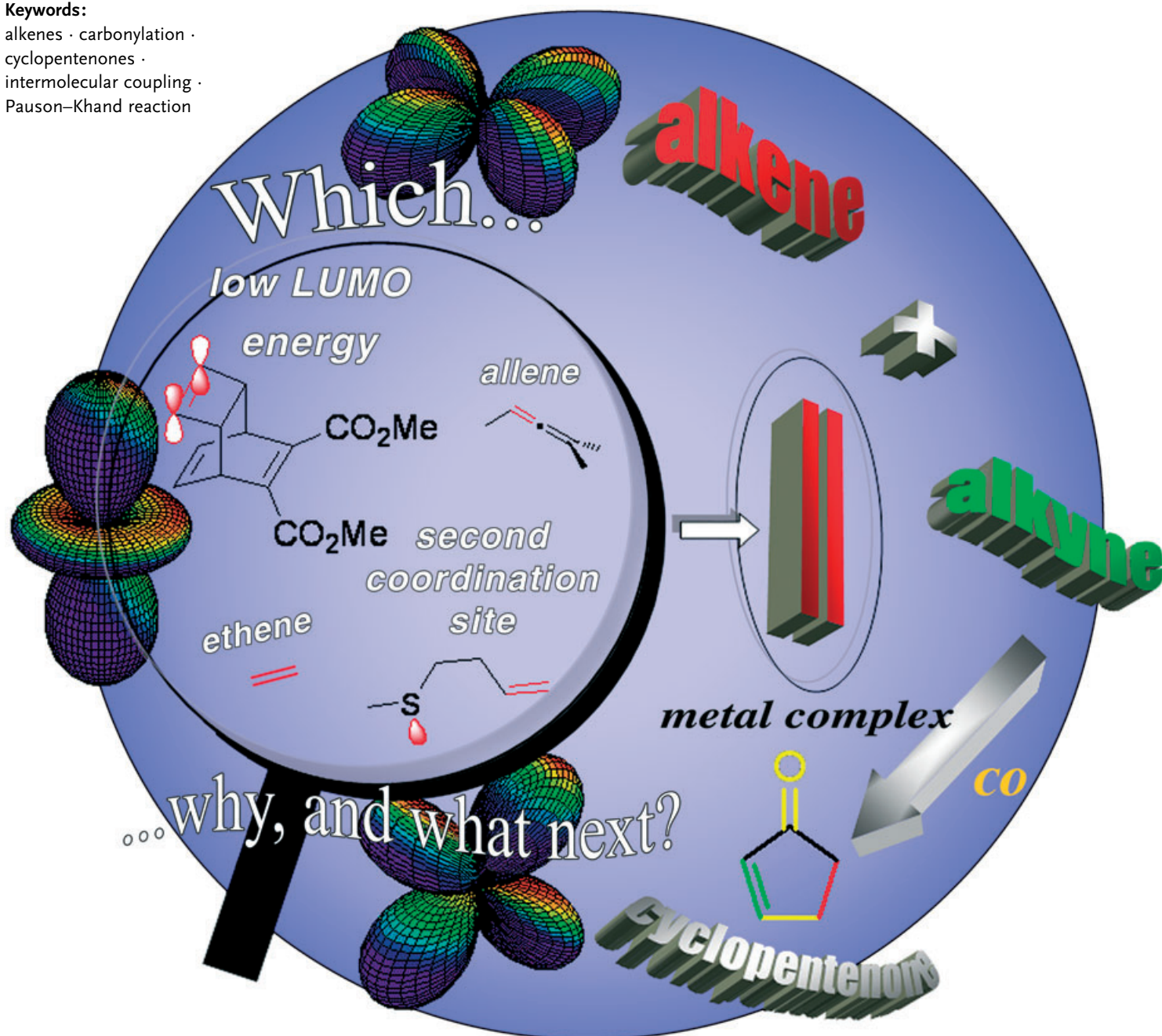


Carbocycle Synthesis

The Intermolecular Pauson–Khand Reaction

Susan E. Gibson* and Nello Mainolfi

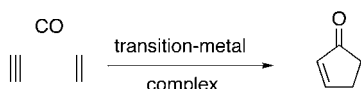
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Five membered carbocycles are important building blocks for many biologically active molecules. Moreover, substituted cyclopentenones (e.g. cyclopentenone prostaglandins) exhibit characteristic biological activity. The efficiency and atom economy of the Pauson–Khand reaction render this process potentially one of the most attractive methods for the synthesis of such compounds. Although it was discovered in its intermolecular form, the scope of the intermolecular Pauson–Khand reaction has always been limited by the poor reactivity and selectivity of the alkene component. The past decade, especially the last three years, has seen concerted efforts to broaden the scope of this reaction. In this overview, we provide a comprehensive and critical coverage of the intermolecular Pauson–Khand reaction based on the reactivity characteristics of different classes of alkenes and a rationalization of successes and misfortunes in this area.

1. Introduction

Metal-mediated reactions play an important role in our continuing search for improved ways of constructing complex molecules. For the synthesis of five-membered rings, there is surely no match for the Pauson–Khand reaction in terms of potential flexibility and atom economy. This reaction, discovered in 1971 by Pauson and Khand,^[1] is a transition-metal-mediated coupling of an alkyne, an alkene, and a molecule of carbon monoxide that results in the formation of a cyclopentenone (Scheme 1).^[2] Originally a cobalt carbonyl medi-



Scheme 1. The Pauson–Khand reaction.

ated process, the past decade has witnessed the introduction of new protocols based on titanium, rhodium, iridium, and ruthenium complexes. Furthermore, there are now many protocols based on transition-metal catalysts.^[2g]

The mechanism of the Pauson–Khand reaction has been the subject of extensive studies. It has proven difficult, however, to detect any intermediates beyond an initially formed hexacarbonylcobalt(o)-alkyne complex. A mechanism for the stoichiometric reaction, proposed by Magnus and co-workers in 1985, is still the generally accepted working mechanism (Scheme 2).^[3] Starting from the initial hexacarbonyl complex **I**, the first step involves the loss of one CO ligand. This step, which is strongly endothermic, creates a vacant coordination site in intermediate **II**.^[4] At this point the alkene coordinates with the cobalt and then inserts into a cobalt–carbon bond to form the cobaltacycle **III**. This is the step in which the regiochemical and stereochemical outcome is determined and is thought to be the rate-determining step.^[5,9] The groups of Pericás,^[5] Nakamura,^[6] and Gimbert^[7–9] have all performed elegant theoretical calculations on the role

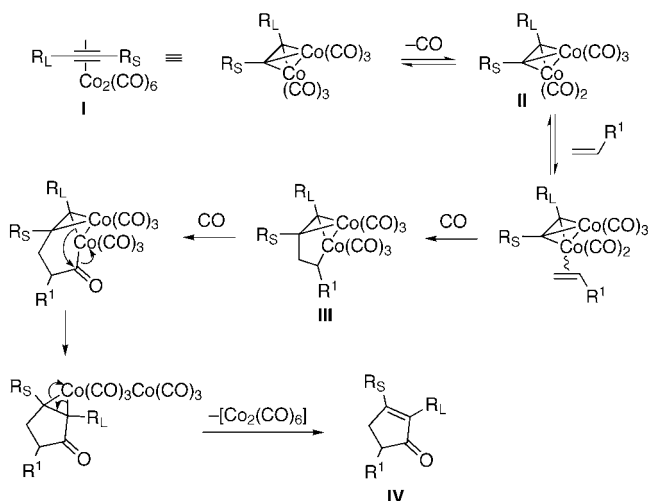
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of the alkene in cobaltacycle formation, and these will be discussed in Section 3. The last two steps involve

insertion of CO and reductive elimination to form the cyclopentenone **IV**.

Five-membered carbocycles are useful building blocks for the construction of complex biologically active molecules. Moreover, many cyclopentenones (e.g. cyclopentenone prostaglandins) exhibit a characteristic biological activity.^[10] Although the Pauson–Khand reaction was discovered in its intermolecular form, the scope of the intermolecular reaction in synthetic projects has always been limited by the poor reactivity and selectivity of simple alkenes. Applications have been restricted to the use of strained alkenes such as



Scheme 2. The proposed mechanism for the $[\text{Co}_2(\text{CO})_8]$ -mediated Pauson–Khand reaction according to Magnus and co-workers;^[3] R_L = larger group, R_S = smaller group.

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norbornene, norbornadiene, and bicyclo[3.2.0]hept-6-ene, whilst the thermodynamically more favored intramolecular version has received most attention.^[2]

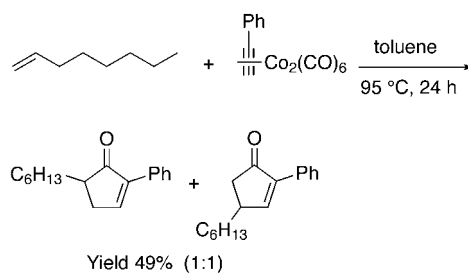
The development of efficient, versatile, environmentally friendly, and possibly asymmetric catalytic *intermolecular* systems would maximize the synthetic attractiveness of the Pauson–Khand reaction and elevate this powerful reaction to a method of choice in the synthetic planning of complex biologically active molecules.^[11] The past decade, and especially the past three years, has seen concerted effort from the chemistry community to broaden the scope of the intermolecular Pauson–Khand reaction.^[12] In this Review we offer a comprehensive and critical coverage of the intermolecular Pauson–Khand reaction based on the reactivity characteristics of the alkene partners. By identifying reactivity patterns for different classes of alkenes, we aim to provide an overview and rationalization of successes and misfortunes in this area.

2. Reactive Alkene Partners: A Second Coordination Site

2.1. Discovery

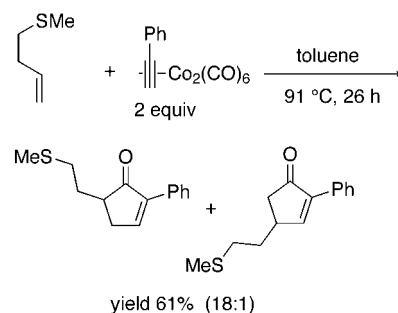
Secondary interactions between molecules are often used to increase the rate and/or the selectivity of a reaction.^[13] A preassociation of molecular partners through, for example, hydrogen bonding or Lewis acid–base interactions, is preserved during the chemical transformation and leads to a highly ordered transition state that often produces a significant enhancement in the rate and the selectivity of the reaction.

This concept was first applied to the intermolecular Pauson–Khand reaction by Krafft in 1988.^[14] The use of terminal or unsymmetrically substituted alkenes usually leads to low yields and poor selectivity (Scheme 3).^[2,15] Krafft and co-workers^[14,16] anticipated that a heteroatom tethered to the alkene by a carbon chain would coordinate to cobalt, thus providing a bidentate complex that would lead to an increase in yield of the products and to control of the regiochemical outcome. Alkenes bearing oxygen, sulfur, and nitrogen substituents were investigated in the reaction. In contrast to alcohols and methoxymethyl ethers, which did not exhibit characteristics that would implicate heteroatom coordina-



Scheme 3. An intermolecular Pauson–Khand reaction of a terminal alkene.

tion,^[17] sulfur and nitrogen ligands led to increased yields and excellent regiocontrol (Scheme 4).



Scheme 4. An example of a substrate-directed intermolecular Pauson–Khand reaction according to Krafft and co-workers.^[14]

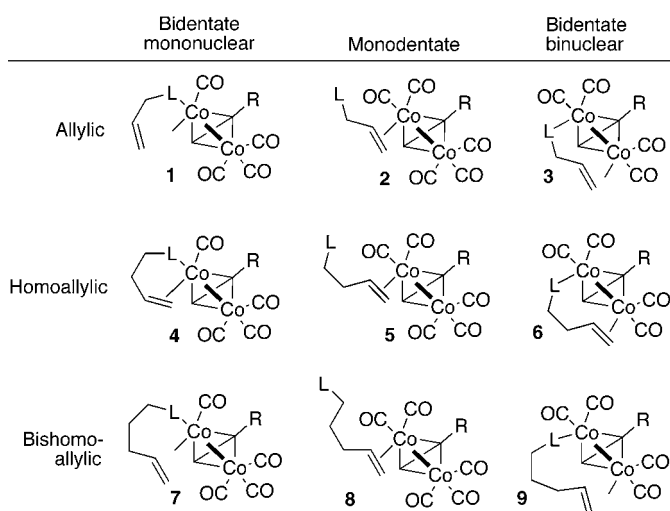
In general allylic and bishomoallylic substrates result in poor yields and selectivities, whereas homoallylic substrates proved to be the most effective. For allylic substrates it was postulated that the tether between the heteroatom L and the alkene is too short to accommodate either a bidentate mononuclear “mode of cycloaddition” **1** (in which the heteroatom and the alkene bind to the same cobalt atom) or a bidentate binuclear “mode of cycloaddition” **3** (in which the heteroatom and the alkene each bind to different cobalt atoms) (Scheme 5). The monodentate “mode of cycloaddition” **2** (in which the heteroatom does not bind to the cobalt) is thus most likely to be the major contributor to the reaction.^[18]



Sue E. Gibson obtained her first degree (1981) in Cambridge and her DPhil (1984) in Oxford (Prof. S. G. Davies). After postdoctoral studies at the ETH, Zürich (Prof. A. Eschenmoser), she lectured organic chemistry at the University of Warwick and at Imperial College, London. In 1999 she took up the Daniell Chair of Chemistry at King's College London, returning to Imperial College London and a Chair of Chemistry in 2003. Her research interests revolve around the application of transition metals in organic synthesis, especially the development and application of new asymmetric catalysts and novel chiral macrocycles.



Nello Mainolfi obtained his BSc from Queen Mary University, London, in 2001. His research project involved a new method to access substituted 2-bromophenols (Dr. Jason Eames). His PhD research (Prof. S. E. Gibson, 2001–2004) focused on the synthesis and investigations of a new class of non-racemic chiral macrocycles as ligands for asymmetric catalysis and as hosts for organic guests. He also prepared highly functionalized cyclopentenones through a new catalytic intermolecular Pauson–Khand reaction. In November 2004 he began postdoctoral studies with Prof. K. C. Nicolaou at the Scripps Research Institute.



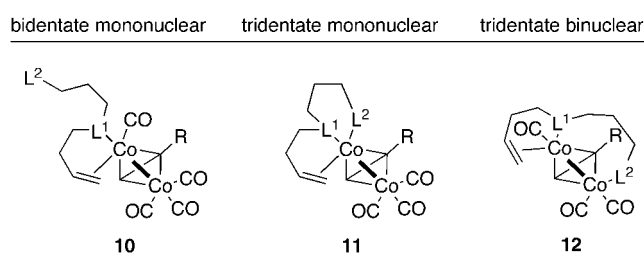
Scheme 5. Modes of cycloaddition for the substrate-directed intermolecular Pauson–Khand reaction ($L = SR$ or NR_2) (Krafft and co-workers^[16b]).

Homoallylic substrates gave very good yields of 2,5-disubstituted cyclopentenones. Therefore, it was postulated that bidentate mononuclear complex **4** (Scheme 5) is the best “mode of cycloaddition” for these substrates (the bidentate binuclear “mode of cycloaddition” **6** would give rise to the minor regioisomer). Bishomoallylic substrates exhibit a modest enhancement in yield and regioselectivity; hence “modes” **7** and **9** (Scheme 5) may well both be operating.

Krafft and Juliano explored the concept of heteroatom-directing reactions further by using tridentate alkenes (that is, alkenes bearing two heteroatoms).^[19] An in-depth study of these ligands revealed that in some of the cases examined, the second tethered directing substituent enhanced the rate of the reaction (Table 1). The significantly shorter reaction times and higher yields than those for the reaction depicted in Scheme 4 and the similar to better regioselectivities observed in the reactions (Table 1, entries 1–3), could be due to the accessibility of tridentate “modes” **11** (tridentate mononuclear) and **12** (tridentate binuclear) as well as the previously discussed bidentate “mode” **10** (Scheme 6).

Table 1: Tridentate alkenes in the substrate-directed intermolecular Pauson–Khand reaction (Krafft and Juliano^[19]).

Entry	L ¹	L ²	R	t [h]	Yield [%] (ratio)
1	S	NMe ₂	Ph	6	85 (15:1)
2	S	SEt	Ph	1.5	70 (8:1)
3	S	SEt	Bu	1.75	85 (>40:1)



Scheme 6. Modes of cycloaddition of tridentate homoallylic substrates (Krafft and co-workers^[19]).

2.2. Applications

The intermolecular Pauson–Khand reaction had to wait 10 years to benefit further from the elegant substrate-directing approach developed by Krafft and co-workers. In 2002, Itami and Yoshida reported the use of alkenyldimethyl-2-pyridylsilanes as the alkene partners for the ruthenium-catalyzed intermolecular Pauson–Khand reaction.^[20] In this reaction, the pyridylsilyl group serves as a removable directing group, which facilitates the generation of desilylated cyclopentenones in moderate to excellent yields (Table 2).

Table 2: The pyridylsilyl-directed Pauson–Khand reaction (Itami and Yoshida^[20]).

Entry	R ¹	R ²	R ³	R ⁴	Reaction conditions	Yield [%] ratio
1	H	H	Ph	Ph	xylenes, 120 °C	88
2	H	H	H	Ph	toluene, 100 °C	55 (100:0)
3	H	H	H	C ₆ H ₁₃	toluene, 100 °C	91 (59:41)
4	C ₄ H ₉	H	H	Ph	xylenes, 140 °C	41 (100:0)
5	H	Me	H	C ₆ H ₁₃	xylenes, 120 °C	40 (62:38)

Dimethyl-2-pyridylvinylsilane acted as an ethene equivalent, producing cyclopentenones in good yields and selectivity when symmetrical alkynes were used (Table 2, entry 1), but moderate yields (Table 2, entry 2) or poor regioselectivities (Table 1, entry 3) when unsymmetrical alkynes were employed.

The application of β - or α -substituted vinylsilanes resulted in the completely regioselective production of substituted cyclopentenones (for R¹ and R²), albeit in low yields and sometimes with poor alkyne selectivity (Table 2, entries 4 and 5). This work provided an excellent example of the exploitation of a second coordination site on the alkene partner and strengthens the validity of Krafft’s postulated homoallylic bidentate mononuclear “mode of cycloaddition” **4** (Scheme 5).

Another study that follows the principle of substrate-directed intermolecular Pauson–Khand reactions and further

widens the scope of this method was reported in 2003.^[21] In an inspiring communication,^[21a] Carretero and co-workers described the use of nonracemic chiral 2-(*N,N*-dimethylamino)-phenyl vinyl sulfoxide as a substrate-directing alkene partner for a stoichiometric asymmetric intermolecular Pauson–Khand reaction (Table 3). After analyzing the results of

Table 3: The (*o*-dimethylamino)phenylsulfinyl-directed intermolecular Pauson–Khand reaction (Carretero and co-workers^[21]).

Entry	R ^[a]	R ¹	t [h]	Yield (d.r.)
1	<i>n</i> Bu	H	4	74 (93:7)
2	Bn	H	14	58 (93:7)
3	(CH ₂) ₂ OTIPS	H	7	66 (>98:2)
4	CH ₃	CH ₃	24	no reaction
5	CH ₃	CH ₃	48 ^[b]	33 (92:8)

[a] TIPS = triisopropylsilyl. [b] Pressure = 10 kbar.

their search for an active vinyl sulfoxide they concluded that the 2-(*N,N*-dimethylamino)phenyl substituent on the sulfoxide yielded by far the most reactive, regio-, and diastereoselective alkene. This behavior is consistent with the operation of Krafft's bidentate mononuclear "mode of cycloaddition".^[21b]

In this NMO-promoted (NMO = *N*-methylmorpholine *N*-oxide)^[22] intermolecular Pauson–Khand reaction the presence of the bishomoallylic dimethylamino group, aided by the sulfoxide-induced polarization of the alkene (see Section 3), promotes a highly diastereoselective, completely regioselective, and reasonable yielding reaction for terminal alkynes (Table 3, entries 1–3). No reaction occurred with an internal alkyne (Table 3, entry 4), although this limitation was partially lifted by performing the reaction at high pressure (Table 3, entry 5). The reaction has been used in the shortest reported synthesis of the antibiotic (–)-pentenomycin I.^[21]

This first section of the review has highlighted the synthetic relevance of the stimulating study by Krafft and co-workers on the heteroatom-directed intermolecular Pauson–Khand reaction.^[14,16,19] The two recent reports by Itami and Yoshida^[20] and by Carretero and co-workers,^[21] which broaden the scope of this approach to new attractive alkene partners, suggest that its synthetic potential has been underestimated for a long time.

3. Reactive Alkene Partners: The LUMO Energy

3.1. Background

Milet, Gimbert, and co-workers recently published an exciting theoretical study of the reactivity of alkenes in the intermolecular Pauson–Khand reaction.^[9] After analyzing the reactivity of cyclohexene, cyclopentene, and norbornene towards the hexacarbonyldicobalt(0) complex of 1-propyne they concluded that the reactivity of the alkenes in the

Pauson–Khand reaction is related to the back donation of electrons from the *d* orbitals of the cobalt atom to the π^* orbitals of the alkene. After CDA (charge decomposition analysis) calculations they discovered that for a given alkene there was an "excellent correlation between the level of back donation and the barrier to cobaltacycle formation" (which is thought to be the rate-determining step for this reaction^[9]). With norbornene they discovered a greater back donation and a lower energy barrier, whereas with cyclohexene there is little back donation and a higher barrier to cobaltacycle formation. For cyclopentene the values were similar to norbornene which is consistent with experimental observations.^[23] Thus it appears that the greater the back donation, the higher the reactivity of the alkene. The common component of back donation and cobaltacycle formation is the LUMO of the alkene, and the theoretical work showed that the lower the LUMO, the higher the reactivity. The authors stated that "the LUMO of a free olefin should be generally useful as a first approximation of relative reactivity." The study also notes that a correlation exists between the C=C–C angle of the alkene (cyclohexene 128°, cyclopentene 112°, norbornene 107°) and the energy level of its LUMO: the smaller the angle, the lower the LUMO energy.

In this section we review the literature of the intermolecular Pauson–Khand reaction and we rationalize the behavior of alkene partners on the basis of this study. This not only validates this exciting work but also generates a novel set of parameters for designing new Pauson–Khand substrates.

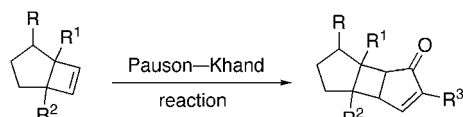
3.2. Endocyclic Alkenes

In light of the study by Milet, Gimbert, and co-workers, reports on the use of cyclopropenes as the alkene partners in the intermolecular Pauson–Khand reaction^[15f,24] come as no surprise. The C=C–C angle of cyclopropene is 64.58°,^[25] and hence a low-lying LUMO and high reactivity are expected. After two reports on the use of substituted cyclopropenes^[15f,24a] in the intermolecular Pauson–Khand reaction, in 2001 Pericás, Riera, and co-workers used cyclopropene itself for the first time in the cobalt-mediated version of this reaction.^[24b] In this NMO-promoted coupling, cyclopropene reacted with bulky terminal alkynes to give synthetically attractive bicyclo[3.1.0]hex-3-en-2-ones **13** in good to excellent yields (Table 4, entry 1). In the case of aromatic and *n*-alkyl-substituted terminal alkynes, however, the yields were poor to moderate (Table 4, entries 2–4) and the production of tricyclic ketone **14** was observed.^[26]

Based on the theoretical study of Milet, Gimbert, and co-workers, cyclobutene and its derivatives, which have a C=C–C angle of 94.2°,^[27] are expected to exhibit high reactivity towards alkyne metal complexes in the intermolecular Pauson–Khand reaction. In fact, there are surprisingly few reports of cyclobutene derivatives being employed in the cobalt-mediated version of this reaction.^[28] They are dominated by the bicyclo[3.2.0]hept-6-ene scaffold depicted in Scheme 7 which has been the subject of several studies that reveal very good reactivity and diastereoselectivity.^[28]

Table 4: The intermolecular Pauson–Khand reaction of cyclopropene with terminal alkynes (Pericás and Riera).^[24b]

Entry	R	13	Yield [%]	14
1	<i>t</i> Bu	93		
2	Ph	50	15	
3	<i>n</i> -hexyl	60	10	
4	<i>p</i> -tolyl	26	23	


Scheme 7: The bicyclo[3.2.0]hept-6-ene scaffold in the Pauson–Khand reaction.^[28]

In 2004, the use of cyclobutene derivatives was extended by our group. We reported^[29] a cobalt-catalyzed intermolecular Pauson–Khand reaction of the readily available cyclobutadiene equivalent **15** (Table 5). The two-step, one-pot

Table 5: The catalytic intermolecular Pauson–Khand reaction with a cyclobutadiene equivalent (Gibson and Mainolfi).^[29]

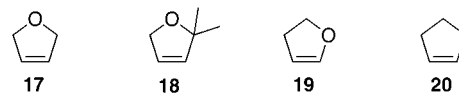
Entry	R ^[a]	Yield [%]
1	<i>n</i> -hexyl	98
2	Ph	75
3	CH ₂ OTBDMS	70
4	COOMe	no reaction

[a] TBDMS = *tert*-butyldimethylsilyl.

protocol employed a cyclobutadiene equivalent for the first time in the intermolecular Pauson–Khand reaction to provide synthetically versatile bicyclo[3.2.0]hepta-3,6-dien-2-ones **16** (Table 5, entries 1–3). A limit of this protocol is that it does not tolerate electron-withdrawing groups on the alkyne (Table 5, entry 4).

After examining cyclopropenes and cyclobutenes, our survey takes us to the cyclopentenes. The literature contains many examples of intermolecular Pauson–Khand reactions with double bonds embedded in a five-membered ring. The calculations of Milet, Gimbert, and co-workers^[9] indicate that cyclopentene is activated to approximately the same extent as norbornene (the most studied alkene for this reaction). In fact, Pauson reported good reactivity for cyclopentene in his early studies of this reaction.^[15a] Over the past 30 years

moderate to good successes have been reported in studies on the use of 2,5-dihydrofuran **17**,^[30] 2,2-dimethyl-2,5-dihydrofuran **18**,^[30a] 2,3-dihydrofuran **19**,^[2a,31] and cyclopentene **20**^[15b,c,28f,30a,c,e-i,32,68a] (Scheme 8).


Scheme 8: Cyclopentenes used in the intermolecular Pauson–Khand reaction.

At this point it is interesting to focus on some examples in which the reactivity of the same alkene changes dramatically upon changing the reaction conditions. In the first example of the Pauson–Khand reaction of cyclopentene with phenylethyne, Pauson and Khand reported a high-temperature, moderate-yield protocol (Table 6, entry 1).^[15a] A decade later

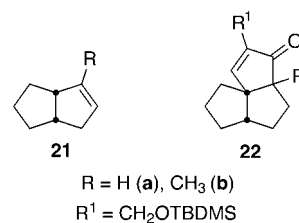
Table 6: Intermolecular Pauson–Khand reaction of cyclopentene with phenylethyne under different reaction conditions.

Entry	20 [equiv]	Additive ^[a] [(equiv)]	<i>t</i> , <i>T</i>	Yield [%]
1 ^[15a]	5.3	none	7 h, 150–160 °C	47
2 ^[30c]	5.9	<i>n</i> Bu ₃ P=O (1)	36 h, 69 °C	70
3 ^[30f]	excess	TMANO (6)	10 min, RT, ultrasound	97
4 ^[32h]	2.0	<i>n</i> BuSMe (5)	2 days, 35 °C	75

[a] TMANO = trimethylamine *N*-oxide.

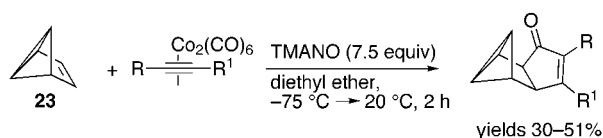
Pauson and co-workers reported an improvement in the yield of this reaction when using tributylphosphine oxide as a promoter (Table 6, entry 2).^[30c] A few years later, Kerr and co-workers showed that the use of an amine oxide under ultrasound conditions rendered this reaction nearly quantitative (Table 6, entry 3).^[30f] In the meantime, Sugihara et al. reported the use of alkyl methyl sulfides as promoters of the Pauson–Khand reaction; under their conditions cyclopentene reacted smoothly at a relative low temperature albeit over a longer reaction time (Table 6, entry 4).^[32h]

An interesting subclass of cyclopentenes is the hexahydropentalenes **21** (Scheme 9). These undergo a double-bond shift prior to the Pauson–Khand reaction to access more-


Scheme 9: Hexahydropentalenes (**21 a**)^[33] and **21 b**^[34] and the corresponding intermolecular Pauson–Khand products **22 a, b** from their reaction with a silyl-protected propargylic alcohol.

strained double bonds. Serratosa and co-workers showed^[33] that the reaction of 1,2,3,3a,4,6a-hexahydropentalene (**21a**) with the hexacarbonyldicobalt(0) complex of a silyl-protected propargylic alcohol gave a single product (albeit in low yield) that corresponded to the angular fused triquinone **22a**. In an independent study Billington et al. showed that a methyl-substituted pentalene group **21b** (Scheme 9) behaved in the same way.^[34] In this case the alkene shift converted a trisubstituted alkene into a tetrasubstituted alkene prior to cycloannulation.^[35]

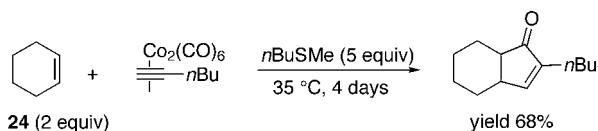
A more strained and exotic cyclopentene, benzvalene (**23**), underwent an intermolecular aminoxide-promoted Pauson–Khand reaction with moderate success (Scheme 10) in the fascinating synthesis of a (CH)₁₀ hydrocarbon by Christl and co-workers.^[36]



R, R' = H, Ph, Me,
nPr, (CH₂)₆

Scheme 10. Intermolecular Pauson–Khand reaction of benzvalene (**23**) with alkynes (Christl and co-workers^[36]).

The theoretical studies of Milet, Gimbert, and co-workers supported by Pauson's experiments,^[15a] reasoned that the poor reactivity of cyclohexene (3% yield with phenylethyne; C=C–C angle of 128° compared to 107° of norbornene) is due to a higher alkene LUMO which leads to a slightly endothermic binding energy value, in contrast to the exothermic binding energies of norbornene and cyclopentene.^[9] Nevertheless, a good yield can be obtained from the reaction of cyclohexene **24** and 1-hexyne with a long reaction time and the use of *n*BuSMe as promoter (Scheme 11).^[15f]

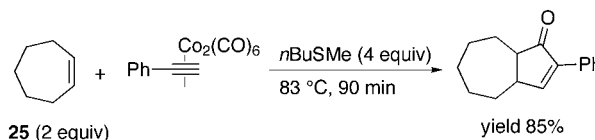


Scheme 11. Intermolecular Pauson–Khand reaction of cyclohexene (Sugihara et al.^[15f]).

There are only a few examples of the use of cycloheptenes and cyclooctenes in the Pauson–Khand reaction. In their early studies,^[15a] Pauson and Khand reported better reactivity for these two cyclic alkenes than for cyclohexene (41% for cycloheptene and 35% for cyclooctene in their reaction with phenylethyne) but not as good as for norbornene and cyclopentene. These experimental observations are also consistent with the results of Milet, Gimbert, and co-workers. Cycloheptene (C=C–C angle of 123°)^[37,38] is predicted to have a lower-lying LUMO (and hence a higher reactivity) than cyclohexene (128°), but a higher-lying LUMO than norbor-

nene (107°) and cyclooctene (112°). The same rationalization is valid for cyclooctene (C=C–C angle of 121.9°).^[38]

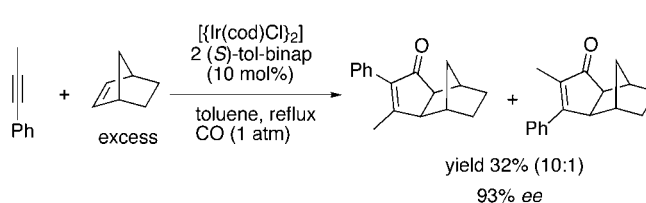
As in the case of cyclohexene, a great improvement in the yield of a reaction of cycloheptene **25** was reported,^[15f] again by using *n*BuSMe as a promoter (Scheme 12). It is important to note at this point that although it has proven possible to improve reactivity by changing reaction conditions, the relative rates of reactions of different alkenes are always maintained.^[39]



Scheme 12. A high-yielding intermolecular Pauson–Khand reaction of cycloheptene (Sugihara et al.^[15f]).

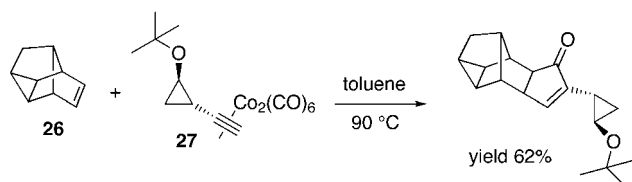
Norbornene and related systems are commonly used in the intermolecular Pauson–Khand reaction. Since the early reports of Pauson and co-workers,^[23a–c] in which they showed norbornenes to be the most successful alkene partners, there have been many examples of their use in the presence of different metals and under different reaction conditions,^[15b–f,30c,f,32b,g,40,68a] in the asymmetric version of the reaction,^[28e,h,32d,i,41] and in heterogeneous systems.^[30g–i,42] Related systems such as 8-oxabicyclo[3.2.1]octenes^[28b,43] and heteroatom-containing bicyclo[2.2.1]heptenes,^[28f,40b,p,42a,43c,44,45] reveal similar or slightly lower levels of reactivity. As the literature contains so many examples, we have selected just two reports, one for its current importance in the field (Scheme 13) and one for its exoticism (Scheme 14).

In 2000, Shibata used norbornene in the only catalytic enantioselective intermolecular Pauson–Khand reaction reported to date based on a chiral catalyst (Scheme 13).^[41p]



Scheme 13. The only catalytic enantioselective Pauson–Khand reaction reported to date (Shibata and Takagi^[41p]).

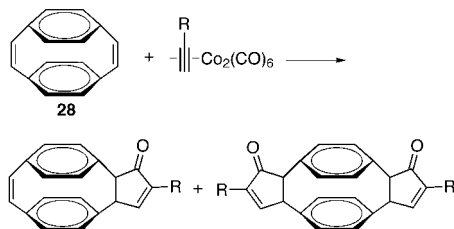
In 1993, de Meijere and co-workers^[46] reported the use of deltacyclene (**26**), a norbornadiene derivative, in a cobalt-mediated intermolecular Pauson–Khand reaction with 2-alkoxy-1-ethynylcyclopropane **27** (Scheme 14). The same group reported that the fascinating cyclic diene [2.2]paracyclophane-1,9-diene (**28**) is a good alkene partner in the intermolecular Pauson–Khand reaction.^[47] With a C=C–C angle of 118.7°^[48] this compound would be expected to be more reactive than cyclohexene (128°), cycloheptene (123°), and cyclooctene (121.9°), but slightly less reactive than



Scheme 14. Intermolecular Pauson–Khand reaction of deltatcyclene (**26**) (de Meijere and co-workers^[46]).

cyclopentene (112°) and norbornene (107°). This is indeed reflected in the experimental results.^[47] The reaction of diene **28** with 2 equivalents of the hexacarbonyldicobalt(0) complex of phenylethyne for 1 day gave a mixture of mono- and diannulated compounds in a moderate yields (Table 7,

Table 7: The intermolecular Pauson–Khand reaction of [2.2]paracyclophane-1,9-diene (**28**) (de Meijere and co-workers^[47]).



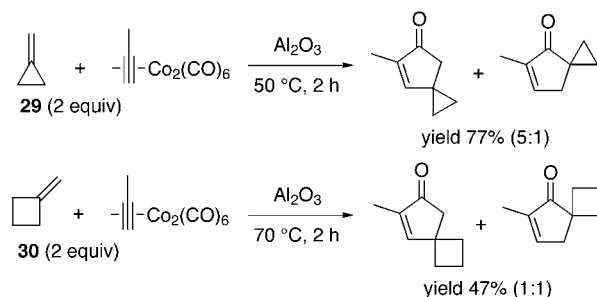
Entry	R ^[a] ([equiv])	t, T	Yield [%]	
			mono ^[b]	di ^[b]
1	Ph (2)	1 day, 70 °C	27	24
2	TMS (2.4)	5 days, 90 °C	35	38
3	TMS (6)	5 days, 90 °C	0	80

[a] TMS = trimethylsilyl. [b] Yields of mono- and diannulated products.

entry 1). The reaction of the same alkene with 2.4 equivalents of the cobalt complex of trimethylsilylethyne gave the mixture in better overall yield, but only after a longer reaction time (Table 7, entry 2). In the presence of 6 equivalents of the latter alkyne complex the reaction proceeded smoothly and gave the diannulated product in high yield as a mixture of isomers (Table 7, entry 3).

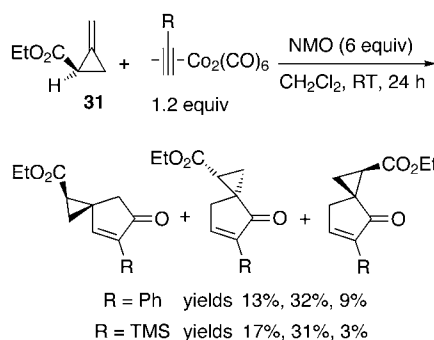
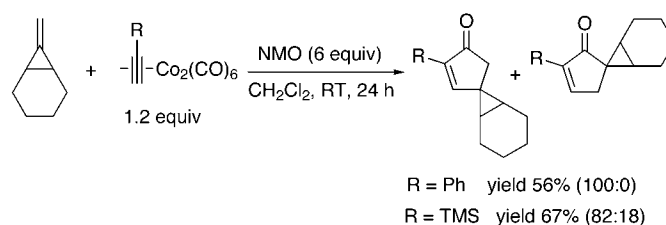
3.3. Exocyclic Alkenes

There are only a few examples of the use of exocyclic alkenes in the intermolecular Pauson–Khand reaction. Smit et al.^[49] described the use of methylenecyclopropane (**29**) in a cobalt-mediated reaction under dry, absorption conditions (SiO₂, Al₂O₃, or zeolites) (Scheme 15). The strain in **29** (C–C(=C)–C angle of 63.9°^[27a]) suggests a low-lying LUMO and predicts good reactivity towards alkyne complexes in the Pauson–Khand reaction. Indeed, its reaction with 2-propyne over Al₂O₃ gave a 5:1 mixture of regioisomers in very good yield after only 2 h at 50 °C (Scheme 15, top). Predictably, the use of methylenecyclobutane (**30**) (C–C(=C)–C angle of 92°^[27b]), resulted in a lower yield (Scheme 15, bottom).



Scheme 15. Intermolecular Pauson–Khand reaction of methylenecyclopropane (**29**) and methylenecyclobutane (**30**) in the presence of solid adsorbents (Smit et al.^[49]).

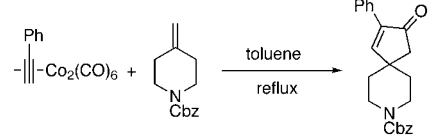
In 1996, Motherwell and co-workers^[50] reported the use of functionalized alkydene cyclopropanes in the NMO-assisted intermolecular Pauson–Khand reaction (Scheme 16). Inter-



Scheme 16. Alkydene cyclopropanes in the NMO-assisted intermolecular Pauson–Khand reaction (Motherwell and co-workers^[50]).

estingly, the presence of an ester group on the cyclopropane ring **31** not only reversed the regioselectivity of the reaction but also gave more-complex mixtures (Scheme 16, bottom).^[51] An independent study of alkydene cyclopropanes by Witulski and Gößmann^[15g] with *N*-alkynyl amides as the alkyne partners gave similar yields and selectivities to those reported by Smit et al.^[49] and Motherwell and co-workers.^[50]

As expected, the use of an exo methylene functionality on a six-membered ring in a thermal intermolecular Pauson–Khand reaction resulted in low yields (Table 8, entry 1).^[52] However, in the presence of a large excess of the alkene (Table 8, entry 2), the desired spirocyclopentenone was produced in good yield.^[53]

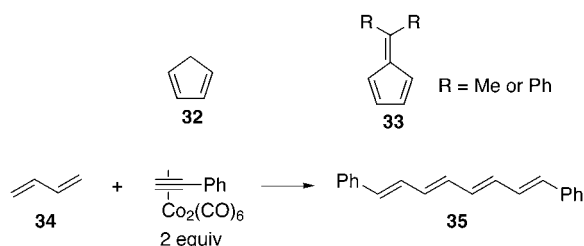
Table 8: Intermolecular Pauson–Khand reaction of methylene piperidines (Ishizaki, Hoshino, and co-workers^[52]).


Entry	Alkene ^[a] [equiv]	t [h]	Yield [%]
1	2	5	30
2	10	3	78

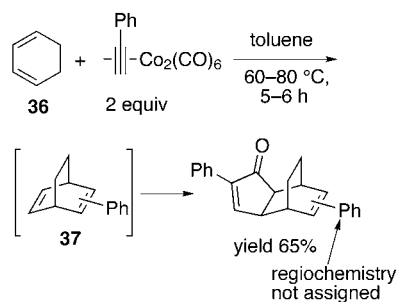
Cbz = benzyloxycarbonyl.

3.4. Conjugated Alkenes

Pauson and Khand examined the reactivity of conjugated alkenes in their early studies on the reaction.^[54] In the case of dienes, they found that although cyclopentadiene (**32**) and fulvenes **33** reacted well,^[54c] cyclohepta-1,3-diene and buta-1,3-diene (**34**) underwent a competing reaction that led to tetraenes such as **35** (hydrogen migration occurs instead of carbon monoxide insertion) (Scheme 17).^[54a] They also

**Scheme 17.** Some conjugated dienes employed in the Pauson–Khand reaction (Pauson and co-workers^[54a,c]).

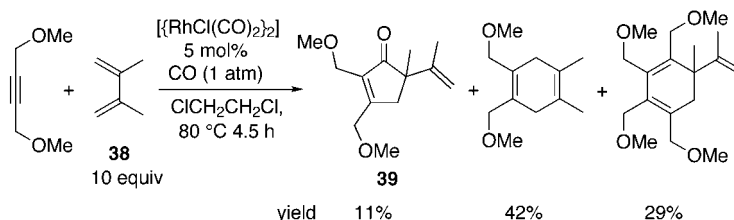
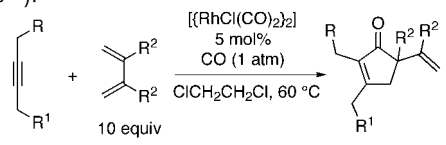
observed^[54b] that treatment of cyclohexa-1,3-diene (**36**; Scheme 18) with 2 equivalents of alkyne complex resulted first in a Diels–Alder reaction and subsequently in a Pauson–Khand reaction with the less-hindered alkene of the cycloadduct **37** (Scheme 18). When cyclohexa-1,4-diene was subjected to the same reaction conditions, a double-bond shift took place to yield **36**, which then entered the cascade sequence.^[54b]

**Scheme 18.** A Diels–Alder/Pauson–Khand cascade reaction (Pauson and co-workers^[54b]).

We believe that it is enlightening to consider these observations in the context of an extension of the hypothesis of Milet, Gimbert, and co-workers. It is known that adding conjugation to a double bond lowers the LUMO of the alkene by at least 0.5 eV.^[55] Thus a conjugated diene has a lower-lying LUMO than a simple alkene, and hence should be more reactive in the Pauson–Khand reaction, if this reaction manifold can be accessed. Interestingly, a comparison of the outcome of similar reactions involving cyclopentadiene^[54c] and cyclopentene^[15a] suggests that the former is indeed more reactive.^[56]

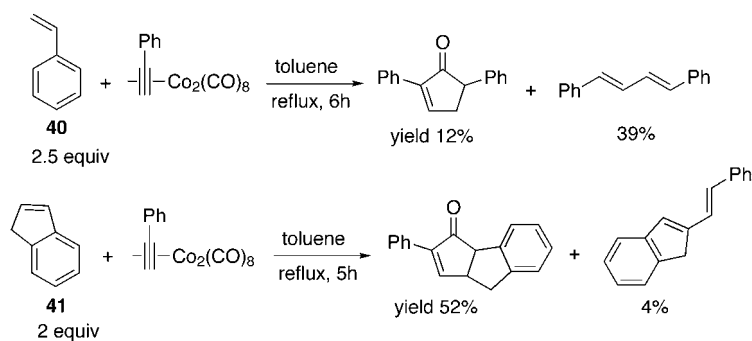
In 2004, Wender and co-workers have started to reveal the full potential of dienes as alkene partners in the intermolecular Pauson–Khand reaction.^[57] Initially they observed that when 10 equivalents of 2,3-disubstituted-1,3-dienes such as **38** react with disubstituted alkynes in the rhodium-catalyzed intermolecular Pauson–Khand reaction at 80 °C, two other competing reactions occur: a [4+2] cycloaddition (as Pauson and co-workers observed for cyclohexadiene),^[54] and a [2+2+2] coupling reaction; the desired Pauson–Khand product **39** was thus generated in low yield (Scheme 19). When the reaction was performed at 60 °C, however, a remarkable increase in selectivity was observed and led to cyclopentenones in excellent yields (Table 9, entries 1–3). Monosubstituted alkynes did not undergo cyclization.

When Pauson and co-workers investigated the reactivity of styrene **40** and its derivatives,^[15a,54c,58] they discovered slightly more encouraging reactivity than with 1,3-dienes such as butadiene. Production of an unwanted coupling product still occurred through a competing pathway, but this time the Pauson–Khand product was observed. Indene (**41**), a strained version of styrene, afforded the Pauson–Khand product in improved yield (Scheme 20).^[15a,54c] The two reactions showed complete regioselectivity with respect to the alkyne and the

**Scheme 19.** Competing [2+2+1], [4+2], and [2+2+2] couplings in the reaction of a diene with a disubstituted alkyne at 80 °C (Wender and co-workers^[57]).**Table 9:** The intermolecular dienylyl Pauson–Khand reaction (Wender and co-workers^[57]).


Entry	R ^[a]	R ¹ [b]	R ²	t	Yield [%]
1	OMe	OMe	Me	6	98
2	OTBS	OTBS	Me	6	87
3	OMe	OBn	Me	9	81

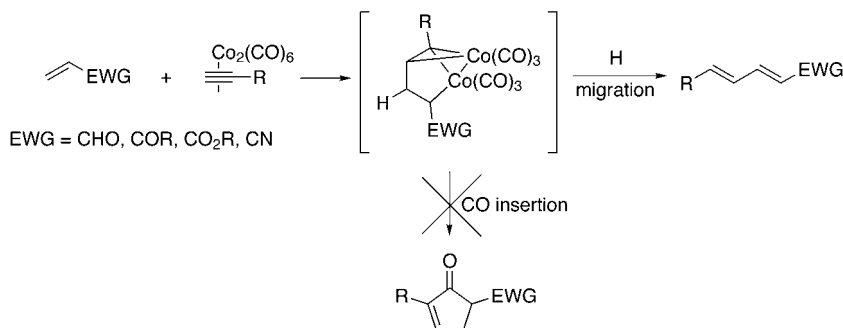
[a] TBS = *tert*-butyldimethylsilyl. [b] Bn = benzyl.



Scheme 20. Intermolecular Pauson–Khand reaction of styrene (**40**) and indene (**41**) (Pauson and Khand^[15a,54c]).

alkene substituents. Although alkyne selectivity was already well-documented, the latter was noteworthy in the early years of the Pauson–Khand reaction. An explanation may be found in the polarization of the LUMO of the double bond by the arene ring which may induce the formation of the first C–C bond at the remote carbon atom of the alkene.

Control of the two observed reactivity modes of conjugated alkenes (hydrogen migration versus CO insertion) could be the key to the successful employment of a range of reactive and synthetically attractive alkene partners. The two reaction pathways can be explained in an example: The LUMO of alkenes that bear electron-withdrawing groups, for example, is very low, typically between -2 and 0 eV,^[55] comparing this to the LUMO of norbornene (0.42 eV), we would expect even higher reactivity in the Pauson–Khand reaction for such alkenes. The extreme polarization of the



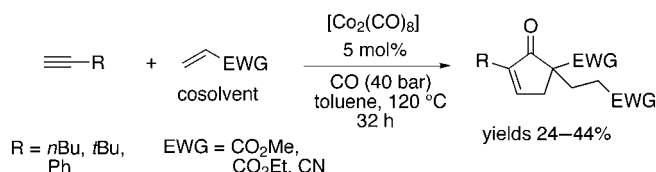
Scheme 21. Hydrogen migration (through β -hydride elimination) prevails over CO insertion in the intermolecular Pauson–Khand reaction of electron-poor alkenes. EWG = electron-withdrawing group.

double bond, however, leads to hydrogen migration and formation of dienes in preference to CO insertion and the formation of cyclopentenones (Scheme 21). In fact, reactions of members of this class of alkenes produced exclusively dienes.^[59]

More recently, however, two reports on the successful employment of electron-poor alkenes have been published. In 1995, Costa and Mor^[60] observed the formation of cyclopentenone products from electron-poor alkenes for the first time. Reaction of terminal alkynes and alkyl acrylates or acrylonitriles (as cosolvents) with catalytic amounts of

$[\text{Co}_2(\text{CO})_8]$ under a high pressure of CO and high temperatures forced the reactants down the CO insertion pathway and led to the isolation of cyclopentenones from a regioselective domino Pauson–Khand/Michael addition (Scheme 22).

In 1999, Cazes and co-workers reported that terminal and internal alkynes react with methyl acrylates and phenyl vinyl sulfones at lower temperatures in the stoichiometric NMO-promoted Pauson–Khand reaction.^[61] They successfully exploited the anticipated high reactivity of electron-poor alkenes and suppressed the β -hydride elimination pathway by using low temperatures. In the presence of only 2 equivalents of the



Scheme 22. The domino intermolecular Pauson–Khand/Michael addition reaction of electron-poor alkenes (Costa and Mor)^[60]

alkene under mild reaction conditions (facilitated by the use of an amine oxide) only cyclopentenones were isolated (Table 10). In contrast to the results of Costa and Mor,^[60] internal alkynes (Table 10, entries 1–2) result in better yields than terminal alkynes (Table 10, entries 3–4). The regioselectivity described in Scheme 22 and Table 10 is consistent with polarization of the LUMO of the alkene as mentioned above for styrene.

4. Reactive Alkene Partners: Miscellaneous

4.1. Allenes

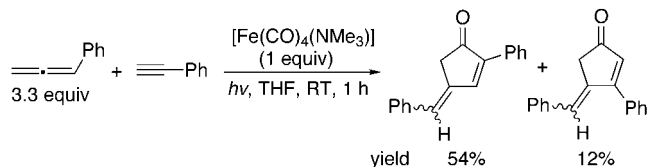
Recent advances in the application of allenes in metal-mediated or -catalyzed reactions^[62] include their use as alkene partners in the intermolecular Pauson–Khand reaction. The unusual structural and electronic characteristics of allenes^[63]

Table 10: The intermolecular Pauson–Khand reaction of electron-poor alkenes (Cazes and co-workers^[61]).

Entry	R	R ¹	EWG	Yield [%]
1	CH ₃	CH ₃	CO ₂ Me	59
2	CH ₃	CH ₃	SO ₂ Ph	71
3	C ₃ H ₇	H	CO ₂ Me	47
4	Ph	H	CO ₂ Me	41

together with the limited number of literature examples available at present have rendered it difficult to classify accurately their reactivity.

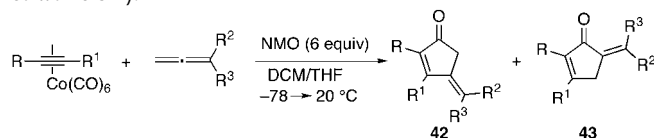
The first example of the use of an allene in the Pauson–Khand reaction was reported by Pauson in his review of 1985.^[2a] He reported the smooth reactivity of cyclonona-1,2-diene with alkyne metal complexes. Apart from a report from Narasaka and co-workers,^[64] in which they showed that $[\text{Fe}(\text{CO})_4(\text{NMe}_3)]$ and irradiation promote the reaction between alkynes and allenes (Scheme 23), the major contri-



Scheme 23. Allene–alkyne intermolecular Pauson–Khand reaction in the presence of $[\text{Fe}(\text{CO})_4(\text{NMe}_3)]$ under irradiation (Narasaka and co-workers^[64]).

bution to this area has originated from the Cazes group. Over the past decade they have described^[65] the reactivity and regioselectivity of allenes in the NMO-promoted intermolecular Pauson–Khand reaction. They showed that the reactions depend on the substitution pattern of both acetylenic and allenic partners. The presence of an electron-donating group on the allene favors the formation of cyclopentenones **42** (Table 11, entry 1),^[65b] whereas an electron-withdrawing

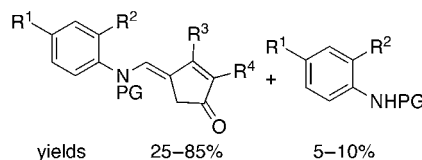
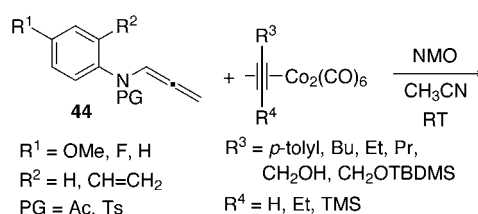
Table 11: The intermolecular allenyl Pauson–Khand reaction (Cazes and co-workers^[65]).



Entry	R	R ¹	R ²	R ³	Yield [%]	
					42	43
1	CH ₃	CH ₃	<i>O</i> tBu	H	30	
2	C ₃ H ₇	C ₃ H ₇	CO ₂ Me	H	33	14

group gives a mixture of cyclopentenones **42** and **43** (Table 11, entry 2).^[65b] The reactivity of allenic hydrocarbons^[65c] and their reactivity with silylated alkynes^[65d] were also the subjects of extensive studies.

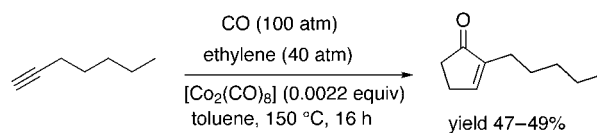
Pérez-Castells and co-workers recently observed high regio- and stereoselectivity in the reactions of allene amides **44** with alkynes in the NMO-promoted version of the reaction (Scheme 24).^[66] Allenes have also been used by Witulski and Gößmann,^[15g] who treated 2-methylbuta-2,3-diene with an alkynyl amide in an aminoxide-promoted intermolecular Pauson–Khand reaction, and Hailes and co-workers who used undeca-5,6-diene in a key intermolecular Pauson–Khand reaction in the synthesis of novel compounds with olfactory properties.^[67]



Scheme 24. Alleneamides in the intermolecular NMO-promoted Pauson–Khand reaction (Pérez-Castells and co-workers^[66]). PG = protecting group; Ts = *p*-toluenesulfonyl.

4.2. Ethene

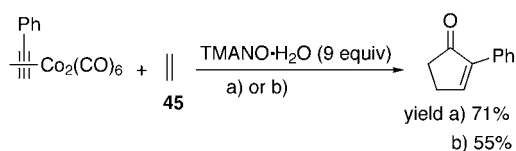
Ethene is one of the most attractive alkene partners in the Pauson–Khand reaction because of the synthetic potential of its products and it has been used since the discovery of the reaction.^[2a, 15a, d, 30c, e, 32c, 40r, 54a, 68] However, its employment has been limited by the need for harsh reaction conditions, that is, elevated temperature and pressure. Use of the latest advances in the area such as catalysis,^[68c] amine oxide promoters,^[68d–f] and supercritical fluids^[68g] does not remove the need to use high pressures to attain reasonable yields (Scheme 25).



Scheme 25. A catalytic Pauson–Khand reaction under high pressures of carbon monoxide and ethene (Rautenstrauch et al.^[68c]).

It was thus a significant development when Kerr and co-workers reported the first use of ethene at atmospheric pressure.^[68d–f] They subsequently enhanced the practicality of the reaction even further through the discovery of an extremely convenient ethene equivalent for the intermolecular Pauson–Khand reaction.^[69] During the synthesis of (+)-taylorione, Kerr and co-workers^[68d–f] used TMANO·H₂O as a promoter for the annulation of alkyne metal complexes with ethene. Satisfactory yields were possible not only at a relatively low ethene pressure (25–35 atm) but also at atmospheric pressure (bubbling ethene) and room temperature (Scheme 26).

Later, Kerr discovered that vinyl esters behave as ethene equivalents when employed in the NMO·H₂O-promoted stoichiometric intermolecular Pauson–Khand reaction (Table 12).^[69] Interestingly, the poor reactivity of ethyl vinyl ethers had already been reported.^[34, 70] The change in reactivity between the ethers and the esters can be understood in terms of the molecular-orbital theory introduced in



Scheme 26. TMANO-promoted Pauson–Khand reaction of ethene: a) 25–35 atm, 40 °C; b) 1 atm (bubbled), room temperature; (Kerr and co-workers^[68d–f]).

Table 12: Ethene equivalents **46** in the intermolecular Pauson–Khand reaction (Kerr and co-workers^[69]).

Entry	R ^[a]	R ¹	R ² [b]	t [h]	Yield [%]
1	Ph	H	OAc	1	53
2	Ph	H	OBz	16	80
3	THPOCH ₂	H	OBz	16	87
4	CH ₃	CH ₃	OBz	16	5

[a] THP = tetrahydropyranyl. [b] Bz = benzoyl.

the previous section. Electron-donating groups raise the energy of the LUMO of the alkenes, thus lowering their reactivity. By converting an electron-rich vinyl ether into an electron-poor vinyl ester **46**, Kerr and co-workers not only improved the reactivity of the alkene, but also obtained the ultimate Pauson–Khand product, the deesterified cyclopentenone **47** (Table 12).^[71] With this new protocol, the yields of the cyclopentenones were comparable and sometimes better than when using autoclave conditions^[68d–f] (Table 12, entries 1–3). Loss of the substituent derived from the alkene may occur by the reduction of the ketone to the corresponding ketyl by low-valent cobalt species. Elimination of the ester, further reduction to the enolate, and subsequent quenching with water (contained in NMO·H₂O) would deliver the deesterified cyclopentenone **47**.^[69b] Vinyl esters **46** showed very little reactivity towards internal alkynes, as does gaseous ethene^[68] (Table 12, entry 4).

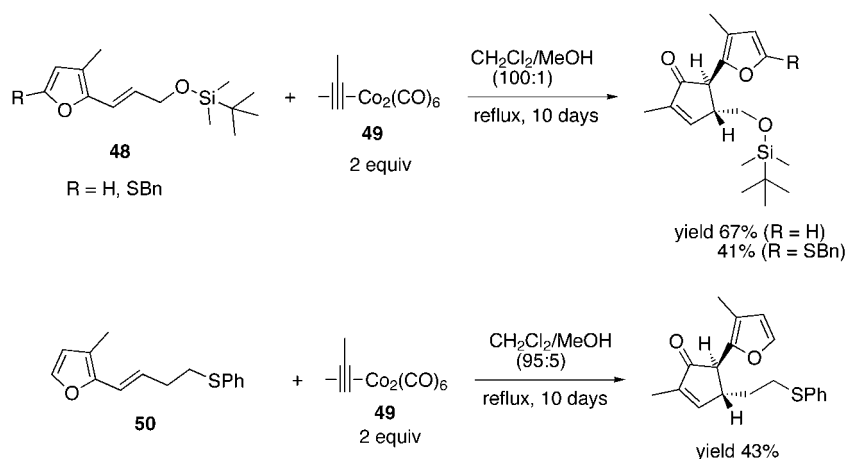
4.3. Low LUMO Energy or Coordination?

In the course of work towards the total synthesis of phorbol, Harwood and Tejera discovered that 2-furyl-substituted alkenes **48** and **50** (Scheme 27) reacted with the hexacarbonyldicobalt(0) complex of propyne **49** in good yield and regioselectivity.^[72] In contrast, Pauson and co-workers showed that 2-vinylfuran reacted with phenylethyne only to produce an unwanted diene.^[58a] As discussed in the previous section, this behavior is characteristic of some conjugated alkenes. In this case Harwood and Tejera showed that not only did the substituted vinyl furans **48** and **50** undergo the

Pauson–Khand reaction, but also that in the case of thioether **50** the Krafft bidentate homoallylic “mode of cycloaddition” (Section 2.1, Scheme 5) was overwhelmed by the polarization of the alkene by the furyl group, thus yielding the furyl cyclopentenone as a single regioisomer.^[72]

5. Summary and Outlook

We have shown how the reactivity of the alkene partners in the Pauson–Khand reaction is influenced by two major factors: the presence of other coordination sites on the alkene (Section 2) and the energy of the LUMO of the alkene (Section 3). In Section 2 it was seen that a second (and even a third) coordination site on the alkene can overcome the problems of reactivity and selectivity normally associated with the intermolecular Pauson–Khand reaction. This conclusion from a landmark study by Krafft and co-workers^[14,16,19] has been underestimated for too many years, as illustrated by two recent literature reports that successfully build on this concept, and in doing so, significantly broaden the scope of the reaction.^[20,21]

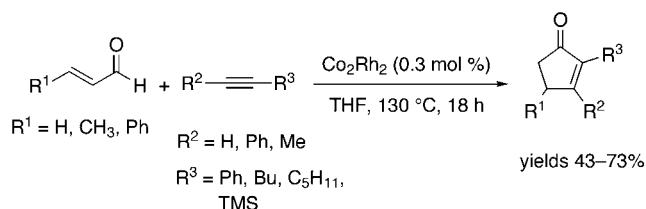


Scheme 27. The overpowering effect of the 2-furyl group in the intermolecular stoichiometric Pauson–Khand reaction (Harwood and Tejera).^[72]

The second important concept is the use of the LUMO energy of the alkene to predict its relative reactivity in the Pauson–Khand reaction.^[9] Our survey of intermolecular reactions in which the alkene reactivity could be rationalized with this theory has underlined the usefulness of the concept. Perhaps, more importantly, it should encourage the design and testing of many innovative Pauson–Khand substrates in the near future. As use of the intermolecular Pauson–Khand reaction in synthesis increases, it is anticipated that more examples will emerge in which electronic and coordination effects compete to determine alkene regioselectivity.

Although the journey to the perfect intermolecular Pauson–Khand reaction—efficient, versatile, environmentally friendly, asymmetric, and catalytic—is still far from over, an important step forward was very recently reported by Chung and co-workers.^[73] They described a catalytic, inter-

molecular, heterogeneous (Co_2Rh_2 bimetallic nanoparticles) reaction in which an unsaturated aldehyde functions as both the alkene partner and the source of CO. It is well-documented that the reaction of aldehydes on metal surfaces releases hydrocarbons and carbon monoxide.^[74,75] Chung and co-workers used this principle in the reaction of α,β -unsaturated aldehydes with terminal and internal alkynes in the presence of catalytic amounts of the nanoparticles to give cyclopentenones in moderate to good yields (Scheme 28).



Scheme 28. The catalytic intermolecular Pauson–Khand reaction with an unsaturated aldehyde as alkene and CO source (Chung and co-workers).^[73]

From a personal perspective, we hope that the report of Chung and co-workers^[73] together with the insight provided herein into the reactivity problems that have, to date, been associated with the intermolecular Pauson–Khand reaction will inspire efforts to widen the scope of this potentially very powerful coupling reaction.

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