7.2
Transition Metal Alkyne Complexes: Pauson–Khand Reaction

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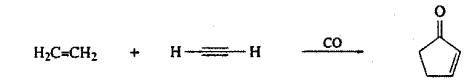
7.2.1 GENERAL CONSIDERATIONS

7.2.1.1 Introduction

The synthesis of organic carbocyclic and heterocyclic systems from acyclic building blocks is typically achieved through the use of either condensation or cycloaddition processes. Organic cycloadditions permit the preparation of a great variety of systems, especially those containing three- to seven-membered rings. While most such processes involve the combination of two reaction partners, numerous examples exist of multicomponent cycloaddition reactions involving selective incorporation of three or more different molecules.[1] While transition metals have long been known to induce a marvelous array of reactions of organic π-systems, including a remarkable variety of formal cycloaddition reactions, the widespread application of this methodology to organic synthesis is a relatively recent phenomenon, coinciding with a rapidly growing body of knowledge concerning the detailed mechanisms of these processes. As a fuller understanding of transition metal-mediated reactions has evolved, the rational development of new and more selective transformations has begun to tak place.[2] This chapter deals with one of the several systems that have been found to be suitable for

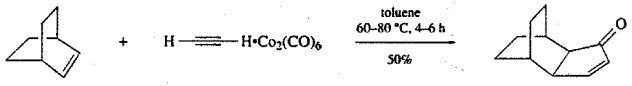
cocycloaddition of alkynes, alkenes, and carbon monoxide to form cyclopentenones,[3–5] the Pauson–Khand reaction.

The Pauson–Khand reaction (sometimes referred to as the Khand–Pauson, or, simply, the Khand reaction) was discovered by Ihsan U. Khand in the laboratories of Professor Peter L. Pauson at the University of Strathclyde, Glasgow, UK. In the course of a study aimed principally at the preparation and characterization of various alkene and alkyne complexes derived from $Co_2(CO)_8$, metal-free compounds possessing cyclopentenone functionality were isolated.[6] The overall process is a formal three-component, [2 + 2 + 1] cycloaddition, incorporating the alkene π-bond, an alkyne π-bond, and the carbon atom of CO into the new five-membered ring (Equation (1)). The initial examples, reported in 1973, displayed significant degrees of regio- and stereochemical selectivity, which have since been developed in a number of directions. At first, the Pauson group was virtually alone in pursuing the development of this reaction, exploring the scope and limitations of the intermolecular version of the process extensively. In the early 1980s the first examples of intramolecular Pauson–Khand cycloadditions were reported. Over the course of the 1980s, the reaction has taken its place as an important methodological approach to the challenging cyclopentenone ring system, is a focus of continuing development by a number of research groups, and has been used in synthetic applications by many more.

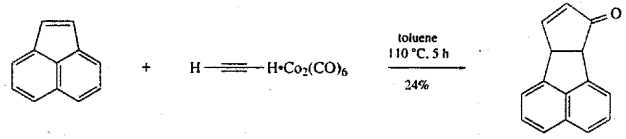


(1)

Pauson–Khand reactions have been carried out under several markedly different types of reaction conditions. In the method used in most of the earlier intermolecular examples, the alkyne is allowed to react with a stoichiometric amount of $Co_2(CO)_8$ (which may be prepared *in situ* from $CoCl_2$) at room temperature over the course of several hours in hydrocarbon or ethereal solvent to generate the thermally relatively stable, readily characterized complex $Co_2(CO)_6{\cdot}R^1C{\equiv}CR^2$.[7] This in turn reacts under heating with a wide variety of alkenes to generate cyclopentenones (Equations (2) and (3)).[8,9] The reaction is normally carried out under either nitrogen or carbon monoxide; if the alkyne in $Co_2(CO)_6{\cdot}RC{\equiv}CR^1$ is a gas it is typically incorporated into the atmosphere above the reaction mixture. Depending on substrate reactivity, reaction times range from hours to days at temperatures between 70 °C and 110 °C for most alkenes. Yields are highly variable, but are usually between 30 and 70%, with favorable combinations of substrates affording yields in excess of 90%. The use of pressure higher than 1 atm is usually unnecessary but has occasionally resulted in improvements in yields when the reaction is carried out in a sealed tube.[10]

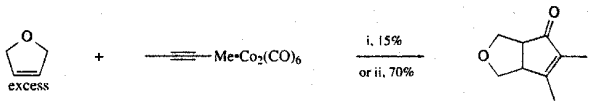


(2)



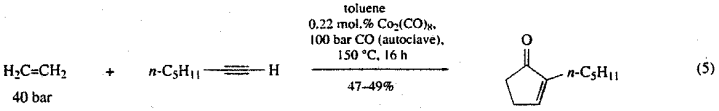
(3)

An obvious area of exploration has been the possibility of employing less than stoichiometric amounts of the metal carbonyl. Early work with gaseous alkynes suggested that the process could be carried out in a catalytic fashion by stirring a mixture of alkene and ca. 10 mol.% $Co_2(CO)_8$ in an inert solvent under a 1:1 alkyne/carbon monoxide atmosphere. The success of these attempts depended upon the continuous supply of excess alkyne being able to trap and recycle reactive cobalt-containing fragments. Although several instances of improved yields were reported, the turnover numbers were very low (Equation (4)).[11] More recent work by Rautenstrauch has critically examined the factors that contribute to the competition for cobalt-containing fragments in such reaction systems. Best results (turnover number = ca. 220) are obtained by using high pressures of CO and alkene in an autoclave. The method appears to be limited to the use of ethene as the alkene reaction partner (Equation (5)).[12]



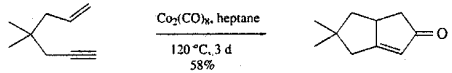
(4)

i, toluene, 110 °C, 8 h, N_2; ii, isooctane, 85 °C, 8 d, 1:1 CO/2-butyne



(5)

The intramolecular variation of the Pauson–Khand reaction, usually involving systems related to 1,6-heptenyne, has most frequently been carried out under thermal conditions, similar to those described for the intermolecular process above (Equation (6)).[13] However, two major methodological improvements appeared in the latter half of the 1980s and in the early 1990s. First, Smit and Caple made the remarkable discovery that adsorption of the cobalt-complexed enynes onto any of a variety of chromatographic supports (silica gel, alumina, zeolites, etc.) enormously facilitates intramolecular Pauson–Khand cycloaddition. Reactions that in solution require 24 h heating at temperatures ranging from 60 °C to greater than 100 °C may be carried to completion in under 2 h by gentle heating of the dry solid adsorbate, usually at temperatures under 60 °C (Equation (7)).[14]



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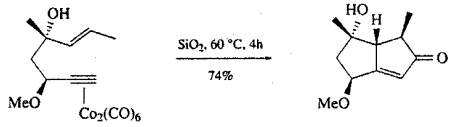
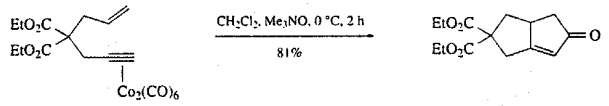


(7)

Second, the reaction was found to be facilitated by the presence of a number of "additives" or "promoters." Pauson first reported the beneficial effects of adding phosphine oxides to intermolecular cycloadditions in 1988.[15] Shortly thereafter Schreiber described the acceleration of intramolecular Pauson–Khand reactions by amine *N*-oxides.[16] Further elaboration of this technique in several laboratories has revealed still other additives that benefit the process.[17] This general approach has become the method of choice for most such cycloadditions, affording high yields and short reaction times, often at room temperature or below (Equation (8)).



(8)

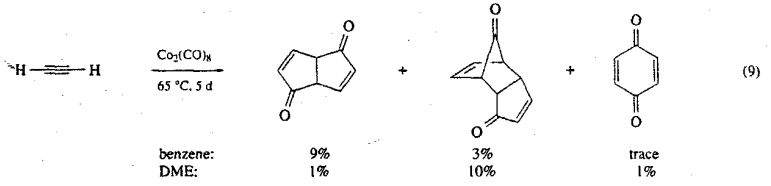
While both of these innovations have been applied predominantly to intramolecular systems, intermolecular examples of each have been reported as well. A catalytic version of the intramolecular Pauson–Khand reaction has also recently been described. In the presence of triphenylphosphite and moderate heat and pressure, cycloadditions have been successfully achieved in 51–94% yields using only 3 mol.% $CO_2(CO)_8$.[17b]

7.2.1.2 Scope of the Reaction

The Pauson–Khand reaction is exceptionally tolerant of both common organic functionality and local environment about the alkene and alkyne reaction partners. Under thermal cycloaddition conditions all alkynes with the exception of derivatives of propynoic acid participate; use of the tertiary amine *N*-oxide

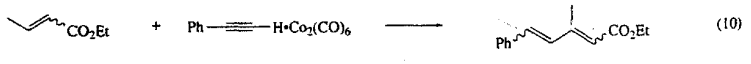
protocol removes this latter limitation provided that the β-carbon is substituted.[18] Hoye has additionally shown that conjugated alkynones may be successfully employed as substrates as long as acetonitrile is employed as the reaction solvent.[19] Ethyne, simple terminal alkynes including arylalkynes, and internal alkynes all react thermally to give cyclopentenones. Again, use of the amine oxide method is beneficial in stubborn cases, such as more hindered internal substrates.

The scope of the intermolecular Pauson–Khand reaction with respect to the alkene is more limited, at least under thermal reaction conditions. Strained cyclic alkenes are the best substrates, typically reacting at 60–80 °C over a period of several hours. Steric hindrance around the double bond exerts a significant deleterious effect on the cycloaddition. In particular, tri- and tetrasubstituted double bonds and double bonds containing bulky allylic substituents, even when contained in a strained ring, frequently give cyclopentenones only in low yields if at all. This is apparently due to a reduction in the ability of the alkene to compete with additional molecules of alkyne for reaction with the initially formed $Co_2(CO)_6$-RC≡CR^1 complex. As a result, reactions such as alkyne trimerization, and multicomponent cycloadditions involving only alkyne and carbon monoxide, normally only minor side reactions, become the major pathways, leading to products that exclude the alkene (Equation (9)).[20] Simple acyclic alkenes and unstrained cyclic alkenes are also generally poor substrates in intermolecular cycloadditions, rarely giving cyclopentenones in yields better than 40%. In many of the aforementioned situations, conversion to an intramolecular process renders the Pauson–Khand feasible. Indeed, intramolecular examples are known for every possible substitution pattern about a simple alkene.



(9)

Thermal conditions are generally unsuitable for conjugated acyclic dienes and alkenes conjugated with electron-withdrawing groups. Formal addition of a vinylic C–H bond across the triple bond of the alkyne results in the formation of linear di- and polyenes (Equation (10)).[21] However, use of lower-temperature protocols (e.g., solid-support adsorption or amine *N*-oxide activation) allows some of these reactions to again succeed to give cyclopentenones as the major products. Further discussions of the reasons behind this situation and possible mechanistic relationships between diene formation and the cycloaddition process leading to cyclopentenones are presented in Section 7.2.2.



(10)

As examples that follow will reveal, the Pauson–Khand reaction is highly tolerant of the common organic functional groups. It is completely compatible with ethers, alcohols, tertiary amines, thioethers, ketones, ketals, esters, amides, aromatic rings including benzene, furan, and thiophene, and even Fischer carbene complexes. Partial tolerance of the following groups has also been observed: alkyl and aryl halides, vinyl ethers and esters (especially under lower-temperature conditions), and less reactive alkenes and alkynes in the presence of more reactive unsaturation.[22] A few examples of reduced or anomalous reactivity have been reported in substrates bearing other allylic or propargylic functionality, but these limitations are largely relieved by the newer methodologies.

Excellent background material on the Pauson–Khand reaction is available in reviews published by Pauson.[23–5] A comprehensive survey of all Pauson–Khand cycloadditions reported through 1989 has also appeared.[26]

7.2.2 MECHANISM

Pauson and co-workers demonstrated the unambiguous intermediacy of the $Co_2(CO)_6$-R^{1}C≡CR^2 complex in the cycloaddition process in their initial investigations. In contrast, although alkene complexes derived from $Co_2(CO)_8$ are well-known, if limited in number, they have been shown not to give rise to cyclopentenones upon treatment with alkynes.[6] Further direct studies of the mechanism of

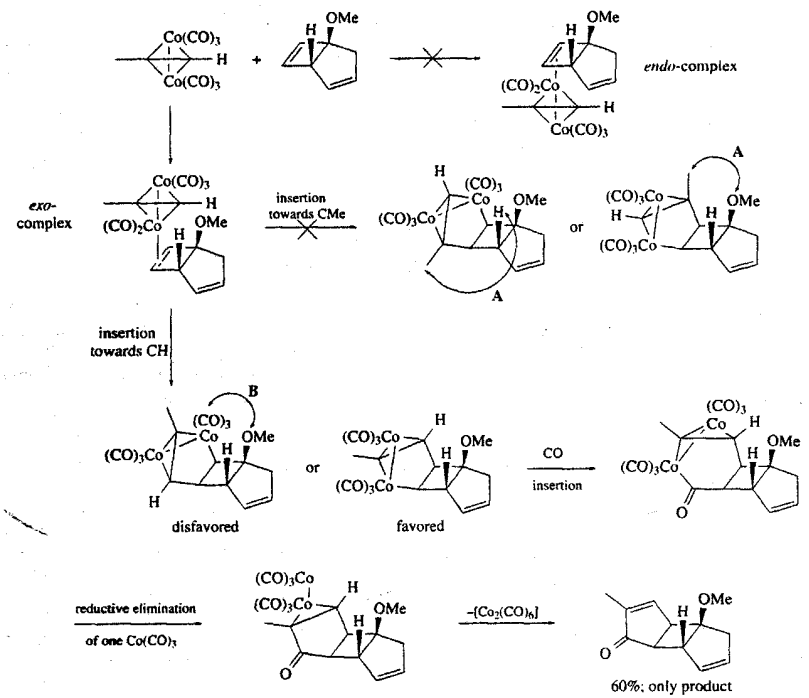
the Pauson–Khand reaction have been limited by the fact that attempts to observe intermediates on the reaction pathway beyond the alkyne complexation stage have been unsuccessful: the only species detected during the course of the reaction are the final products. The sole exception to the latter has been Krafft's observation and isolation of two complexes in which bidentate complexation of both an alkyne and a remote (bishomopropargylic) thioether function are observed at a single $Co_2(CO)_5$ moiety (Section 7.2.4.1).[27] The evidence indicates that these complexes lie off the direct pathway to cycloaddition, although intramolecular heteroatom–cobalt interactions at later stages of the mechanism may affect the course of the Pauson–Khand process. It is generally assumed that, whatever the mechanistic sequence that follows alkyne complexation, the rate determining step occurs early in the sequence, precluding the buildup of any subsequent intermediates to observable levels.

In the absence of direct evidence, a reasonably complete mechanistic hypothesis has been inferred from observations of regio- and stereochemistry in a large number of examples of Pauson–Khand cycloaddition.[28] This is illustrated using the reaction between the $Co_2(CO)_6$-propyne complex and 1-methoxybicyclo[3.2.0]hepta-3,6-diene, reported by Pauson and co-workers in 1977 (Scheme 1).[29] In common with many transition metal mediated organic cycloaddition reactions,[2] the principal interactions that control regio- and stereochemistry appear to be steric in nature. Complexation of the alkene to cobalt initiates the sequence. This step is presumed to follow a dissociative mechanism, thus explaining the need for heat or other agents that can serve to promote the loss of carbon monoxide, such as amine oxides. With bicyclic alkene substrates such as the one shown the less hindered *exo*-face of the π-bond preferentially complexes to the metal. This process is almost certainly reversible. The step that follows, insertion of the complexed face of the alkene π-bond into one of the formal cobalt–carbon bonds of the alkyne complex, is thought to be both the rate- and product-determining step. Both regio- and stereochemistry are kinetically controlled, chiefly by steric interactions in this irreversible insertion process. In the example shown, the diastereofacialselectivity upon alkene complexation is preserved upon insertion, a stereospecific process that leads exclusively to a *cis-exo* ring fusion. This result is nearly universally observed with bicyclic alkenes, including those employed in the first reported examples of the reaction, norbornene, norbornadiene, and several of their derivatives.[6]

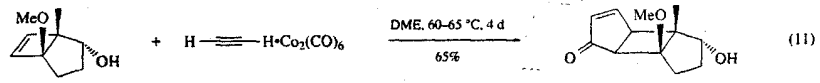
Regiochemistry with respect to both alkyne and alkene is determined during the insertion into the cobalt–carbon bond. The incipient carbon–carbon bond is most susceptible to steric crowding; for example, a 1,3-pseudodiaxial interaction ("A" in Scheme 1) develops between the substituent on the alkyne carbon and any allylic group on the alkene. As a result, if the alkyne is unsymmetrical, insertion and carbon–carbon bond formation proceed exclusively at the alkyne carbon possessing the smaller substituent (i.e., hydrogen in a terminal alkyne, leading eventually to a 2-substituted enone). With steric hindrance at the alkyne carbon thus removed, a second 1,3-pseudodiaxial interaction comes into play, capable of exerting regiocontrol of an alkene unsymmetrically substituted at the allylic positions. This interaction ("B" in Scheme 1) involves an allylic substituent with the $Co(CO)_3$ moiety. In order to minimize this interaction, the alkene carbon bearing the larger allylic substituent inserts away from the cobalt, thus forming the new carbon–carbon bond with the alkyne carbon. Subsequent CO insertion, reductive elimination of one cobalt, and decomplexation of the other give the final product.

Briefly summarized, the less hindered face of the alkene inserts into the less hindered formal cobalt–carbon bond of the starting complex, with the orientation of alkene insertion placing the larger allylic substituent away from cobalt. The overall result is (i) *cis-exo* ring fusion stereochemistry, (ii) alkyne regiochemistry placing larger alkyne substituents α to the new ketone carbonyl, and (iii) alkene regiochemistry placing larger allylic substituents *anti* to the new ketone carbonyl. The first two preferences are strong ones; no exceptions to the second are known. As to the third, it should be pointed out that the bicyclo[3.2.0]hept-6-ene system is an unusually regioselective substrate. The steric sensitivity of this system is strikingly illustrated in the total reversal of regiochemistry upon replacement of a ring fusion hydrogen with methyl, which is effectively larger than methoxy (Equation (11)).[30]

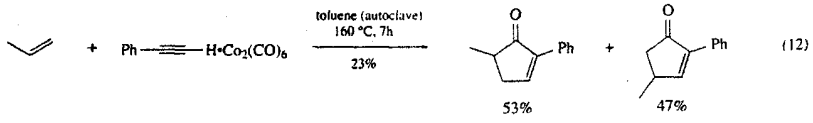
Alkene regiochemistry in the Pauson–Khand reaction is less readily predicted, as it is dependent on the nature of both the alkene and the alkyne. Thus, while the systems depicted in Scheme 1 and Equation (11) are totally regioselective, most other types of bicyclic alkenes give mixtures of regioisomers, although the isomer predicted on the basis of the analysis above predominates most of the time. The situation with simpler alkenes is somewhat different. Upon reaction with ethyne or terminal alkynes, terminal alkenes typically display minimal regioselectivity which may vary with reaction conditions, although incorporation of the alkyne remains totally regioselective (Equations (12) and (13)).[17,31–3] Alkyne regiocontrol stays high even in reactions with ethene, even though some of the steric interactions alluded to earlier are obviously absent (Equations (14) and (15)).[25] Krafft has suggested that steric effects may play a role prior to insertion, by favoring specific configurational and conformational isomers of the alkene complex for subsequent reaction.[32] Thus, of the three possible configurational isomers at pseudooctahedral cobalt, the one most likely to lead to insertion contains the alkene



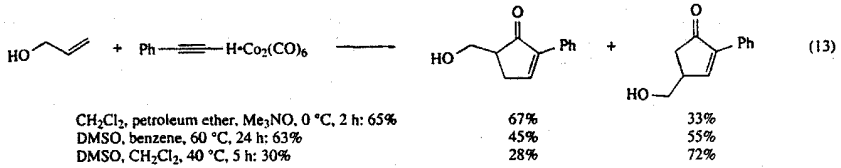
Scheme 1

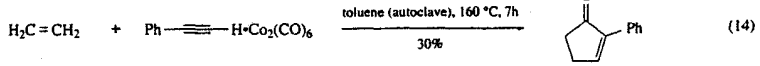


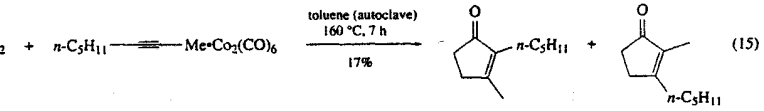
complexed *trans* to the bond between cobalt and the substituted alkyne carbon, avoiding a steric interaction with the latter. Insertion can therefore only occur into the other cobalt–carbon bond, fixing the alkyne regiochemistry (Scheme 2, R^1 = H). With most terminal alkenes, there will be little preference between the two possible reactive conformations about the cobalt–alkene bond, resulting in no regioselectivity in alkene incorporation (cf. Equations (12) and (13)). However, if the R^1 group on the alkene is sufficiently large, conformation (**2**) is preferred (Scheme 2), placing the large group *anti* to the cobalt–carbon bond. This results in a preference for the 5-substituted cyclopentenone, as has been observed by Pauson in the case of 3,3-dimethyl-1-butene (*t*-butylethene) (Equation (16)).[25]

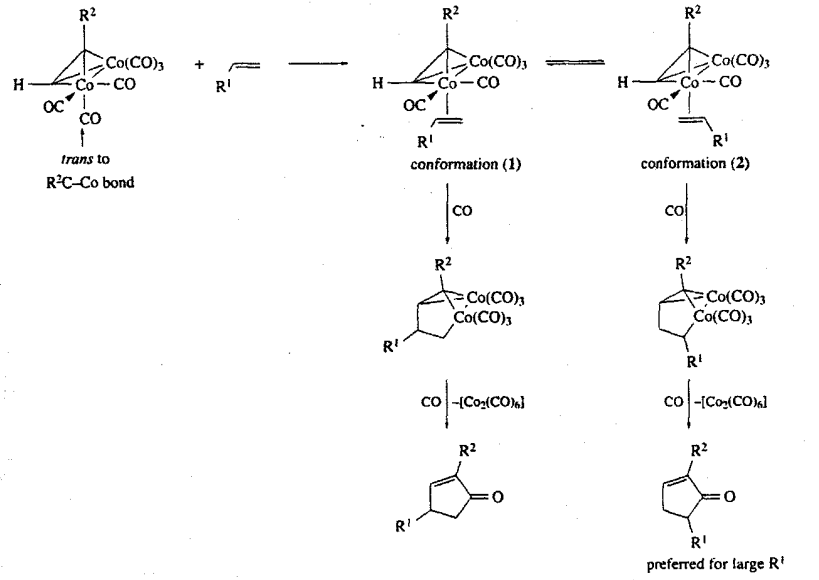


One must always be careful in attributing product selectivities to energetic preferences among equilibrating species. In the cases described above this approach may be justified, because steric interactions associated with the possible alternative alkene insertion processes appear to be comparable and rather small, leading to similar activation energies for the competing insertion steps. As a result, the energy difference between the available reactive conformations may contribute in a significant way to the overall activation energies for the two possible modes of reaction.

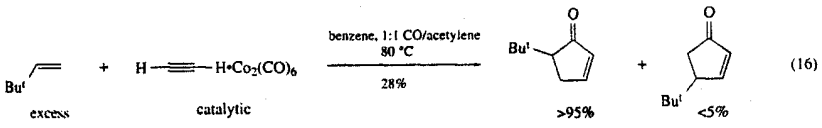






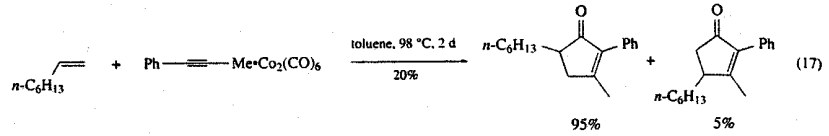


Scheme 2



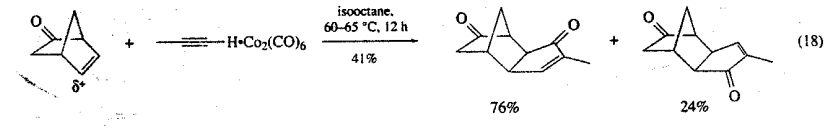
Strong support for this picture has been provided by Krafft in the observation of greatly increased alkene regioselectivity in Pauson–Khand cycloadditions with internal alkynes (Equation (17)).[32] As above, the site of coordination of the alkene determines alkyne regioselectivity, while the conformation of the coordinated alkene prior to insertion contributes to alkene regioselectivity. The presence of groups larger than hydrogen on both alkyne carbons introduces unavoidable steric interactions that bias the

system more strongly towards alkene insertion from an arrangement similar to conformation (2) in Scheme 2. While such considerations are unlikely to be applicable to reactions of internal alkenes, where steric differentiation is reduced, they can play a role in intramolecular cycloadditions (Section 7.2.4).



(17)

Weak electronic effects on alkene regioselectivity in the Pauson–Khand reaction have been observed. The regioselectivity observed in cycloadditions of norbornen-2-ones has been interpreted as arising from an electronic preference for attachment of the δ^+ 5-carbon of the alkene to an alkyne carbon rather than cobalt in the bond-forming insertion step (Equation (18)). In these systems electronic and steric effects have been separated by carrying out identical reactions with the corresponding norbornen-2-ols, in which the alkene-polarizing homoconjugation interaction has been removed. The observation of ca. 1:1 product ratios from the latter (Equation (19)) supports the interpretation given above, and is consistent with Pauson's results from reactions of styrene derivatives (Section 7.2.3.1).[11b]



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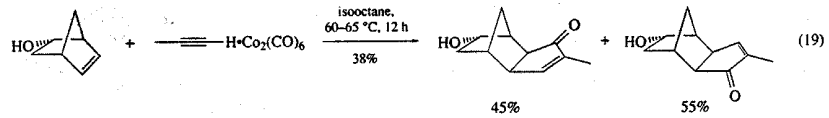
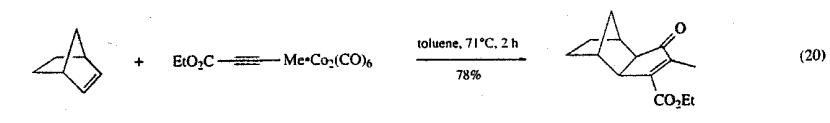


(19)

Cycloadditions of conjugated alkynones and alkynoate esters proceed exclusively to give cyclopentenones in which the ketone or ester function is located at C-3 (Equations (20) and (21)).[18,19] While this result is consistent with a steric origin (i.e., tetrahedral carbon being "larger" than trigonal carbonyl carbon), the complete regioselectivity is surprising in view of the rather small size differential involved. Again, an electronic component has been invoked, suggesting that bond formation between the more electron-rich α-carbon of the triple bond and an alkene carbon is favored (Scheme 3, metallacycle (1)). The variable cyclopentenone yields in these systems allow consideration of another possibility: both possible metallacycles may form, but only (1) proceeds to product, (2) either forming reversibly or being a dead-end by virtue of the well-known reluctance of CO insertion to occur at carbons substituted by electron-withdrawing groups.[34]



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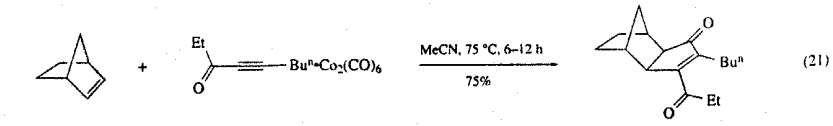
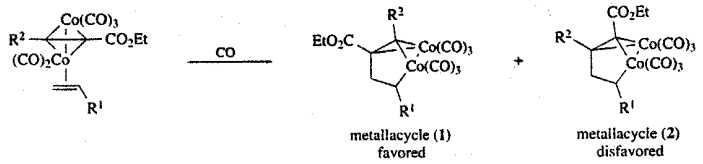


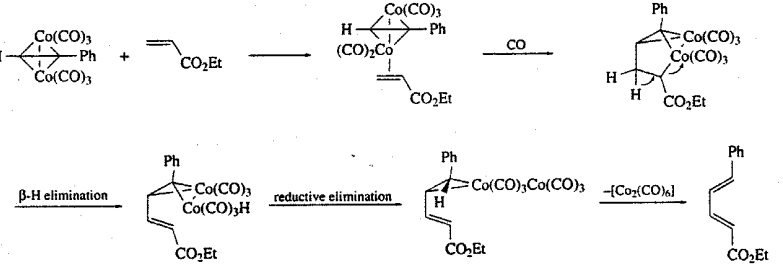
(21)

As already mentioned, alkenes attached to electron-withdrawing groups react anomalously, giving 1,3-dienes (Equation (10)).[21] The reaction is completely regioselective, with the new carbon–carbon bond forming between the less hindered alkyne carbon and the less hindered alkene carbon, which also



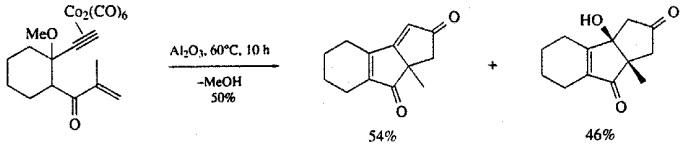
Scheme 3

happens to be the δ^+ polarized alkene carbon. It is therefore reasonable to assume that complexation of the alkene and subsequent insertion still occur as illustrated in Scheme 1, and are controlled by the same steric and electronic factors. The electron-withdrawing group in every example of this reaction is π-conjugating. This probably renders a β-hydrogen elimination/reductive elimination sequence competitive with CO insertion (which, again, is disfavored by the electron-withdrawing substituent), by providing a driving force for regeneration of the alkene function (Scheme 4).

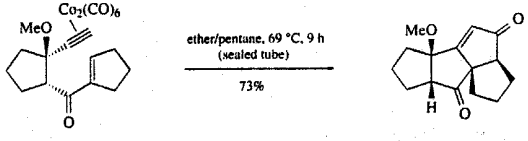


Scheme 4

Smit has found a limited subset of structural types in which alkenes substituted with electron-withdrawing groups participate in successful Pauson–Khand cycloadditions (Equations (22) and (23)).[35] These reactions are intramolecular, and in each case the internal (β) position of the alkene component is disubstituted. The latter feature structurally precludes β-hydride elimination and may promote attainment of favorable conformations for cycloaddition as well. Although these examples presumably benefit from having the keto group located β rather than α on the alkene, one example of a successful Pauson–Khand reaction has been reported with the opposite arrangement (Section 7.2.4.3).



(22)



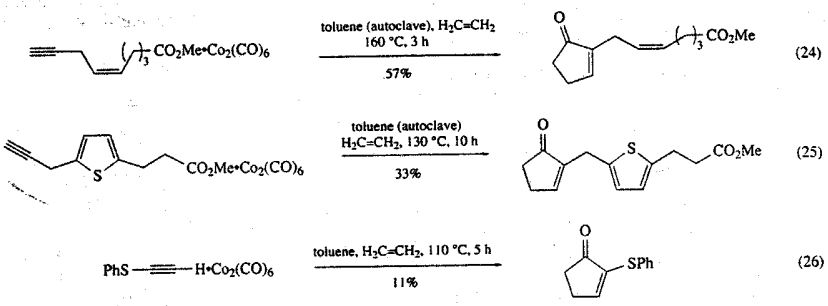
(23)

7.2.3 INTERMOLECULAR PAUSON–KHAND REACTION

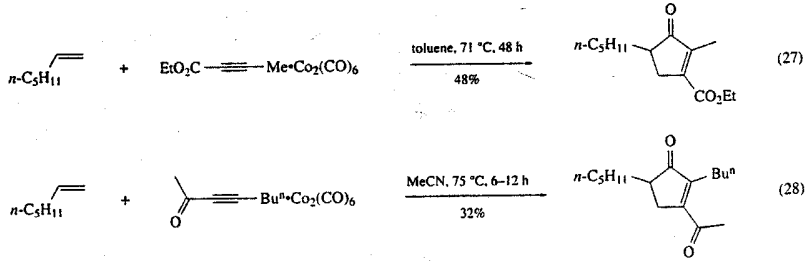
7.2.3.1 Reactions Involving Acyclic Alkenes

Before the advent of the use of reaction promoters, application of the Pauson–Khand reaction to simple acylic alkenes was limited by both low reactivity and lack of regiocontrol in incorporation of the alkene. Although only a limited number of examples of intermolecular cycloadditions employing promoters have been reported, indications are that alkene reactivity is generally considerably improved and some control of the regioselectivity is possible from terminal substrates.

Among simple alkenes, ethene provides the most consistently useful results under thermal conditions. Yields with terminal alkynes range from 30 to 60% (Equations (14), (24), and (25));[36-7] internal alkynes have also been used with some success (Equation (15)).[25] Forcing conditions (toluene, 130–160 °C, 60–80 atm, autoclave) are usually required for best results, although the reaction proceeds, albeit slowly, at reduced pressures and temperatures (Equation (26)).[15,25,38] The optimization of catalytic conditions for the reaction between ethene and 1-heptyne has been discussed (Equation (5), Section 7.2.1.1).



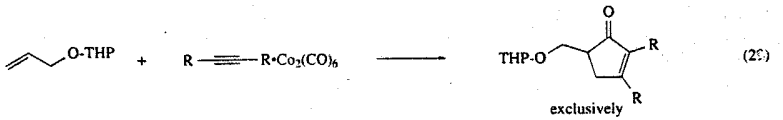
As already mentioned, terminal alkenes usually give modest yields but no meaningful regioselectivity in reaction with ethyne and terminal alkynes. The higher regiocontrol available upon reaction with internal alkynes (Section 7.2.2) extends to conjugated, electron-deficient systems as well. Thus, reactions of 1-heptene with two such substrates proceed with complete regioselectivity to single products, albeit in modest yields (Equations (27) and (28)).[18-19]



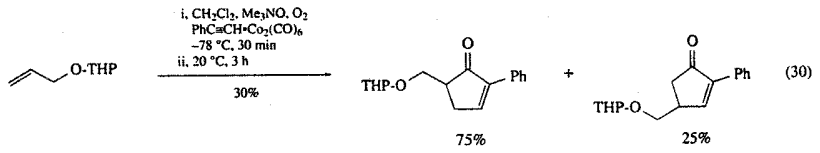
Allyl alcohol is an interesting case in that the regioisomer ratio appears to be dependent upon the promoter used. Amine oxides give more 5-(hydroxymethyl)cyclopentenones, while use of DMSO leads to more of the 4-substituted isomer (Equation (13)).[17,33] It is unclear whether these are true kinetic results or if dehydration is destroying one of the products selectively (the lack of success of allyl alcohol cycloaddition under thermal conditions may well be a consequence of such a secondary transformation).

Isolated examples of high regiocontrol have been reported in the case of allyl ethers (Equation (29)).[25,39] In this case thermal conditions compare favorably with amine oxide activation (Equation (30)).[33] In the case of ethyne (R = H), the regioselectivity is highly solvent-dependent. Note that the result with 2-butyne (R = Me) is consistent with Krafft's observations (cf. Equation (17)).[32]

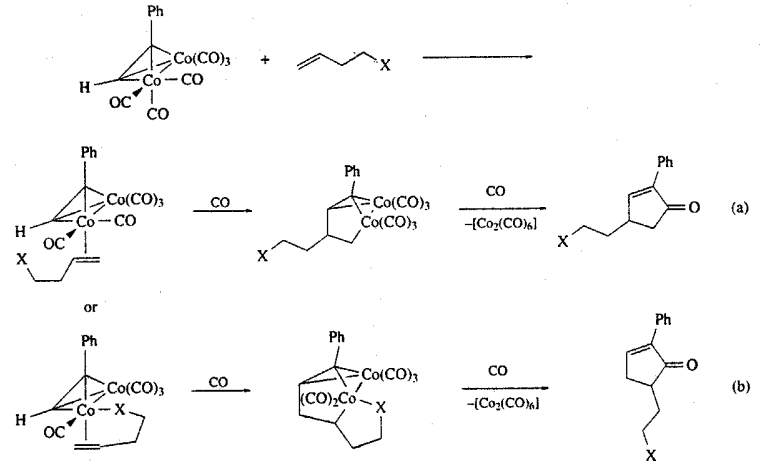
Of considerable potential is another observation by Krafft that alkenes containing groups capable of acting as soft ligands at a homoallylic position (e.g., RS–, Me_2N–) give both enhanced yields and



R = H: benzene, 80 °C, 8 h, 48%; R = Me: toluene, 110 °C, 8 h, 32%

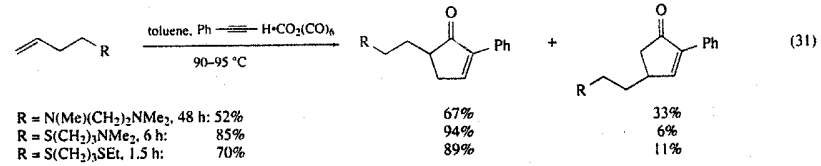


regioselectivities. This is thought to result from coordination of the heteroatom to cobalt prior to insertion, thereby fixing the conformation of the alkene to favor the 5-substituted product (Scheme 5).[27,40-1] Reduced but still usable (ca. 3:1) selectivity is observed when the heteroatom is one carbon further removed from the double bond. Addition of a second heteroatom attached to the first by a two or three methylene tether gives mixed results in term of both yield and selectivity (Equation (31)).[42] Exclusion of carbon monoxide from the atmosphere above the reaction is required for optimal yields in these situations (see Section 7.2.4.1).



	(a)	(b)
R = NMe_2: 72%,	1	5
R = SMe: 61%,	1	18

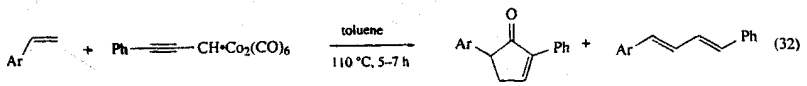
Scheme 5



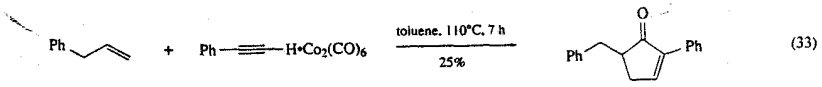
R = $N(Me)(CH_2)_2NMe_2$, 48 h:	52%	67%	33%
R = $S(CH_2)_3NMe_2$, 6 h:	85%	94%	6%
R = $S(CH_2)_3SEt$, 1.5 h:	70%	89%	11%

Conjugated acyclic dienes (in contrast to cyclic dienes, see Section 7.2.3.2), like alkenes conjugated to electron-withdrawing groups, give only linear oligomerization, resulting in acyclic polyene

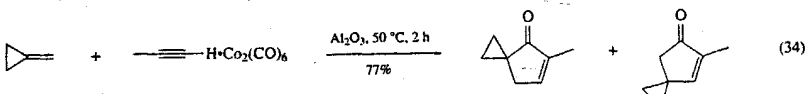
products.[23] Styrene derivatives have been extensively studied and are intermediate, giving both dienes and 5-arylcyclopentenones, both with complete regioselectivity. Attempts to explain and control chemoselectivity in such systems have been made in several studies by the Pauson group. Initial notions that product distribution might be related to the electron-withdrawing capability of the aryl substituent have not been supported by the evidence. For a variety of styrene derivatives containing *para* substitution the product ratio of cyclopentenone to linear diene varies in no readily interpretable way with the nature of the substituent; nor does complexation of the strongly electron-withdrawing $Cr(CO)_3$ unit to the arene have a consistent effect (Equation (32)).[31,43–4] Fragmentary data indicate that alkyl alkynes give more cyclopentenone and less diene than do aryl alkynes in reactions with styrenes. Allyl arenes (3-arylpropenes) give 5-substituted cyclopentenones with complete regioselectivity (Equation (33)).

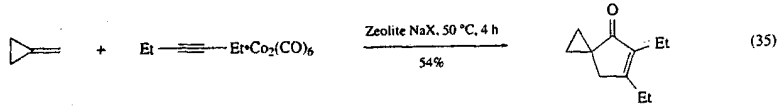


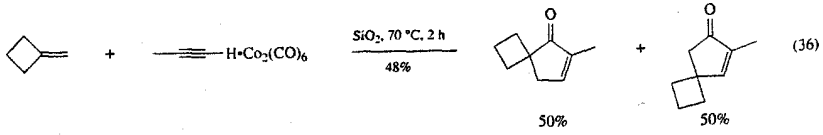
Ar = Ph:	51%	23%	77%
Ar = Ph•Cr(CO)$_3$:	69%	54%	46%
Ar = *p*-Me-Ph:	39%	33%	67%
Ar = *p*-Me-Ph•Cr(CO)$_3$:	73%	40%	60%
Ar = *p*-Cl-Ph:	29%	55%	45%
Ar = *p*-Cl-Ph•Cr(CO)$_3$:	29%	0%	100%



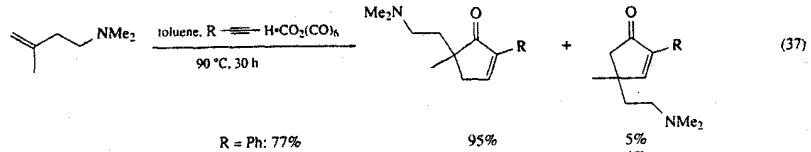
Methylenecyclopropanes and methylenecyclobutanes afford only poor yields of cyclopentenones under homogeneous conditions but react well on the surfaces of solid supports such as silica and several zeolites. Cycloadditions of methylenecyclopropanes with ethyne or terminal alkynes give predominantly 4-spiroannulated cyclopentenones, perhaps a consequence of a weak electronic effect. In contrast, internal alkynes afford virtually exclusively the 5-spiroannulated isomers in a reaction that is evidently controlled by the same steric interactions discussed earlier. Methylenecyclobutenes give regioisomeric mixtures (Equations (34)–(36)).[45]

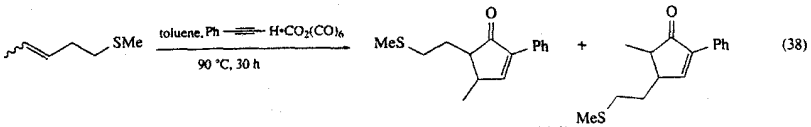




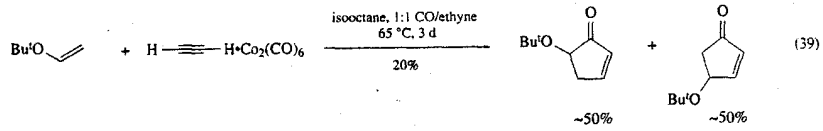


Regarding other more highly substituted acyclic alkenes, very little has been reported and it is not encouraging: (*E*)-1-propenylbenzene affords only 15% cyclopentenone upon thermal Pauson–Khand reaction with phenylacetylene.[43] No attempts to employ promoters in these systems have been reported; thus terminal alkenes must be considered the useful limit in intermolecular cycloaddition at the present time. A significant exception exists in the reactivity of the homoallylically derivatized systems of Krafft: again, greatly improved yields are observed along with impressive regioselectivity (Equations (37) and (38)). It is not known at what stage stereochemistry at the saturated α-carbon is lost.[46]



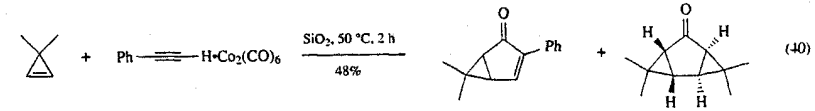


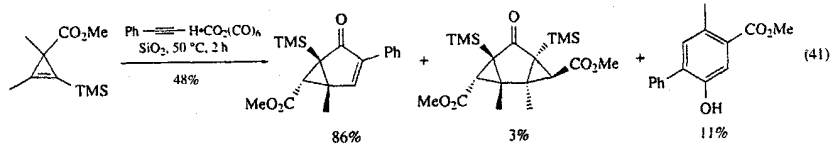
Limited work has revealed that vinyl and allyl halides cyclize only in low yield, and the products suffer halogen loss in the process.[31] Also, unlike allyl ethers, vinyl ethers and esters are only marginally suitable substrates for Pauson–Khand cycloaddition (Equation (39)).[46] Both the substrates and the products appear to be subject to decomposition under the reaction conditions.



7.2.3.2 Reactions Involving Monocyclic and Fused Bicyclic Alkenes

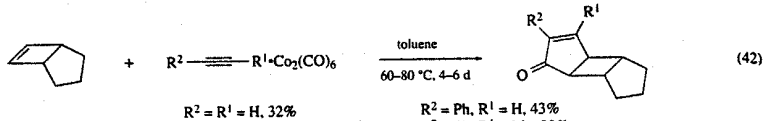
Cyclic alkenes exhibit varied degrees of reactivity in the intermolecular Pauson–Khand reaction. It has been typically found that reactivity increases with ring strain. The first alkenes studied as substrates for Pauson–Khand cycloaddition were strained bicyclics containing double bonds in four- or five-membered rings. Cyclopropenes unsubstituted at the double-bond carbons are poor Pauson–Khand substrates, because an alternative process occurs in which two molecules of cyclopropene and one of CO cocyclize, affording a tricyclo[4.1.0.0^{2,4}]heptan-5-one as virtually the sole major product. Blocking this process by disubstitution of the alkene permits cocyclization with alkynes to succeed using dry adsorption on SiO_2 at 50 °C (Equations (40) and (41)).[47]





Simple cyclobutenes do not appear to have been examined as substrates, but bicyclo[3.2.0]hept-6-enes have been used with considerable success. Pauson found the parent system to be generally reactive towards both terminal and internal alkynes, forming expected *cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]dec-4-en-3-ones via *exo*-face-selective cycloaddition (Equation (42)). As mentioned earlier, total regioselectivity was obtained in the case of substrates with ring fusion (i.e., allylic) substitution, with the larger allylic

group ending up *anti* to the newly introduced cyclopentenone carbonyl (Scheme 1; Equations (11), (43), and (44)).[29–30]



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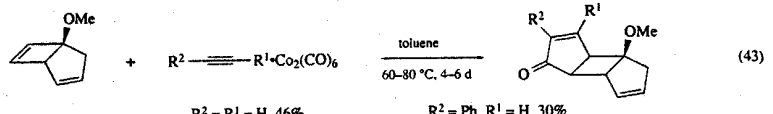
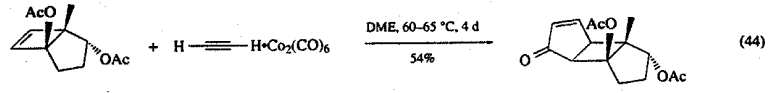
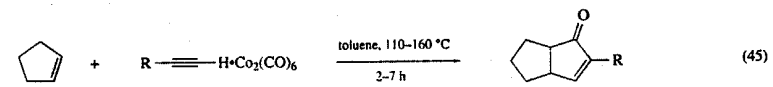


(43)



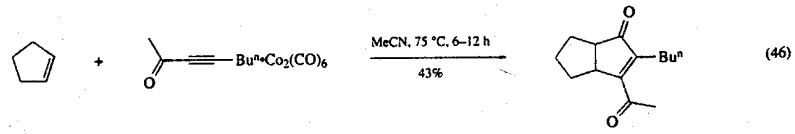
(44)

Although unstrained cyclic alkenes are generally less reactive than strained systems, cyclopentene and dihydrofuran are important exceptions. Required reaction temperatures are higher in some cases (120–160 °C), but no other special conditions are necessary and yields are frequently excellent. Cyclopentene reacts with terminal alkynes to give 30–60% yields of cyclopentenones (Equation (45)).[31,37] A single successful result with an internal alkynone suggests that this particular modification may have synthetic potential (Equation (46)).[19]



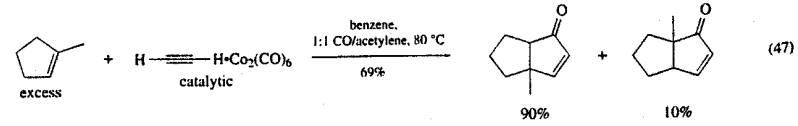
R = Ph, 47%; R = SPh, 53%; R = $(CH_2)_6CO_2Me$, 33%

(45)



(46)

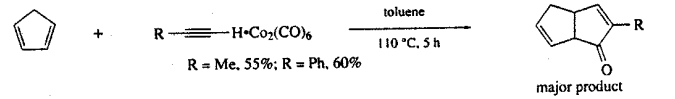
Pauson–Khand cycloadditions involving cyclopentene have seen extensive and imaginative development by de Meijere in the use of cyclopropylacetylenes as cycloaddition partners (Section 7.2.3.4). 1-Methylcyclopentene, which reacts with ethyne to give <20% yields of cyclopentenones under normal conditions, becomes a better substrate when catalytic conditions are used (Equation (47)).[25,38] The reasons behind the remarkable regioselectivity are uncertain as neither electronic nor steric interactions appear to be particularly large.



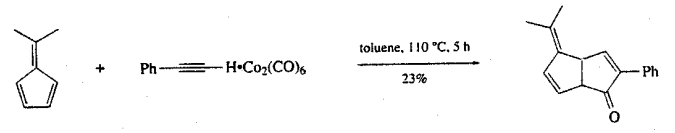
(47)

In contrast to acyclic dienes, cyclopentadienes and fulvenes react chemoselectively with alkynes to give cyclopentenones, the former in excellent yield but somewhat reduced regioselectivity, the latter less efficiently although only one regioisomer is obtained (Equations (48) and (49)). Note that the favored

position of conjugated unsaturation is the 5-position of the product, as was the case with styrene derivatives. Indene derivatives behave similarly. The fact that dienes are observed only as very minor products, if at all, reflects the superiority of the cyclopentene system over acyclic alkenes (Equation (50)). The same is true for acenaphthalene (Equation (3)), which also reacts with propyne and phenylacetylene to give exclusively cyclopentenones.[9]



(48)



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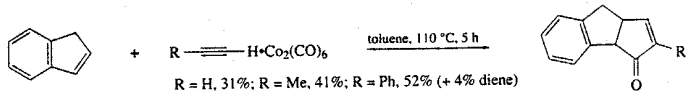
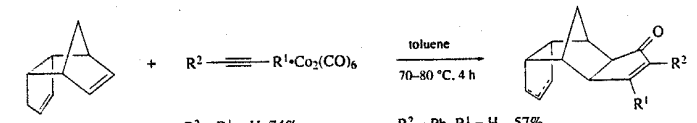


R = H, 31%; R = Me, 41%; R = Ph, 52% (+ 4% diene)

(50)

Other ring-fused cyclopentenes have been studied by both Pauson and Serratosa. Pauson's studies show the expected chemoselectivity when a cyclopentene is present together with a more reactive alkene moiety. In the system shown (Equation (51)), the cyclopentene is totally inert under conditions required for the norbornene double bond to react.[22] Pentalene-derived substrates present an interesting variation on the basic theme. Serratosa's group has found an unexpected alkene isomerization to precede cycloaddition in the bicyclo[3.3.0]oct-2-ene system. Thermodynamics favors the double bond between C-2 and C-3; however, the double bond at C-1 is more reactive in spite of its increased steric hindrance. Under a variety of conditions, contrathermodynamic double bond isomerization is observed, and only products resulting from reaction of the double bond towards the ring fusion are observed (Equation (52)).[48] The regioselectivity is in the same direction as that observed for another trisubstituted alkene, 1-methylcyclopentene (Equation (47)). A standard H-transfer mechanism involving π-allyl complexes presumably mediates this process; certainly the presence of a tertiary allylic C–H bond in the starting alkene renders this feasible. Cyclopentenone yields in this system increase with temperature, but so do the yields of side products, including the corresponding cyclopentanones and products in which hydrogenolysis of the silyl ether has taken place. These reductions are evidence for the participation of metal hydrides. Pauson has found that the 2-methyl-substituted analogue undergoes similar reaction: isomerization of the alkene again precedes cycloaddition (Equation (53)). Although the yield is low, the reaction is noteworthy as the only case in which a tetrasubstituted alkene gives an isolable enone product from a Pauson–Khand reaction. The lack of regioselectivity in the more symmetrical system is expected.[25,38]



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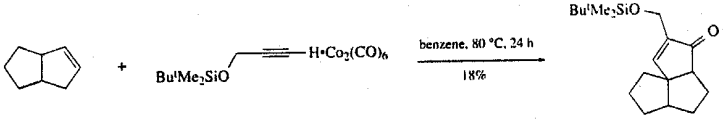
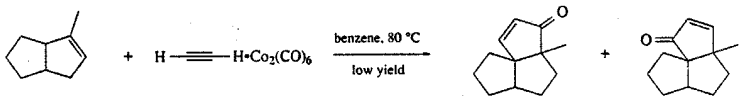
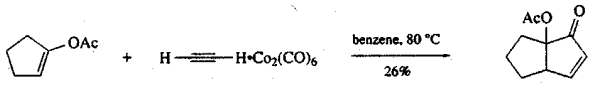


(52)



(53)

Regarding five-membered ring systems which involve heteroatoms, 1-acetoxycyclopentene gives a single isolated product, although the conditions are such that the other regioisomer may not have survived (Equation (54)). Another case of alkene isomerization is presented in Equation (55). Reaction from the internal double bond isomer exclusively again gives a single regioisomer; it is not known whether this results from the same factors controlling the reactions of other trisubstituted alkenes, or if this is another artifact arising from further chemistry under cycloaddition conditions.[25,38]



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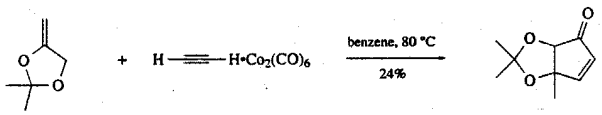
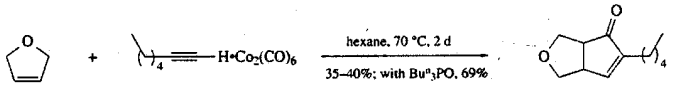


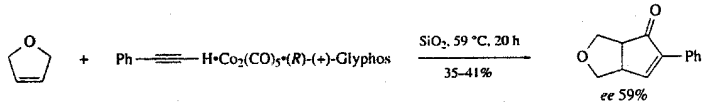
(55)

Dihydrofurans have seen considerable use as substrates in the Pauson–Khand reaction. The parent 2,5-dihydrofuran reacts in excellent yield with ethyne, terminal, and internal alkynes. Yields in this system respond well to the use of catalytic conditions (Equation (4)). Another unusual experimental modification has also been found by Pauson to be useful in this system: addition of tri-*n*-butylphosphine oxide nearly doubles the product yield in certain cases (Equation (56)). The role of the added substance is unclear. It is possible that it may loosely coordinate to $Co_2(CO)_5$·alkyne fragments, inhibiting the reattachment of CO but still permitting alkene complexation to occur. Addition of phosphine oxide does not always improve efficiency; its effects follow no obvious pattern.[15,23]



(56)

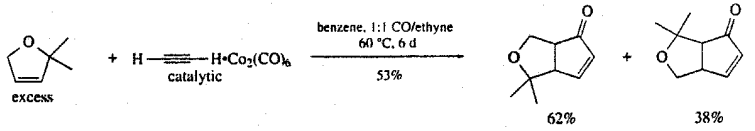
A nonracemic version of the Pauson–Khand cycloaddition of 2,5-dihydrofuran and phenylacetylene has been described.[49] Reaction of $Co_2(CO)_6$·PhC≡CH with (*R*)-(+)-2,3-*O*-isopropylideneglycerol-1-diphenylphosphine ("Glyphos") affords the two diastereomers of $Co_2(CO)_5$·PhC≡CH·glyphos as a mixture separable by fractional crystallization. Interconversion of the diastereomeric complexes occurs at elevated temperatures (>60 °C) in solution, but Pauson–Khand reaction with 2,5-dihydrofuran in the solid state (SiO_2) affords moderate yields of products with fair enantiomeric excesses (Equation (57)).



ee 59%

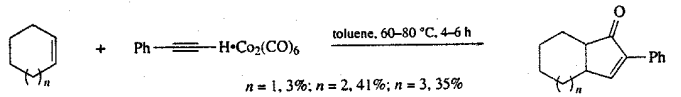
(57)

Substituted dihydrofurans give somewhat lower but still acceptable yields; the poor regioselectivity in unsymmetrical cases is the more significant difficulty with these substrates (Equation (58)).[50]

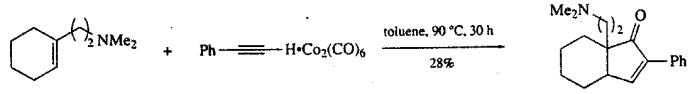


(58)

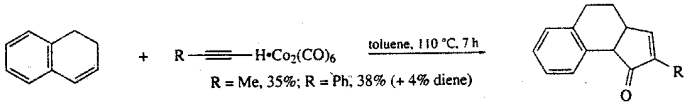
Alkenes in larger rings show varied reactivity. Cycloheptene and cyclooctene give moderate yields of cyclopentenones upon reaction with phenylacetylene (Equation 59); simple cycloalkenes do not react well with alkyl alkynes; for example, cyclohexene is a very poor substrate.[31] Attachment of a 2-dimethylaminoethyl chain onto cyclohexene (i.e., homoallylic nitrogen) introduces useful reactivity (Equation (60)).[40] Dihydronaphthalene is also a usable substrate, perhaps due to reduced steric hindrance in the flattened ring. It displays the expected regioselectivity for a styrene analogue (Equation (61)).[43] Cyclohexadienes do not give cyclopentenones directly under Pauson–Khand conditions. Instead, an apparently catalyzed Diels–Alder reaction takes place with the alkyne first, giving a bicyclo[2.2.2]octa-1,4-diene; this then participates in Pauson–Khand cycloaddition with additional alkyne (Equation (62)) (Section 7.2.3.3). The product thus contains two molecules of starting alkyne, one of alkene, and one of CO.[8]



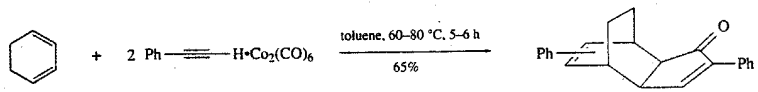
(59)



(60)



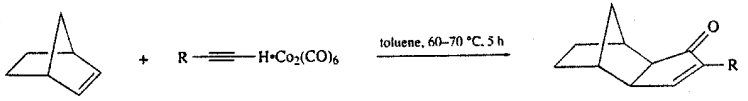
(61)



(62)

7.2.3.3 Reactions Involving Bridged Bicyclic Alkenes

Five-membered ring alkenes contained in bridged bicyclic or polycyclic systems are by far the most extensively studied substrates for intermolecular Pauson–Khand reactions. Comprehensive surveys carried out by the Pauson group identified many of the key features of the process in these substrates.[6,22] Norbornene displays such a wide scope of reactivity towards alkynes that it is usable as a test of the suitability of an alkyne as a Pauson–Khand substrate (Equations (20), (21), and (63)).[10,24,37] Yields of cyclopentenones, all of which are formed with complete regio- and *exo*-diastereofacialselectivity, range for internal alkynes typically between 20 and 40%, and for terminal alkynes from 30 to greater than 90%.

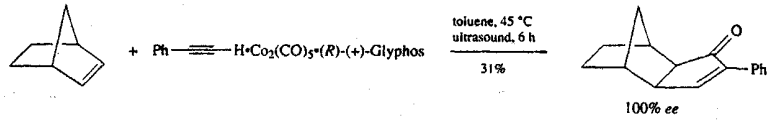


(63)

R = OEt, low yield; R = SPh, 59%, R =  , 30%; R = TMS (isooctane, 80–90 °C), 93%

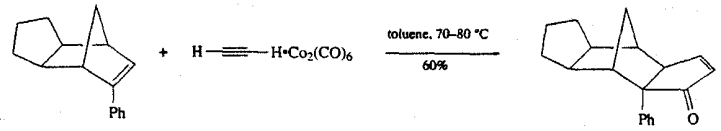
Norbornene provides the best example of cycloaddition to give a nonracemic product (Equation (64)). Using $(-)_{546}$-$Co_2(CO)_5$·PhC≡CH·glyphos as the reagent, the product is obtained in modest chemical yield, but completely optically pure.[51] Note that this result does not necessarily rely on direct steric interaction by the chiral ligand in the cycloaddition transition state. Reaction of norbornene is completely *exo*-face selective. Since the two cobalt atoms in $Co_2(CO)_5$·PhC≡CH·glyphos are already diastereotopic, total stereoselection thus merely requires that the phosphine direct alkene complexation is to one cobalt atom (presumably the $Co(CO)_3$ moiety) and not the other. Stereoselectivity is

presumably lost in the reaction of 2,5-dihydrofuran (Section 7.2.3.2) in the availability of multiple reactive alkene coordination geometries.



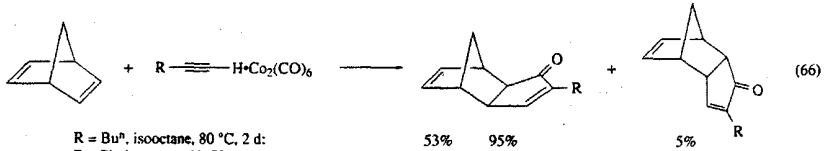
(64)

Monoaryl substitution on the double bond of norbornene is tolerated to a certain extent (Equation (65)). Regioselectivity with norbornenones and norbornenols was discussed earlier (Equations (18) and (19)).[11]

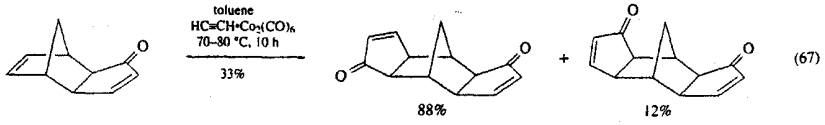


(65)

Both double bonds in norbornadiene are comparably reactive, so yields of tricyclic enones are limited by continued reaction of the initial product.[6,22,37] Use of a large excess of the diene is a partial remedy. This substrate is unique in affording small amounts of *endo*-fused products in some cases, probably as a result of reduced steric differentiation between the faces of the double bond. The proportion of *endo* product is greatest with ethyne as the reaction partner. Substituted alkynes give very little *endo* isomer under thermal conditions, more when the reaction is promoted by amine oxides at low temperature (Equation (66)).[33,52] When cycloaddition is permitted to proceed at the second double bond the result is low-yield but regioselective formation of *anti*-diketones (Equation (67)).



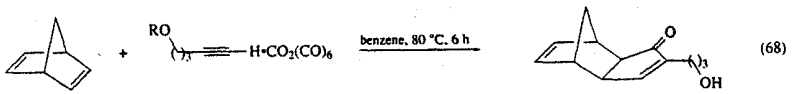
(66)



(67)

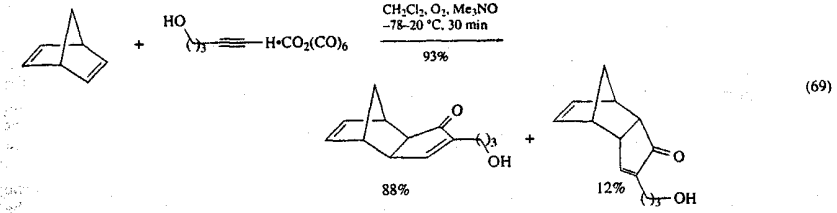
Norbornene-derived systems have been employed in an examination of the reactivity of polymer-bound alkyne substrates. Under the usual thermal conditions, certain functionalized systems such as propargyl alcohol and 3-butyn-1-ol are very poor substrates. Although the cause of this situation was unclear, it was thought that partial isolation of the alkyne by attachment to an insoluble cross-linked polymer might benefit the Pauson–Khand process, at least relative to possible alkyne–alkyne side reactions. Attachment of several alkynols to 2% cross-linked polystyrene (Merrifield's resin) followed by successive treatment with $Co_2(CO)_8$, alkene, and heat leads to polymer-bound cyclopentenones which subsequently may be liberated from the polymer in high yield and purity. Comparison with amine-oxide activation shows that the latter gives still higher yields, but *exo–endo* selectivity with norbornadiene is lower (Equations (68)–(70)).[53]

Chemoselectivity in systems containing less-strained double bonds has been mentioned (Equation (51));[22] this is also observed in systems with less electron-rich double bonds (Equation (71)). Among heterocyclic analogues, 2,3-diaza-5-norbornene shows Pauson–Khand reactivity, but 7-oxanorbornadiene deoxygenates to an aromatic system.[23,4]

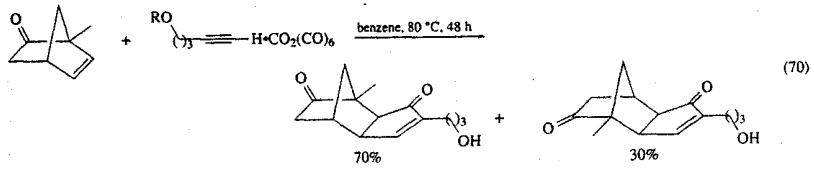


(68)

R = H, 24%; R = ester with Merrifield polymer, 59% (yield after hydrolysis)

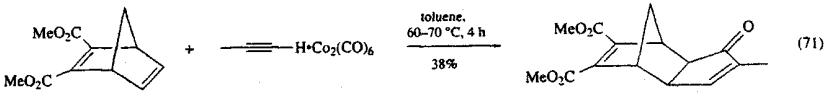


(69)



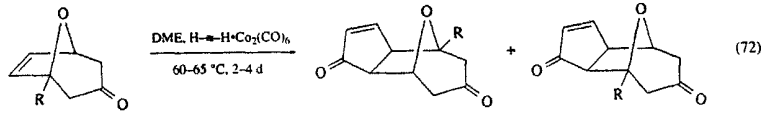
(70)

R = H, < 5%; R = ester with Merrifield polymer, 99% (yield after hydrolysis)



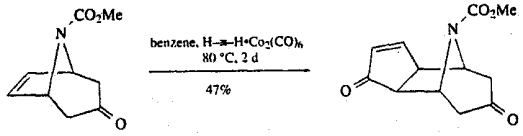
(71)

As bridged dihydrofuran analogues, 8-oxabicyclo[3.2.1]oct-6-enes are also useful substrates. Only low to moderate regioselectivity is observed in the cycloaddition of bridgehead-substituted examples of these compounds (Equation (72)). In this system Pauson–Khand reactivity is eliminated by either further substitution on the double bond or bulky bridgehead substitution.[28] The analogue containing an amide nitrogen in place of the oxygen bridge has also been cyclized successfully (Equation (73)).[54]



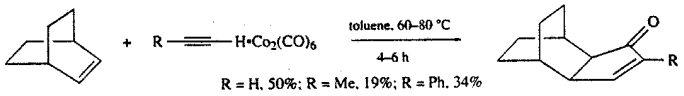
(72)

R = H, 45%
R = Me, 49% 60% 40%
R = Ac, 24% 75% 25%



(73)

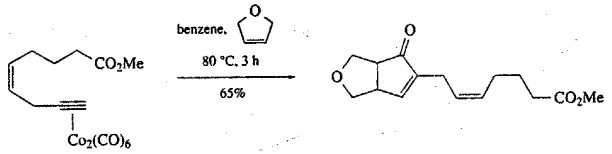
Bicyclo[2.2.2]octenes are good to excellent substrates, quite comparable to norbornene-based systems (Equation (74)).[8]



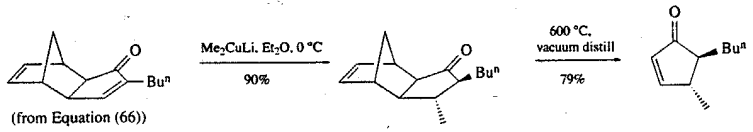
(74)

7.2.3.4 Synthetic Applications

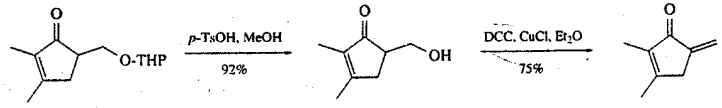
Numerous synthetic applications of the intermolecular Pauson–Khand reaction have been reported. Pauson has reported a number of direct applications of intermolecular cycloadditions of ethene in the synthesis of prostanoids and jasmone analogues (e.g., Equations (24) and (25)).[36–7,55] This is in general a reliable entry to 2-substituted cyclopentenones. The suitability of cyclopentene and dihydrofuran as substrates has permitted the extension of this work to the preparation of still further varieties of prostaglandin analogues (e.g., Equations (45) and (75)).[56] Simple 4,5-disubstituted-2-cyclopentenones are not as directly accessible, but may be prepared from the cycloaddition products of norbornadiene (Equation (66)). A sequence of conjugate addition followed by *retro*-Diels–Alder reaction affords the product (Scheme 6).[52] Dihydrofuran cycloadditions have seen additional use by Billington in the syntheses of the antibiotic methylenomycin B (Scheme 7),[39] as well as cyclomethylenomycin A (synthetic precursor to the antibiotic methylenomycin A), cyclosarkomycin (precursor to the antitumor agent sarkomycin),[11a] and the iridoid Japanese hop ether.[50]



(75)



Scheme 6

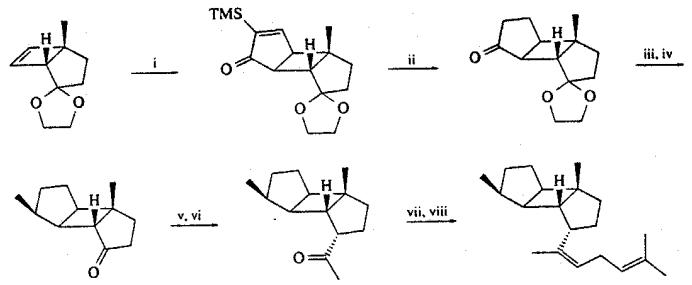


Scheme 7

Dauben has reported a particularly direct application of Pauson–Khand cycloaddition of a bicyclo[3.2.0]heptene in the formal synthesis of the natural product spatol. The cycloaddition proceeds with complete stereo- and regioselectivity (Scheme 8).[57]

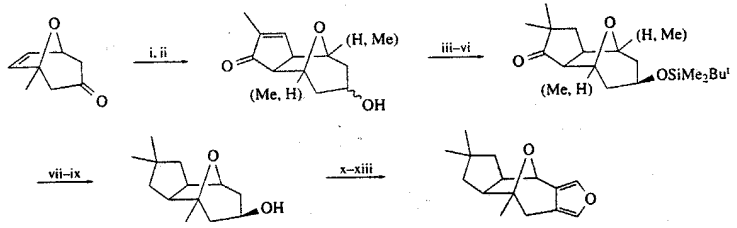
Variations on the hydrazulene skeleton have been approached via Pauson–Khand reaction, several with high regio- and diastereoselectivity. Pauson's cycloadditions of cycloheptene provided the first entries but were limited in scope and efficiency (Equation (59)).[31] More useful synthetic equivalents of cycloheptenes include 8-oxa- and 8-azabicyclo[3.2.1]oct-6-enes (Equations (72) and (73)),[28] and bicyclo[3.2.0]hept-6-enes (Equation (11)). Two syntheses of the sesquiterpene furanether B have been completed based on cycloaddition reactions in the 8-oxa series (Scheme 9).[58] The bicyclo[3.2.0]heptenes provide especially versatile access to systems transformable into both the guaianolide and pseudoguaianolide natural product structural types (Scheme 10).[30]

In a novel combination of Pauson–Khand cycloaddition with vinylcyclopropane chemistry, de Meijere has described an entry to linearly-fused triquinanes beginning with cyclopropyl alkynes. Cyclopentenone formation has been carried out with a variety of substitution patterns on the cyclopropane, and moderate yields achieved with both norbornene and cyclopentene as substrates.



i, TMSC≡CH•Co2(CO)6, 86%; ii, H2, Pd/C, then 0.01 M HCl, 89%; iii, Ph3PMe+I-, NaOCMe2Et, 94%; iv, H2, Pd/C, then HCl, H2O/THF, 78%; v, Ph3PEt+I-, NaOCMe2Et, then BH3, THF, –78 to 20 °C, then NaOH, H2O2, 76%; vi, Swern oxidation, 83%; vii, LiC(TMS)CH2CH=CMe2, THF, –78 °C, 9%; ix, H+ (one diastereomer), 75% or KH (other diastereomer), 100%

Scheme 8



i, LAH, Et2O, 96%; ii, MeC≡CH•Co2(CO)6, benzene, 65–70 °C, 2 d, 75%; iii, separate; iv, But Me2SiCl, imidazole, DMF, 98%; v, H2, 5% Pd/C, EtOAc, M eOH, 100%; vi, MeI, KOBut, ButOH, benzene, 100%; vii, LAH, Et2O, 100%; viii, NaH, then CS2, then MeI, THF, 100%; ix, Bun3SnH, AIBN, toluene, 110 °C, 50%; x, PCC, CH2Cl2; xi, EtOCHO, NaOMe, benzene, ~50%; xii, BunSH, p-TsOH, benzene, 80 °C, 100%; xiii, Me3S+MeSO4-, CH2Cl2, NaOH, H2O, then HCl, THF, 46%

Scheme 9

Thermal vinylcyclopropane–cyclopentene rearrangement on the cycloaddition products leads to the final tricyclic (Scheme 11).[10,59]

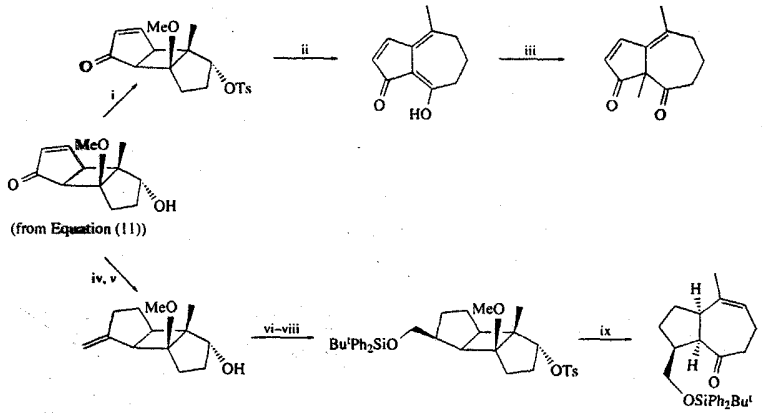
The product of cycloaddition of norbornadiene and propyne is readily converted by cleavage of the two-carbon bridge to highly functionalized and completely stereodefined diquinanes, suitable for further elaboration in a number of directions (Scheme 12).[60]

Serratosa's entry into the angularly-fused triquinanes (Equation (52)) succeeds for terminal but not internal propargyl ethers. The *in situ* alkene isomerization that precedes cycloaddition renders synthesis of the bicyclo[3.3.0]oct-1-ene isomer unnecessary, making this a most direct entry in spite of the modest yields.[48]

7.2.4 INTRAMOLECUALR PAUSON–KHAND REACTION

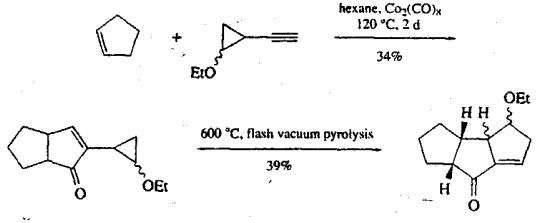
7.2.4.1 Reactions Involving Acyclic All-carbon Enynes

Enynes in which three or four atoms separate the double and triple bonds cyclize upon complexation to $Co_2(CO)_8$ and either subsequent heating or treatment with appropriate promoters to give bicyclic enones (Equation (76)). Hex-1-en-5-yne, which would give a four-membered ring upon intramolecular cycloaddition, instead undergoes alkyne trimerization exclusively.[61]



i, *p*-TsCl, pyridine, 0 °C, ~100%; ii, $NaHCO_3$, $CaCO_3$, pyridine, MeOH, H_2O, 65 °C, 90%; iii, MeI, K_2CO_3, acetone, 55 °C, 82%; iv, H_2, 5% Pd/C, MeOH, 98%; v, $Ph_3P{=}CH_2$, $Ph_3PMe^+Br^-$, DMSO, 60 °C, 88%; vi, $BH_3{\cdot}SMe_2$, THF, then NaOH, H_2O_2, 60 °C, 90%; vii, Bu^tPh_2SiCl, Et_3N, dmap, 76%; viii, *p*-TsCl, pyridine, 0 °C, 94%; ix, $NaHCO_3$, $CaCO_3$, pyridine, MeOH, H_2O, 65 °C, 72%

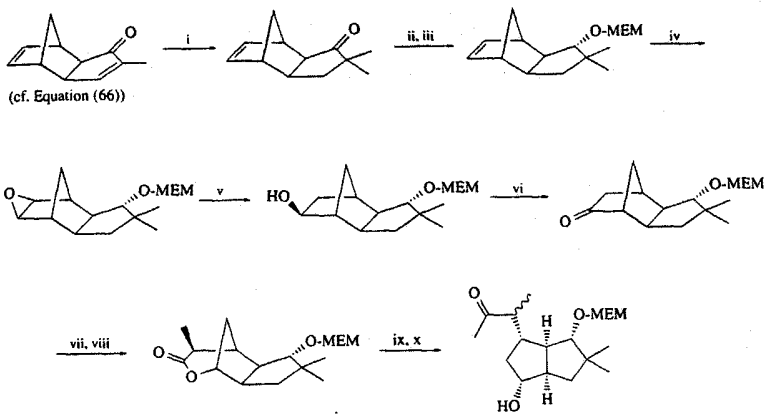
Scheme 10



Scheme 11

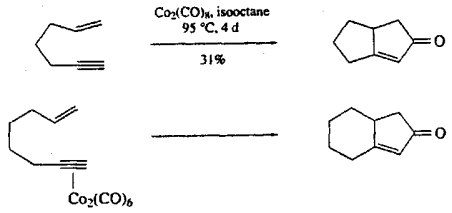
With the exception of slightly elevated temperatures the thermal conditions required are no different than those for intermolecular Pauson–Khand reactions. Promotion by amine oxides gives similarly comparable results. However, the latter protocol appears to offer the dual benefits of very short reaction times and, in some cases, greater stereoselectivity and superior yields (Equations (77) and (78)).[16,27,61]

The most extensively studied systems are those derived from hept-1-en-6-yne, as the products, bicyclic[3.3.0]oct-1-en-3-ones, are useful in the synthesis of numerous cyclopentane-based polycyclics. Considerable information on the effects of substitution on these reactions has been collected from the work of Magnus, Hua, and Serratosa. Magnus carried out the first systematic examinations of the factors that contribute to diastereoselectivity in these reactions, and all three workers have compiled results bearing on the effects of substitution on yields and reaction rates. Toleration and effect of substitution in these cyclizations is a function of position. The detailed effects of substitution on Pauson–Khand reactivity have been readily accommodated by a mechanism that is in all important aspects identical to that previously described.[62] As alkene insertion takes place into a cobalt–carbon bond of the enyne-hexacarbonyldicobalt complex, pseudodiaxial interactions develop between any substituent on the terminus of the alkyne (C-7) and those substituents at the allylic (C-3) and propargylic (C-5) positions of the original enyne that are positioned to end up on the *endo* face of the product. Thus the insertion is preferentially directed to place the larger of these substituents in *exo* orientations. The larger these substituents are, the greater the diastereoselectivity obtained (Schemes 13 and 14). Additional work of Serratosa suggests the intervention of an isomerism process that may affect stereoselectivity in the case of labile propargyl substituents (Section 7.2.4.3).



i, Li, NH_3, MeOH, –33 °C, 5 h, then MeI, Et_2O, 25 °C, 12 h, 90%; ii, Li, NH_3, MeOH, –33 °C, 5 h, 94%; iii, MEM-Cl, Pr^i_2NEt, CH_2Cl_2, 25 °C, 4 h, 87%; iv, mcpba, CH_2Cl_2, 25 °C, 4 h, 79%; v, $LiBHEt_3$, THF, 65 °C, 48 h, 53%; vi, PCC, NaOAc, CH_2Cl_2, 25 °C, 7 h, 100%; vii, mcpba, $NaHCO_3$, $CHCl_3$, 100 °C, 42 h, 84%; viii, LDA, THF, –78 °C, 2.5 h, then MeI, HMPA, –78 –25 °C, 1 h, 94%; ix, NaOH, MeOH, 25 °C, 12 h, 88%; x, MeLi, THF, 0 – 25 °C, 6 h, then TMS-Cl, 0 – 25 °C, then HCl to pH = 4, 86%

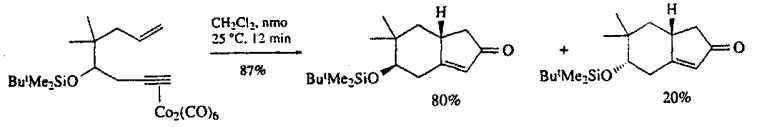
Scheme 12



(76)

(77)

Isooctane, 95 °C, 4 d:	35%
CH_2Cl_2, *N*-methylmorpholine-*N*-oxide (nmo), 25 °C, 1.25 h:	52%
CH_2Cl_2, THF (1:1), nmo, 25 °C, 15 min:	41%

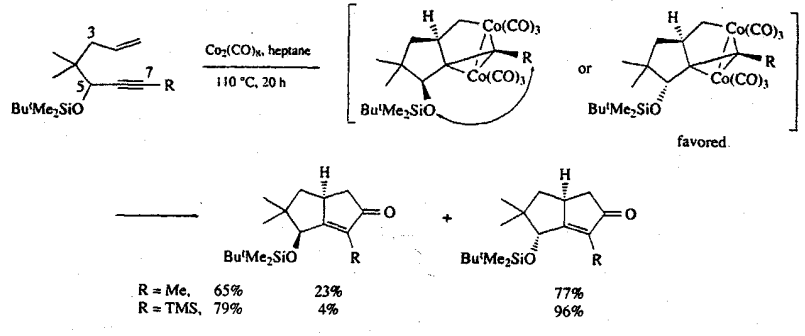


(78)

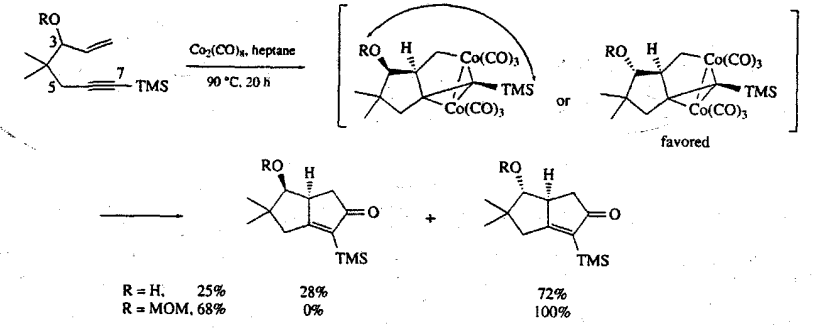
Unprotected alcohols occasionally interfere with the intramolecular thermal reaction. Although the *t*-butyldimethylsilyl protecting group has been most frequently used in these situations, it too is occasionally unsuitable, in which case the methoxymethyl (MOM) group is preferred.

Comparison of Equation (76) with Schemes 13 and 14 suggests that substitution at C-4 confers benefit in terms of both yield and reaction time. This is most likely a result of a *gem*-dialkyl effect in which conformations placing the alkene and complexed-alkyne ends of the system in close proximity are rendered enthalpically more favorable by increasing substitution on the intervening atoms. The reduced contribution of $\Delta H^{\ddagger}$ to $\Delta G^{\ddagger}$ associated with alkene complexation allows it to better compete with intermolecular side reactions (i.e., trimerization of the otherwise more reactive alkyne moieties). Hua has made similar observations in simpler systems (Equation (79)).[63] No stereocontrol at C-4 is available, however, the position being too remote from the reaction centers (Equation (80)).[64]

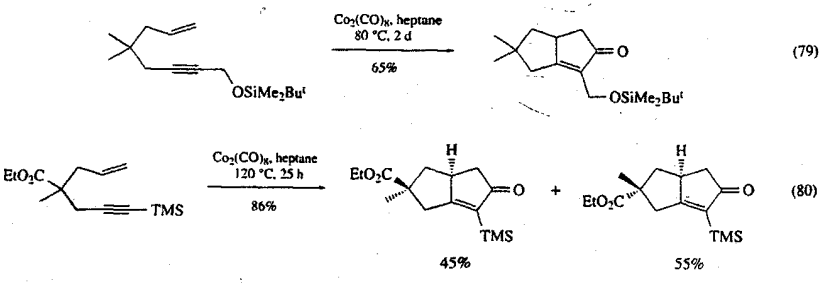
3,4-Disubstituted heptenynes display stereoselectivity upon Pauson–Khand cycloaddition that appears to be a composite of the steric effects described above, which occur upon alkene insertion, and



Scheme 13

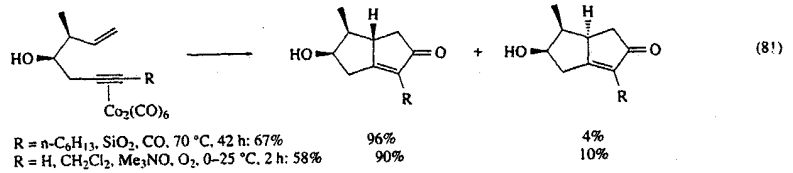


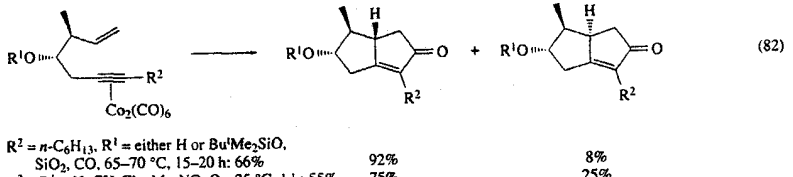
Scheme 14

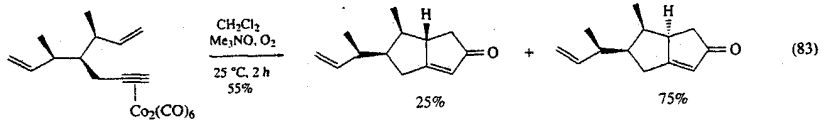


the conformational effects mentioned earlier (Section 7.2.2). The preference for *exo*-methyl product formation from the 3-methyl-4-hydroxy system depends both on the size of the group at the alkyne terminus and on the relative stereochemistry at C-3 and C-4. Thus, of the examples shown in Equations (81) and (82), the order of *exo* selectivity is (3*R*,4*R*)-1-substituted enyne > (3*R*,4*S*)-1-substituted > (3*R*,4*R*)-1-unsubstituted > (3*R*,4*S*)-1-unsubstituted.[65,66]

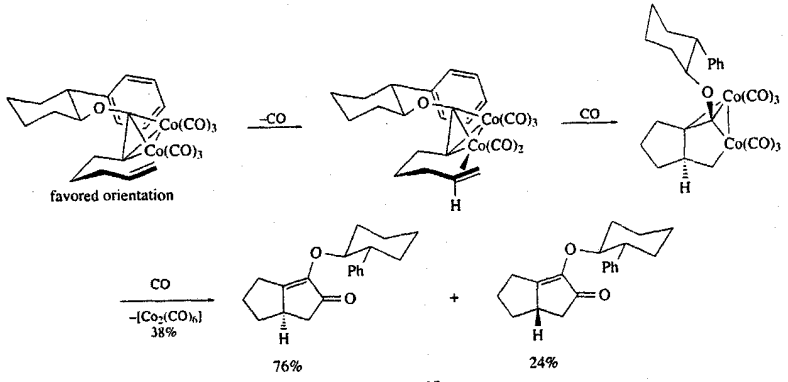
The insensitivity of the product ratio to the size of R^1 suggests that more than steric effects upon insertion play a role. In the case of the 3*R*,4*S* (but not 3*R*,4*R*) enyne, the conformation with the fewest *gauche* interactions is the precursor to the *endo*-methyl product. Reduction of the main *exo*-favoring steric interaction by removal of the alkyne substituent may increase the relative importance of conformational preferences prior to alkene complexation. Cycloaddition of the symmetrical dienyne below (Equation (83)) actually affords the *endo*-methyl product primarily, a result that can be explained only by invoking conformational effects.[66]







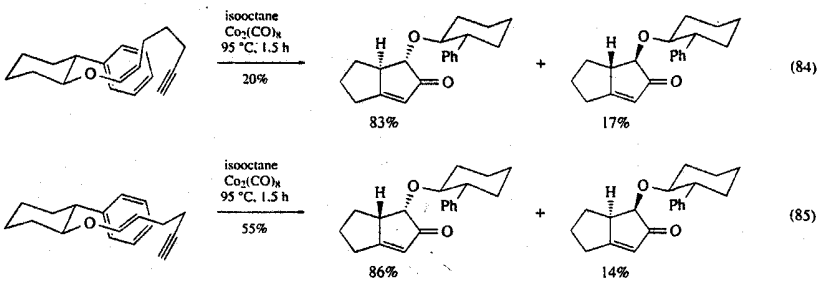
Moyano *et al.* have demonstrated diastereoselection induced by chiral auxiliaries in intramolecular Pauson–Khand reactions. 7-[(1*S*,2*R*)-2-Phenylcyclohexoxy]-1,6-heptenyne, the alkynyl ether derived from *trans*-2-phenylcyclohexanol, cyclizes with 52% *de* (i.e., 3.2:1 isomer ratio) favoring the *R* configuration at the bridgehead position of the bicyclo[3.3.0]octenone product. The preferred product is derived from reaction of the alkene at the cobalt remote from the phenyl ring of the auxiliary. Alkene insertion is face-selective, favoring the orientation that leads to a cobaltabicyclooctane with a *cis* ring fusion (Scheme 15).[67]



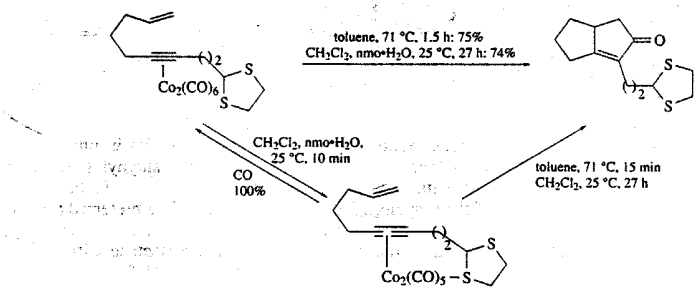
Scheme 15

The related vinyl ethers, (*Z*)- and (*E*)-1-[(1*S*,2*R*)-2-phenylcyclohexoxy]-1,6-heptenyne, show even higher degrees of induction. In these cases the phenyl ring of the auxiliary shields one face of the alkene (Equations (84) and (85)).[68]

Krafft's study of the effect of heteroatoms separated by one, two, and three carbons from the alkyne terminus of 1,6-enynes has provided further insight into the role that amine oxides play in Pauson–Khand processes.[27] Thermal reactivity increases as the separation between the heteroatom and the alkyne decreases. With amine oxides at room temperature, some substrates react faster, some slower. In two cases complexes have been identified in which one cobalt is chelated by the alkyne and a

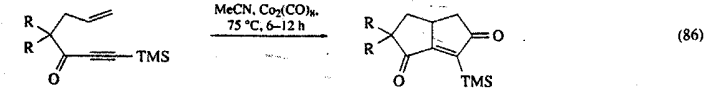


thioether moiety. These species revert to the original $Co_2(CO)_6$-alkyne complex upon exposure to CO, but convert to cyclopentenones slowly at room temperature and rapidly upon heating (Scheme 16). It thus appears that cycloaddition in the presence of an amine oxide may be inhibited if such a heteroatom-bound complex forms and is too stable to dissociate readily to permit alkene complexation to occur at room temperature.



Scheme 16

1,6-Heptenynes unsubstituted at C-4 but containing substituents at positions besides C-1 and C-7 tend to be poorer substrates.[69] The reaction of a 1-hepten-6-yn-5-one is illustrative (Equation (86)).[19]

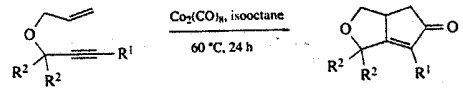


R = Me, 82%; R = H, 32% (86)

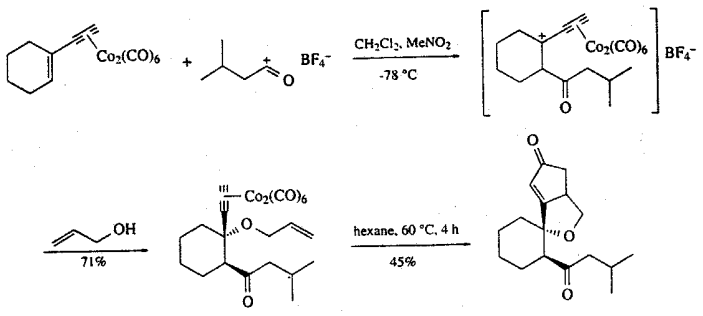
Equation (22) (Section 7.2.2) illustrates one of several successful cycloadditions from substrates in which two carbons of the ene-yne bridge of a heptenyne are contained in a carbocyclic ring.[35]

7.2.4.2 Reactions Involving Acyclic Heteroatom-containing Enynes

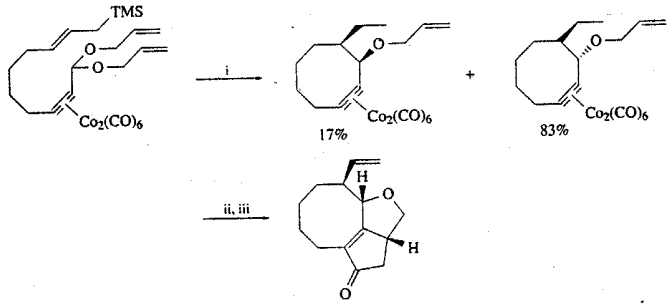
The ready access of allyl propargyl ethers from $Co_2(CO)_6$-complexed propargyl cations, whose chemistry has been extensively developed by Nicholas,[70] has made them the most frequently studied heteroatom-containing substrates for intramolecular Pauson–Khand cycloaddition. Initial work by Billington established the feasibility of these systems as substrates, albeit in only moderate yields (Equation (87)).[71] The Smit–Caple collaboration has combined more extensively developed versions of Nicholas chemistry with Pauson–Khand cycloaddition to access novel heteropolycyclics (Scheme 17).[72] Schreiber has demonstrated still another direction of development. Incorporation of an alkyne in a medium-sized ring is achieved by exploiting the "bending" of the triple bond by cobalt complexation in the course of alkylative ring formation via the stabilized propargyl-cation complex. The resulting system is then capable of both inter- as well as intramolecular Pauson–Khand cycloaddition (Scheme 18).[16,73]



$R^2 = R^1 = H$, 14%; R^2 = Me, R^1 = H, 29%; R^2 = H, R^1 = Me, 41% (87)



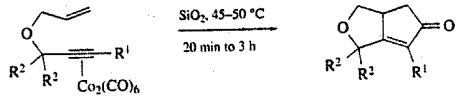
Scheme 17



i, BF_3•Et_2O, CH_2Cl_2, -78 °C – 25 °C, 75%; ii, separate and purify *trans* isomer; iii, CO, PhH, 60 °C, 4 h, 85% or CH_2Cl_2, NMO, 25 °C, 90%

Scheme 18

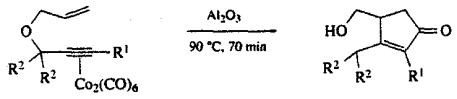
Allyl propargyl ethers were the first systems for which the benefits of adsorption of the cobalt-complexed enyne ether onto silica gel were demonstrated (Equation (88)).[74] Apparently adsorption favors reactive conformations in a manner similar to that of bulky substitution at C-4 of all-carbon enynes, facilitating cycloaddition by means of a novel variant of the *gem*-dialkyl effect. The solid-phase process is remarkably tolerant of substitution throughout the molecule although bulky groups on the alkyne terminus do not appear to have been examined, and little stereochemical work has been reported. The technique is also applicable to ordinary enynes containing polar substituents and enynes containing heteroatoms other than oxygen. Sonication also helps, reducing reaction temperatures still further (e.g., ≤45 °C).[75]



$R^2 = R^1 = H$, 58%; R^2 = Me, R^1 = H, 75%; R^2 = H, R^1 = Me, 60% (88)

In the "dry" Pauson–Khand reaction system oxygen is necessary in order to prevent hydrogenolysis of the allylic carbon–oxygen bond in the product. This process is presumably effected by hydridocobalt

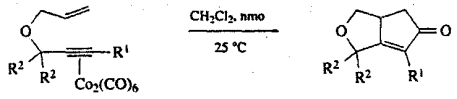
species. The oxygen may serve simply to scavenge such species. Hydrogenolysis may be selectively promoted if desired by carrying out the reaction under "dry" conditions on alumina under an argon atmosphere. This results in 3-alkyl-4-(hydroxyalkyl)cyclopentenones directly, in yields consistently in the 70% range (Equation (89)).[76]



(89)

$R^2 = R^1 = H$, 70%; $R^2 = Me$, $R^1 = H$, 69%; $R^2 = H$, $R^1 = Me$, 73%

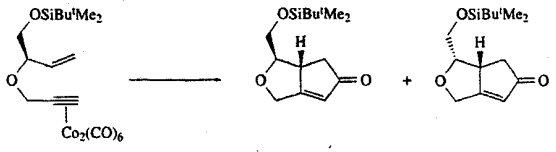
The mildest conditions for which Pauson–Khand reactions succeed with these substrates are found, again, through the use of amine oxides. Equation (90) illustrates these results (cf. Equations (87) and (88)).[16]



(90)

$R^2 = R^1 = H$, 85%; $R^2 = Me$, $R^1 = H$, 92%; $R^2 = R^1 = Me$, 77%

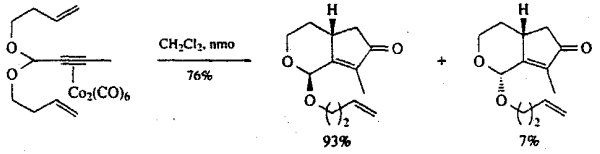
In a single case where stereochemistry was examined over a range of conditions, a substrate with allylic substitution gave better yields but reduced stereoselectivity upon promoted cycloaddition (Equation (91)).[17]



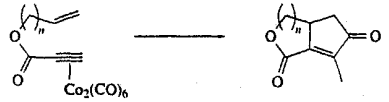
(91)

PhH, 80 °C, 20 h:	8%	>95%	<5%
SiO_2, 50 °C, 3 h:	28%	>95%	<5%
DMSO, 20 °C, 6 d:	54%	88%	12%
CH_2Cl_2, Me_3NO, 20 °C, 4 h:	73%	80%	20%

Cycloadditions of bis(allyl) and bis(homoallyl) acetals of alkynals give protected bicyclic lactols, and allyl and homoallyl alkynoates afford lactones (Equations (92) and (93)).[18,77]



(92)

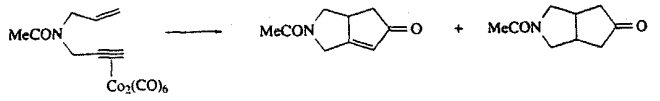


(93)

$n = 1$: toluene, 71 °C, 16 h, 22%; CH_2Cl_2, nmo, 25 °C, 4–5 h, 72%
$n = 2$: toluene, 71 °C, 4 d, 14%; CH_2Cl_2, nmo, 25 °C, 4–5 h, 66%

Pauson has studied a variety of cyclization conditions for *N*-acylated allyl propargyl amines and allyl homopropargyl amines.[78] Azabicyclo[4.3.0]nonenones form from the latter in moderate yields thermally, under UV irradiation, with sonication, and on silica. However, azabicyclo[3.3.0]octenones are usually

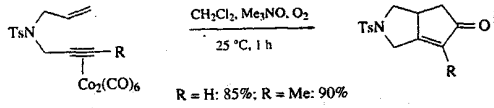
not the major thermal products from these amines: reduction to saturated ketones accompanies the Pauson–Khand process (Equation (94)).



(94)

isooctane, 100 °C, 24 h:	5%	0%	100%
isooctane, *hν*, 50 C, 20 h:	33%	0%	100%
isooctane, ultrasound, 60 °C, 5 h:	36%	0%	100%
benzene, ultrasound, 60 °C, 4 h:	34%	65%	35%
SiO_2, 70 °C, 1.5 h:	67%	0%	100%

However, enones may be obtained using amine oxides under an oxygen atmosphere (Equation (95)).[33,79]



(95)

R = H: 85%; R = Me: 90%

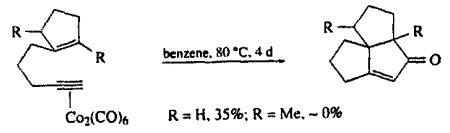
Finally, an extraordinary report by Moretó describes the Pauson–Khand reaction of alkynyl allylamino chromium and tungsten carbene complexes upon treatment with $Co_2(CO)_8$ in THF at room temperature (Equation (96)).[80] The corresponding *N*-allyl amides fail to cyclize.

(96)

$R^2 = Et$, $R^1 = H$, 70%; $R^2 = Ph$, $R^1 = H$, 75%; $R^2 = Ph$, $R^1 = Me$, 72%

7.2.4.3 Reactions Involving Cyclic Enynes

As might be expected from comparable intermolecular situations, incorporation of the alkene partner in a ring of appropriate size is compatible with intramolecular Pauson–Khand reaction. However, steric and functional group considerations are essential in order to achieve acceptable results. Cycloadditions have been reported from both cyclopentenes and cyclohexenes containing pendant alkynes. Many 1-(4-pentynyl)cyclopentenes and 3-(3-butynyl)cyclopentenes have been examined, and a reasonably useful framework for determining the applicability of the reaction has emerged. Pauson–Khand cycloaddition of 1-(4-pentynyl)cyclopentene itself gives rise to the angularly fused triquinane (tricyclo[6.3.0.0.^{1,5}]-undecane) ring system, the basis of a number of compounds of synthetic interest (Section 7.2.4.4). This substrate, containing a trisubstituted alkene partner, is at the substitution limit for useful reactivity: its derivative containing an additional methyl group and therefore a tetrasubstituted double bond gives only trace amounts of enone (Equation (97)).[81]

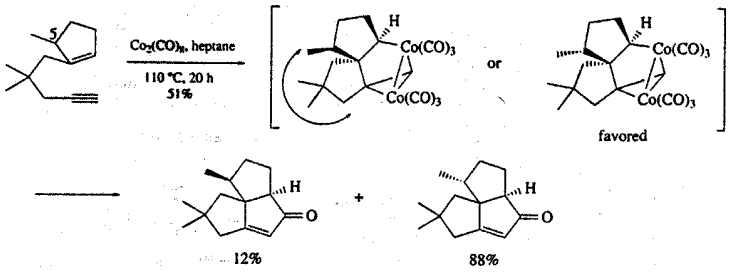


(97)

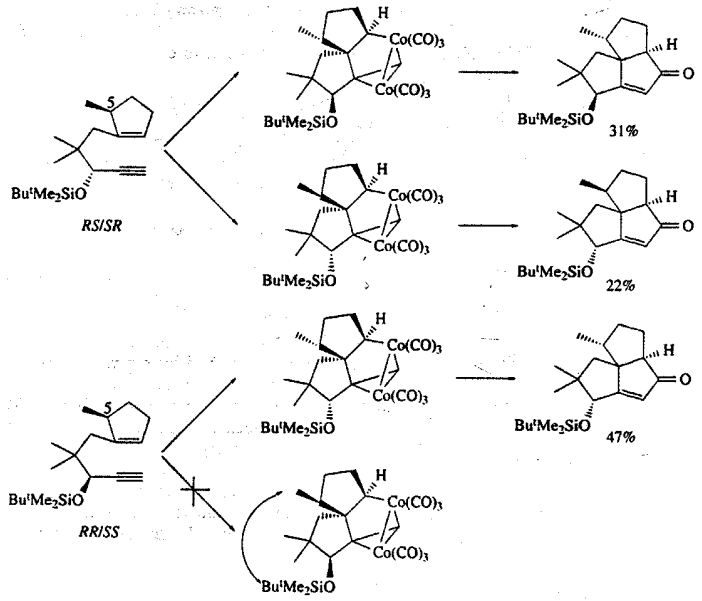
R = H, 35%; R = Me, ~ 0%

The reaction benefits from *gem*-dialkyl acceleration and exhibits useful stereoselectivity in the cycloaddition of appropriately substituted derivatives (Scheme 19).[82] In this case the twist about the newly formed spiro center generates a 1,3-pseudodiaxial interaction between the propargyl methylene and the *endo*-group at the C-5 allylic position on the cyclopentene ring, thus favoring the formation of

the *exo*-methyl stereoisomer. This stereocontrol is compromised by substitution in either the allylic or propargylic positions. The *RS/SR* diastereomer of the derivative shown in Scheme 20 gives a nearly 1:1 mixture of *endo*- and *exo*-methyl substituted enones as the pathways leading to both isomers experience similar steric interactions. The situation with the *RR/SS* diastereomer is more straightforward: the *endo*-methyl product forms exclusively. In this situation the *exo* isomer experiences an interaction between the methyl and the alkoxy group that is far more severe than the *endo*-methyl/propargyl-methylene interaction that controls its deoxygenated analogue.[83]



Scheme 19



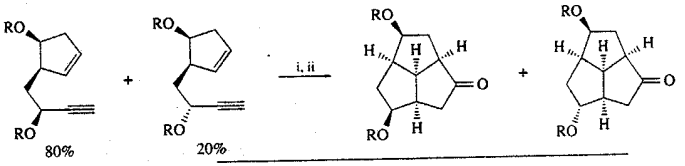
Conditions: heptane, $Co_2(CO)_8$, 115 °C, 19 h, 33%

Scheme 20

Several additional examples of cycloadditions of hydroxy- and alkoxy-substituted 1-(4-pentynyl)cyclopentenes, some using silica adsorption, have been reported.[35,84] However, trimethylsilyl substitution at the alkyne terminus eliminates cycloaddition reactivity in these systems.[84] Examination of possible structures of Pauson–Khand intermediates reveals steric interactions involving this silyl group occurring at both the alkene complexation and insertion stages, principally with the allylic methylene groups of both the side chain and the ring. It is generally found that intramolecular

Pauson–Khand reactions involving either 2,2-disubstituted or 1,2,2-trisubstituted alkene partners succeed only when the alkyne terminus is unsubstituted. An additional limitation has been found in the lack of cycloaddition from a 1-(*cis*-1,4-pentenynyl)cyclopentene, a substrate containing a *cis* double bond in the linkage between the desired ene and yne reaction partners. Strain is presumed to be responsible.[85] Note, however, the successful cycloaddition of the extraordinary 1-(4-pentynyl)cyclopentene·$Co_2(CO)_6$ complex shown in Equation (23), a reaction which gives rise to a tetraquinanedione possessing the molecular framework of the natural product crinipellin-B.[35]

Similar intramolecular cycloadditions of cyclic alkenes containing alkynyl substitution have been explored by Serratosa in the 3-(3-butynyl)cyclopentene series. The product in this case is a triquinacene derivative, a tricyclo[5.2.1.$0^{4,10}$]decane. Since the targets in Serratosa's studies required functionalization of all three five-membered rings, all substrates utilized contained varying degrees of substitution. In this system the alkene is *cis*-1,2-disubstituted and therefore may complex to a cobalt in an orientation that avoids steric interaction with a substituent on the alkyne terminus. Substrates in which the alkyne is not terminally substituted undergo cycloaddition in variable yields.[86] The reaction tolerates free hydroxyl groups somewhat when carried out under "dry" (Smit–Caple) conditions (Scheme 21).

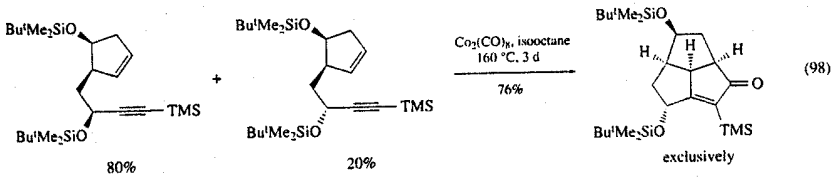


R	Total yield		
Bn	60%	70%	30%
Bu^tMe_2Si	various	78%	22%
H	16%		

R = Bn: i, $Co_2(CO)_8$, *t*-butylbenzene, 170 °C, 2–3 h; ii, H_2, 10% Pd/C, EtOH, Et_3N
R = Bu^tMe_2Si: i, $Co_2(CO)_8$, isooctane, 160 °C, 3 d; ii, H_2, 10% Pd/C, EtOH, Et_3N
R = H: i, $Co_2(CO)_8$, benzene, then SiO_2, remove solvent, 120 °C, 2 h; ii, H_2, 10% Pd/C, EtOH

Scheme 21

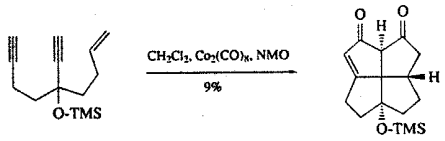
That the apparent changes in diastereomer ratio between reactants and products shown in the above examples were significant was confirmed by the results of cycloadditions of silyl-substituted alkyne analogues. In these cases only a single product, with the opposite stereochemistry to the dominant isomer in the examples above, is formed (Equation (98)). This result plus the high chemical yield requires a pathway for substrate isomerization. Serratosa proposed that the diastereomer that would lead to the unobserved *endo*-5-alkoxy isomer is rendered unreactive towards cycloaddition by steric interference from the silyl group. Instead, ionization of the propargylic leaving group, facilitated by the strong stabilization imparted to the propargylic cation by complexation to cobalt, allows the center to isomerize to the diastereomeric precursor to the 5-*exo* product, which then forms readily.[87] This result is of interest in the context of Magnus' earlier results (e.g., Scheme 13). In those systems the substrate contains only a single stereocenter and is racemic. Its isomerization merely interconverts enantiomers and therefore is an "invisible" process. However, substrates with a second stereocenter may be worth examination for such isomerization, and future applications of this chemistry that aim towards the preparation of enantiomerically pure enones will face obvious difficulties if isomerization at a labile propargyl stereocenter cannot be prevented.



(98)

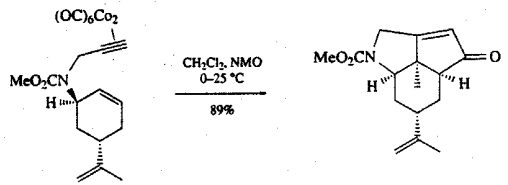
Keese has reported amine oxide promoted Pauson–Khand reactions of 8-(3-butynyl)bicyclo-[3.3.0]oct-1-enes, leading to tetraquinanes with a fenestrane configuration. Most impressive was the successful demonstration of a tandem process, in which one cycloaddition, forming an

8-(3-butynyl)bicyclo[3.3.0]oct-1-en-3-one, is followed in the same pot by the second Pauson–Khand process (Equation (99)).[88]



(99)

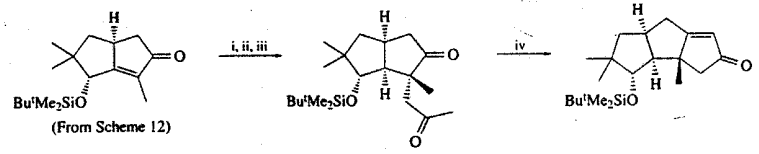
Cycloadditions of 3-(2-propynyloxy)- and 3-(2-propynylamino)cyclohexenes, reported by Schreiber[16] and Takano,[89] respectively, have added yet another dimension to the variety of ring systems accessible through Pauson–Khand methodology. The latter system is a proposed precursor in a synthesis of the alkaloid dendrobine (Equation (100)).



(100)

7.2.4.4 Synthetic Applications

Magnus was the first to develop extensive synthetic applications of the Pauson–Khand preparation of the bicyclo[3.3.0]oct-1-en-3-one system. His efforts amply demonstrated the degree to which the high level of functionality in the Pauson–Khand products could be directly utilized in building more complex structures. A formal synthesis of the antitumor sesquiterpene coriolin illustrates a very efficient sequence for construction of the third ring in the linearly-fused triquinane series in the presence of considerable functionality (Schemes 13 and 22).[62a] A synthesis of the related triquinane hirsutic acid utilizes the observation that the proper stereochemical relationship between the substituents at C-7 and the ring-fusion carbon (C-5) of the bicyclo[3.3.0]oct-1-en-3-one system, while not controllable in the cycloaddition reaction, may be readily established by acid- or base-catalyzed equilibration (Equation (80) and Scheme 23).[64]

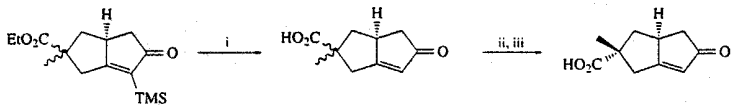


i, H_2, 10% Pd/C, EtOH, 92%; ii, NaH, allyl bromide, DME, 79%;
iii, O_2, $PdCl_2$, CuCl, DMF, 64%; iv, Bu^tOK, Bu^tOH, 74%

Scheme 22

Pericás, Greene, and co-workers more recently incorporated a chiral auxiliary mediated Pauson–Khand process into a formal synthesis of optically active (+)-hirsutene (Scheme 24).[68]

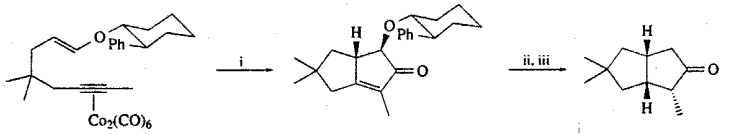
In a short and completely diastereoselective synthesis of the unusual tetracyclic natural product quadrone, Magnus minimized an interfering hydrogenolysis problem by adding a hindered pyridine base to scavenge highly acidic cobalt hydrides (Equation (101)). In contrast, addition of a phosphine oxide only exacerbated the problem.[90] Both Magnus and Mulzer have described stereoselective syntheses of optically active carbocycline analogues.[91,92] Magnus derived enyne stereochemistry from D-(+)-ribonolactone, but Pauson–Khand reaction on a *trans*-disubstituted γ-butyrolactone was thwarted by excessive strain. Instead, a seven-membered ring ketal analogue was used successfully (Equation (102)). Mulzer's stereochemistry was derived from derivatives of (+)- or (−)-glyceraldehyde.



(From Equation (80))

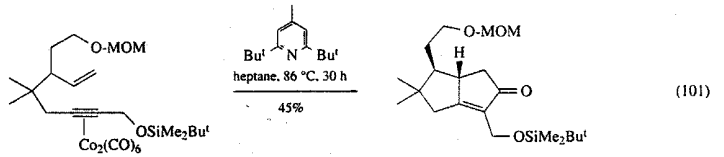
i, $MeSO_3H$, 75 °C, 135 min, 96%; ii, *p*-TsOH, benzene, 80 °C, 4 h, 100%;
iii, separate and recycle undesired isomer 3x, 90% yield of isomer shown

Scheme 23

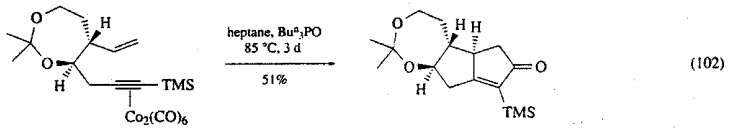


i, hexane, 42 °C, 12 h, 55%; ii, Li, NH_3, 80%; iii, SmI_2, 85%

Scheme 24



(101)



(102)

Hua has used the products of Pauson–Khand cycloadditions for syntheses of optically active pentalenene and racemic pentalenolactone *(E)*-methyl ester. The racemic ketone in the first case was converted to the necessary optically active intermediate by kinetic resolution via 1,4-addition of an optically active allyl sulfoxide anion. These represented the first syntheses of natural products containing the angularly fused triquinane skeleton from bicyclic Pauson–Khand products (Scheme 25).[63]

A formal synthesis of the natural product aucubigenone by Billington made use of a very direct route involving Pauson–Khand cycloaddition of an allyl propargyl ether (Scheme 26).[67]

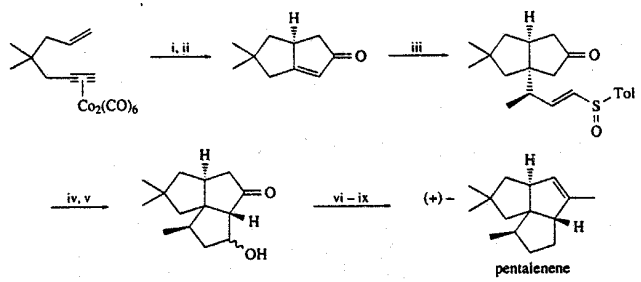
Jeong's formal total synthesis of racemic loganine showcases the development of the chemistry of an 8-oxabicyclo[4.3.0]non-1-en-3-one Pauson–Khand product (Scheme 27).[77]

An application of the reductive cycloaddition of an *N*-allyl-*N*-propargyl amide has been published by Becker, in the course of the preparation of a novel azetidine-containing tricyclic system (Scheme 28).[93] The conditions chosen (inert atmosphere, dry silica) led to complete reduction of the initial enone product.

In contrast, a synthesis of the biologically active (−)-kainic acid by Yoo employs the amine oxide at low temperature to preserve the unsaturation of the primary product (Scheme 29).[94]

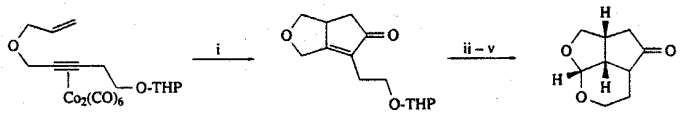
Since the cycloaddition of 1-(4-pentynyl)cyclopentenes is limited to trisubstituted alkenes and simple terminal alkynes, bisnorisocomene, but not isocomene, could be prepared (Scheme 30).[81,84] However, this limitation is not a factor for most other compounds in this class of natural products, and the steric interactions described earlier permit a diastereocontrolled synthesis of pentalenene (see Scheme 25). The natural product was obtained by subjecting the product of Scheme 19 to the sequence (i) Li, NH_3, MeOH; (ii) MeLi, Et_2O; (iii) *p*-TsOH, benzene, reflux.[82] Similarly, two of the products of Scheme 20 have been converted into pentalenic acid.[83,85]

Serratosa has critically evaluated the various entries to the triquinacene system, concluding that a route from the dibenzylated enyne substrate (Schemes 21 and 31) is operationally the simplest for



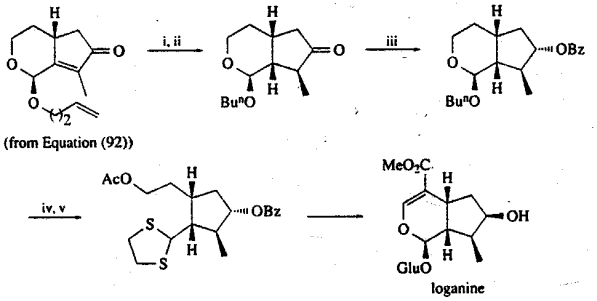
i, heptane, 120 °C, 3 d, 58%; ii, 0.5 equiv. (*S*)-*trans*-*p*-$MeC_6H_4S(O)CH{=}CHCH_2Li$, THF, –78 °C, 30 min, 45%; iii, 2.0 equiv. racemic *trans*-*p*-$MeC_6H_4S(O)CH{=}CHCH_2Li$, THF, –78 °C, 45 min, 91%; iv, Zn, AcOH, 95%; v, HCO_2H, CF_3CO_2H, 60 °C, 24 h, then K_2CO_3, MeOH, 64%; vi, MeMgBr, Et_2O, 0 °C, 70%; vii, $(Me_2N)_2POCl$, Et_3N, dmap, toluene, 60 °C, 10 h, 96%; viii, Li, Bu^tOH, $EtNH_2$, THF, 0 °C, 30 min, 97%; ix, BF_3, Et_2O, CH_2Cl_2, 99%

Scheme 25



i, isooctane, 60 °C, 24 h, 41%; ii, H_2, Raney Ni, EtOH; iii, *p*-TsOH, MeOH; iv, $NaNO_2$, H_2SO_4, H_2O, –10 °C, 1 h; v, *hv*, benzene, 0 °C, 15 h

Scheme 26



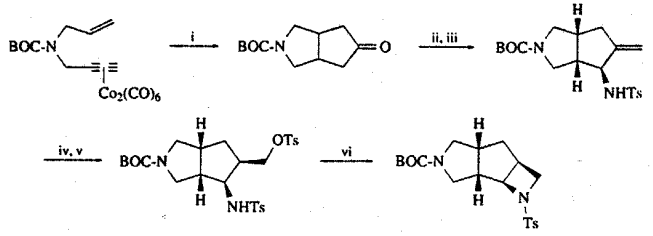
i, H_2, Pd/C, 25 °C, 12 h, 97%; ii, NaOMe, MeOH, 0 °C, 2 d, 90%; iii, $NaBH_4$, MeOH, 25 °C, 30 min, then NaH, BzBr, DMF, 25 °C, 2 h, 94%; iv, $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O/CH_2Cl_2$, –15 °C, 1 h, 0 °C, 5 h, 89%; v, Ac_2O, dmap, Et_3N, CH_2Cl_3, 25 °C, 30 min, 100%

Scheme 27

preparation of multigram quantities of tricyclo[5.2.1.$0^{4,10}$]decane-2,5,8-trione. This in turn is a key intermediate for the study of synthetic entries to dodecahedrane and its derivatives. An optically active version of this synthesis has also been developed.[86c]

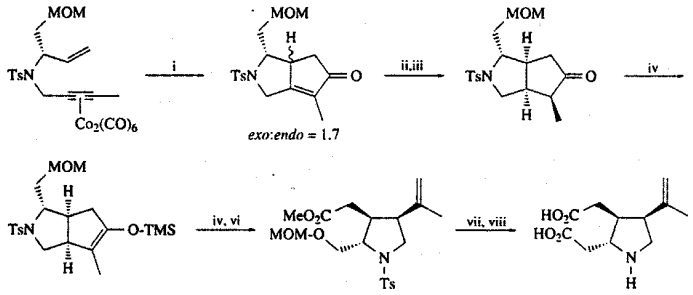
ACKNOWLEDGEMENT

Financial support for our work in this area has been provided by the National Institutes of Health (GM26294) and is gratefully acknowledged.



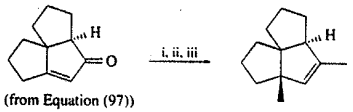
i, SiO_2, N_2, 70 °C, 2.5 h, 85%; ii, $Ph_3PMe^+Br^-$, Bu^tOK, THF, 40 °C, 45 min, 82%; iii, TsNSNTs, CH_2Cl_2, 0 °C, 1 h, 25 °C, 16 h, 81%; iv, thexylborane, then NaOH, H_2O_2, 44%; v, TsCl, pyridine, 100%; vi, $LiBEt_3H$, 100%

Scheme 28



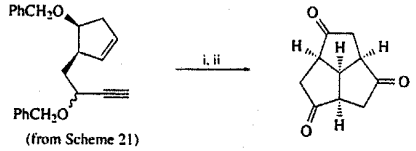
i, CH_2Cl_2, Me_3NO, 25 °C, 95%; ii, H_2, Pd/C, EtOAc, 98%; iii, separate; iv, $FeCl_3$, EtMgBr, TMS-Cl, Et_2O, THF, 25 °C, 95%; v, O_3, then Me_2S, then CH_2N_2, 90%; vi, $Ph_3P{=}CH_2$, THF, 0 °C, 72%; vii, CF_3CO_2H, CH_2Cl_2, 25 °C, then PDC, DMF, then CH_2N_2, 78%; viii, LiOH, MeOH, H_2O, 25 °C, then Li, NH_3, THF, –78 °C, 87%

Scheme 29



i, Me_2CuLi, Et_2O, 0 – 25 °C, 2 h, 89%; ii, MeLi, Et_2O, THF, –78 °C, 150 min, 91%; iii, $SOCl_2$, pyridine, THF, –45 – 25 °C, 15 min, 66%

Scheme 30



i, $Co_2(CO)_8$, *t*-butylbenzene, 170 °C, 2–3 h, 60–70%; ii, H_2, 10% Pd/C, EtOH, then PCC, Celite, 63%

Scheme 31

7.2.5 REFERENCES

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