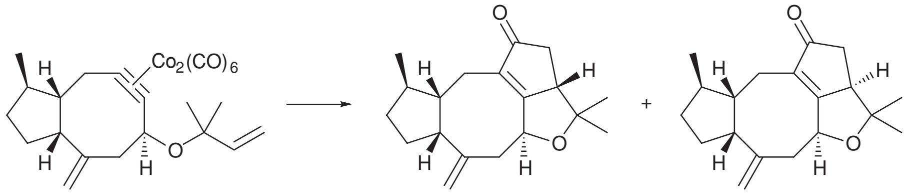
N-oxide promotion: NMO, CH_2Cl_2, r.t., ~12 h: 92%[31]

Scheme 1.15

In relation to these amine *N*-oxide promoted methods, it is important to note that the PK reactions with such additives appear to be significantly more clean, with the final cyclopentenone products normally requiring a trivial filtration or short silica column purification. Having stated this, one issue that is often overlooked or dismissed within publications in this area relates to the hydration state of the *N*-oxide additive used. More specifically, we[6,34] and others[12a] have found that the monohydrate of NMO and the dihydrate of TMANO offer optimal yields in most instances. The equivalent anhydrous *N*-oxides tend to lead to varying degrees of alkyne decomplexation or decomposition, unless there is a requirement for such, more active, *N*-oxides, for example, with less reactive alkyne complexes.[35]

Additional techniques that have emerged around this area include the formulation and use of recyclable polymer-supported amine *N*-oxides,[36] which provide the added advantage of sequestering cobalt by-products to deliver an even cleaner reaction process, and the use of molecular sieves in combination with *N*-oxide promoters.[37]

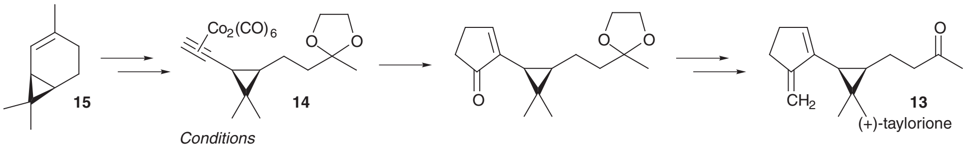
As stated above, the emergence of *N*-oxide promoted PK methods has significantly enhanced the preparative applicability of this annulation process. This point is beautifully illustrated within Schreiber's total synthesis of the diterpene natural product, (+)-epoxydictymene.[26,31,38] In this particular example, the central PK cyclisation proceeds under extremely mild *N*-oxide conditions to deliver the desired cyclopentenone product with elevated levels of selectivity over that obtained under the more standard thermal protocol (Scheme 1.16).



Conditions
Thermal: CH_3CN, reflux, 15 min: 85% (5:1)
N-oxide promotion: NMO, CH_2Cl_2, r.t., 12 h: 70% (11:1)

Scheme 1.16

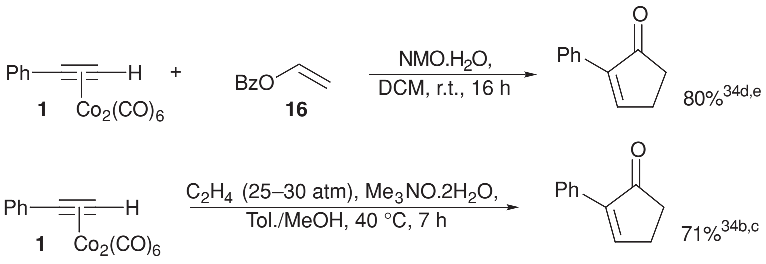
As discussed previously, conditions for use of gaseous olefins in the PK annulation require more forcing conditions and generally lead to only low to moderate yields of cyclopentenone products.[7] In relation to this, work in our own laboratory has formulated optimised conditions with *N*-oxide promotion for the use of ethylene as the alkene reaction partner under appreciably more moderate temperatures and pressures.[34a–c] Indeed, whilst mild autoclave pressure (25–30 atm) and temperatures (40 °C) provided optimum yields in most instances, it was also found that atmospheric pressures of ethylene at room temperature also delivered the targeted cyclopentenones. It is also worth noting that both techniques result in considerably cleaner product reaction mixtures than those obtained under the more traditional thermal protocols. As shown in Scheme 1.17, these developments allowed us to efficiently complete a total synthesis of the sesquiterpene, (+)-taylorione **13**;[34a,c] the requisite chiral alkyne complex **14** was prepared in seven steps from the inexpensive and readily available starting material, (+)-2-carene **15**, and, following successful application of the *N*-oxide promoted PK conditions with ethylene, (+)-**13** was obtained in short order and with high optical purity.



Conditions
Thermal: C_2H_4 (50 atm), C_6H_6, 80 °C, 5 h: 38%
N-oxide promotion: C_2H_4 (25 atm), $Me_3NO.2H_2O$, tol./MeOH, 40 °C, 24 h: 81%
N-oxide promotion at atmospheric pressure and r.t:
C_2H_4 (bubbling), $Me_3NO.2H_2O$, C_6H_6/MeOH, r.t., 18 h: 41%

Scheme 1.17

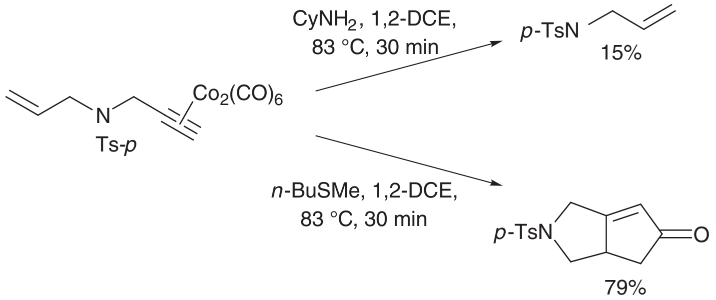
In continuing efforts to further develop the PK reaction towards delivering cyclopentenones from ethylene incorporation, when vinyl esters, such as vinyl benzoate **16**, were employed with *N*-oxide promotion, the products which resulted were those where the expected ester unit had been cleaved, presumably via an *in situ* reduction process with low valent cobalt.[34d–f] This outcome clearly establishes an extremely mild and utilisable protocol for employment of the vinyl ester as an ethylene equivalent, without the requirement for handling of gaseous reagents. Moreover and as illustrated in Scheme 1.18, the new vinyl benzoate technique is at least comparable with the optimum ethylene methods (*vide supra*) and, in most instances, significant enhancement in the yield of cyclopentenone can be realised. It should also be noted that similar reductive outcomes have been observed in PK reactions with vinyl halide substrates.[9, 39]



Scheme 1.18

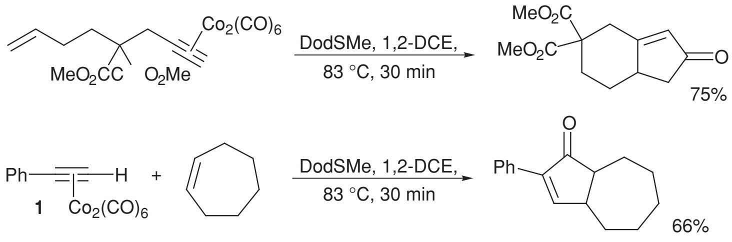
1.4.5 Sulfide Promoters

In 1997, Sugihara and Yamaguchi introduced the concept of employing Lewis basic additives to promote the PK reaction, and demonstrated this with the use of, in particular, cyclohexylamine to enhance a series of both intra- and intermolecular examples,[40] albeit under considerably greater forcing temperatures than those used with amine *N*-oxides. Despite the apparent success of the amine additive method, less reactive alkenes did not perform well under the developed conditions and cleavage of carbon-heteroatom bonds was also observed. Accordingly, further advances by the same researchers using sulfide-based promoters have become significantly more widely employed by the preparative community.[41] An example using the recommended *n*-butyl methyl sulfide promoter compared with the cyclohexylamine additive in reaction with the allyl propargyl amine is shown in Scheme 1.19.



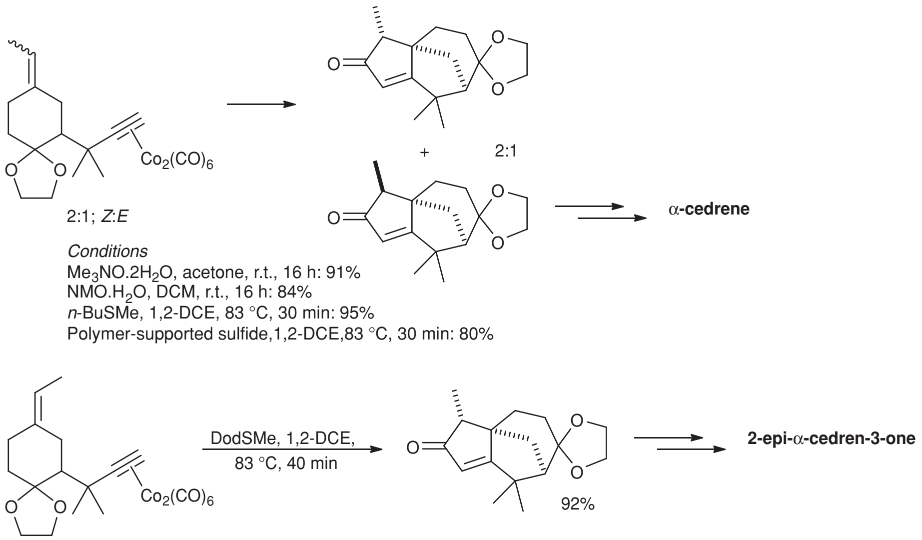
Scheme 1.19

Despite the more elevated temperatures that are required, this sulfide-based method appears to be complementary with the amine *N*-oxide techniques. Having stated this, some appreciable practical drawbacks are encountered when employing this low molecular weight sulfide, which possesses a rather unpleasant smell and is lachrymatory in nature. Accordingly and in seeking to establish a more user-friendly protocol, work from our own laboratory has shown that the inexpensive and stench-free alternative, *n*-dodecyl methyl sulfide (DodSMe) is a highly effective promoter of both intra- and intermolecular PK annulations (Scheme 1.20).[42] Additionally, in every case investigated, the reaction efficiencies and yields obtained when utilising DodSMe were at least comparable with those from the use of the less practically convenient sulfide, *n*-BuSMe.



Scheme 1.20

In a similar fashion to that described for amine *N*-oxide promoters (*vide supra*), work from our own laboratory has shown how the sulfur additive can be attached to a solid support. These polymer-bound and odourless materials display PK promoting abilities in line with the solution-phase additives, with the further advantage that they can be reused extremely effectively over a number of cycles.[43] Further practical benefit arises from the reaction work-up now merely involving filtration and minimal cyclopentenone purification. Finally in this section, and by way of illustrating how these sulfide-promoted methods can provide further techniques for use within natural product synthesis (when compared to other available protocols), Scheme 1.21 illustrates the key PK cyclisations used within our



Scheme 1.21

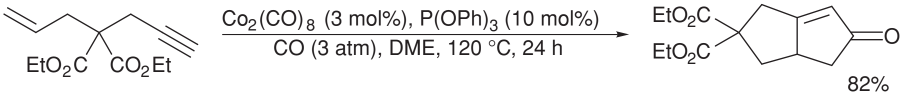
laboratory in routes towards the tricyclic sesquiterpenes, α-cedrene and 2-epi-α-cedren-3-one.[6, 34g, 42]

In relation to how these Lewis base additives operate to enhance the efficiency of PK reactions, it had been assumed that such species accelerate the decarbonylative-Lewis base ligand exchange process and, in turn, promote the loss of a further CO ligand to provide a vacant coordination site for olefin complexation. Despite these assumptions, a more recent theoretical study by Milet and Gimbert has provided quite a different scenario, and leading to the proposal that the Lewis base promoters achieve their PK annulation enhancing effects by making the olefin insertion step of the reaction pathway an irreversible process.[44]

1.5 Catalytic Pauson-Khand Protocols

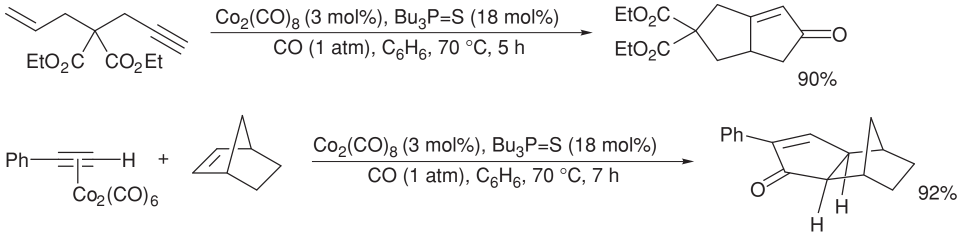
Moving the cobalt-based PK reaction into the catalytic domain would allow this already widely utilised transformation to assume magnified importance not only within industrial settings but within the synthetic community as a whole. In this regard, attempts were made to employ sub-stoichiometric quantities of octacarbonyldicobalt in some of the earliest studies on the PK annulation process,[2a, 21] with efficient cyclisations only being achieved at relatively high catalyst loadings and when the most reactive strained alkenes were used. In 1990 an appreciably more productive catalytic system was divulged by Rautenstrauch and co-workers.[45] Despite the employment of only 0.22 mol% catalyst leading to a high turnover number of 220 for $Co_2(CO)_8$, the reaction conditions for this PK annulation between 1-heptyne and ethylene required partial pressures at room temperature of 100 bar CO and 40 bar C_2H_4, and heating to 150 °C (to deliver a total pressure of 310–360 bar) over 16 h reaction time, leading to a 49% yield of the desired cyclopentenone product. From this stage and over recent years a number of significantly more effective Co-catalysed processes have been formulated by a number of research groups.[5j] Since the protocols using cobalt-based catalysts will be discussed in more detail elsewhere (Chapter 3), only a selection of methods will be discussed here to provided a flavour of the advances made to date.

In 1994 Jeong and co-workers divulged the first practically efficient catalytic PK system.[46] As illustrated in Scheme 1.22, with the key introduction of a phosphite ligand, low levels of $Co_2(CO)_8$ could be employed combined with relatively modest CO pressures. Despite the obvious successes of this approach, this method appeared to be limited to intermolecular examples, coupled with a requirement for 120 °C reaction temperatures. Following on from this, Krafft has also formulated a series of equally effective catalytic $Co_2(CO)_8$-based protocols (at lower temperatures and CO pressures) with cyclohexylamine as the reaction additive.[47]



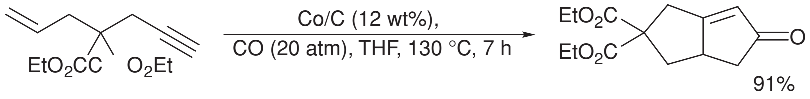
Scheme 1.22

In a further example with $Co_2(CO)_8$ as catalyst, Hashimoto and Saigo have shown that the introduction of tributylphosphine sulfide allows the use of only atmospheric pressure CO to deliver efficient cyclisations in a series of intramolecular PK reactions (Scheme 1.23).[48] Notably with this method, an intermolecular reaction was also reported, albeit with the strained and reactive olefin, norbornene.



Scheme 1.23

Heterogenous cobalt-based catalysis has also been applied, in particular with the use of Co loaded onto a range of supports, or by the employment of recyclable colloidal Co nanoparticles, as divulged in an extensive series of reports by Chung, Hyeon, and co-workers.[49] As illustrated in Scheme 1.24, cobalt on charcoal can be employed effectively in intramolecular PK annulations, albeit at relatively elevated temperature and CO pressure. Interestingly, the Co on C catalyst can be recycled extensively without loss in efficiency and with <0.1 ppm of Co being bled from the support. This specific technique has also been shown to be successful in intermolecular examples, again, with the reactive alkene, norbornadiene.



Scheme 1.24

From this brief summary of cobalt-based catalytic methods, it is clear that systems have yet to be developed that would allow less reactive alkenes to be applied in an intermolecular sense and, more generally, the employment of milder reaction conditions to be adopted. Accordingly, catalytic PK protocols continue to be a focus of the preparative chemistry community. In relation to this, a series of additional and complementary catalytic techniques using other metal species are adding extensively to the growing repertoire of PK methods, and these will be detailed in Chapter 7.

1.6 Concluding Remarks

From relatively modest beginnings at the University of Strathclyde, due to the outstanding contributions of an extensive spectrum of international researchers, the Pauson-Khand reaction has grown to become a synthetic method of immense value to the global chemistry community. As discussed above, a series of methodological advances now allow this annulation process to be used with preparative confidence, to deliver generally very good levels of efficiency and selectivity in both an intra- and intermolecular sense. Accordingly and as illustrated with some examples above, the PK technique is finding continual use in targeted natural product synthesis (see Chapter 8). Furthermore and as will be detailed in Chapters 4, 5, and 6, an array of enantioselective methods have also now been developed.

This monograph will describe the development and application of the Pauson-Khand reaction and related processes over the 40-or-so years since the initial discovery of the original cobalt-mediated annulations. The development of this method forms just one, albeit significant, part of Peter Pauson's seminal contributions to organometallic methods and organic synthesis. As for Dr Khand, one feels that he would be immensely pleased to observe where his serendipitous discovery had been elevated to, as well as the impact that this cyclisation process has had on preparative organic chemistry.

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