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Very Important Publication

The Intermolecular Pauson-Khand Reaction: Applications, Challenges, and Opportunities

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Abstract: The rapid assembly of complex organic molecules from simple and structurally diverse building blocks is a prevalent challenge in organic synthesis. The Pauson-Khand reaction (PKR) is a method of choice for the construction of five membered rings that has historically been popularized as a late-stage intramolecular cyclization method. The intermolecular version of the PKR, on the other hand, constitutes a powerful approach for the rapid assembly of densely functionalized cyclopentanic cores at early stages of a synthetic sequence. Despite its potential, the intermolecular PKR is much less prevalent in the organic synthesis literature due to several historical limitations, most importantly a reduced scope with respect to the alkene component of the reaction. The last decade has witnessed important developments in the area including a) experimental and theoretical studies that provide a good mechanistic understanding of the reaction and its selectivity, b) methodological developments that have broadened the scope of potential alkene partners, and c) the development of catalytic enantioselective versions that provide useful levels of enantioselectivity. In parallel, remarkable synthetic applications of the intermolecular PKR have emerged, including (enantioselective) total syntheses of complex natural products (polycyclic terpenes, alkaloids, prostanes) as well as examples of industrial relevance. A fundamental limitation of the PKR that needs to be addressed in the future is the current lack of a ligand-accelerated version of the reaction, which would be a promising advance towards developing more efficient and general catalytic (enantioselective) reactions.

Keywords: Cycloaddition; Carbonylation; Transition metals; Homogeneous catalysis; Total synthesis

1. Introduction

The Pauson-Khand reaction (PKR) is a formal [2+2+1] cycloaddition reaction between an alkyne, an alkene and carbon monoxide to yield a cyclopentenone, first reported by Ihsan U. Khand and Peter L. Pauson in 1973.[1] The PKR is often introduced in advanced organometallic and organic synthesis courses as a paradigmatic example of transition metal mediated carbonylation reaction allowing the efficient assembly of five-membered rings. The PKR can be catalyzed or mediated by a host of transition metals, although cobalt and rhodium are the most popular choices by far in synthetic applications. Both Rh(I) and Co(0) catalysts and/or mediators are extensively used in *intramolecular* PKRs of enyne precursors to yield fused polycyclic systems. This method is used as an *advanced* or *late stage* cyclization strategy in the synthesis of complex natural products, most notably polycyclic terpenoids bearing fused five membered rings (Scheme 1a).[2] The

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intramolecular PKR is typically quite robust and very often provides good yields and diastereoselectivities, constituting a reliable approach for the cyclization of an elaborate advanced acyclic precursor at a *late stage* in a synthetic sequence. On the other hand, the *intermolecular* variation is almost exclusively mediated or catalyzed by dinuclear Co(0) clusters.[3] This variation is much less prevalent in total synthesis applications, arguably because of the limited scope with regards to the alkene partner when compared with intramolecular variations. Nevertheless, the *intermolecular* PKR has an untapped potential for the rapid build-up of molecular complexity from simple building blocks, forming three new C–C bonds and forging up to two new stereocenters in a single operation. If reactivity and selectivity issues are circumvented, the intermolecular PKR appears as an ideal method to assemble densely functionalized five membered rings at *early stages* of a synthetic sequence (Scheme 1a). This review focuses on the intermolecular PKR in its more common Co-mediated or catalyzed version. We seek to demonstrate its hidden potential, foster further methodological research, and promote its use among the synthetic organic chemistry community. The review is structured in the following sections:

Mechanistic and practical aspects of the PKR. Previous reviews focus mostly on synthetic aspects of the PKR with assorted transition metals, making it difficult for the practitioner to construct a useful mechanistic foundation. We present a unified experimental and theoretical vision of the Co-catalyzed reaction that will help understand the challenges for the development of enhanced PKRs. The main practical aspects to be considered for a newcomer in the field are intertwined with the mechanistic discussions, given the tight relation between both aspects.

Scope and selectivity. Understanding the limitations in scope, especially with respect to the alkene, is crucial in the development of improved versions of the PKR, and will be discussed in relation to the mechanistic foundations.

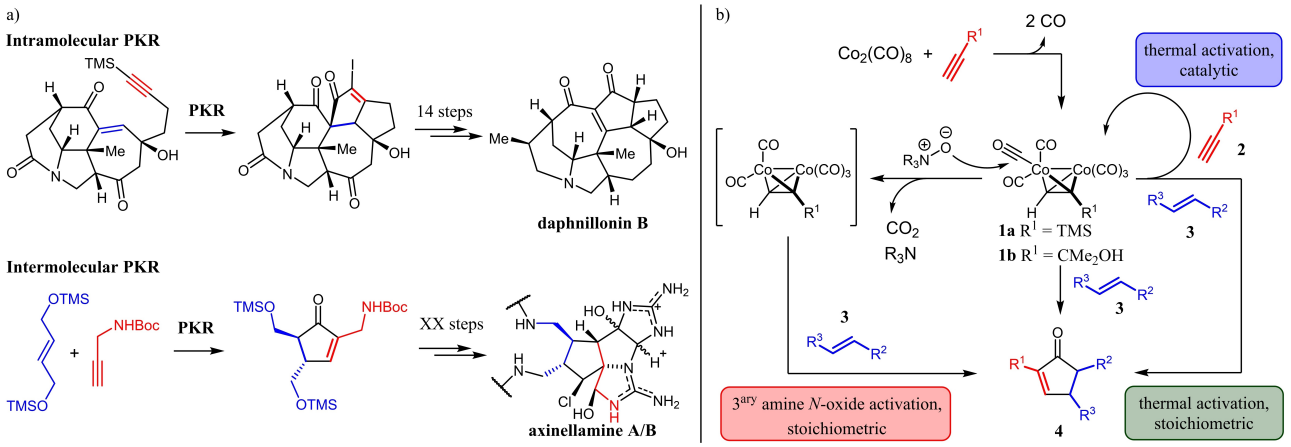
Enantioselective PKRs. The development of enantioselective versions is a key point for the valorization of the PKR as a synthetically valuable multicomponent reaction. The advent of catalytic enantioselective versions is a promising advance in this direction.

Synthetic applications. A selection of syntheses of natural products and other relevant compounds is presented, showcasing the utility and potential of the PKR.

Limitations and future challenges. We make the case that ancillary ligands so far tested in the PKR catalyzed by dicobalt-alkyne complexes are detrimental for the reaction kinetics. We analyze the viability of ligand designs with potential for accelerating the reaction, a feature that would likely expand the alkene scope and facilitate development of more general enantioselective versions.

2. Mechanistic and Practical Aspects of theIntermolecular PKR

The PKR mediated or catalyzed by dinuclear Co(0) species – the actual seminal discovery by Khand and Pauson – has been studied in detail from a mechanistic point of view. The mechanism first postulated by Magnus in the context of studies in the synthesis of coriolin[4] was later on validated by theoretical studies from Nakamura and Pericàs (pathway **A**, Figure 1).[5] Although other Co(0) clusters can be used as precursors or pre-catalysts, the more common approach is to start with dicobalt(0) octacarbonyl, which reacts



Scheme 1. a) Intra- vs intermolecular applications of the Pauson-Khand reaction (PKR). b) Typical experimental protocols for the Co-mediated intermolecular PKR.

with the alkyne releasing two CO molecules in a typically fast reaction at room temperature. The resulting dicobalt alkyne complex **1** features a distorted tetrahedral geometry with the two cobalt atoms and the two alkyne carbons at the vertices (Scheme 1b). The alkyne dicobalt complex is relatively robust in most cases and can be isolated by flash column chromatography on silica gel or alumina. When the PKR is run stoichiometrically, the usual approach is to react the alkyne with an excess of $Co_2(CO)_8$ (or vice versa if the alkyne is not a precious compound and its excess can be easily removed), isolate the complex, and then subject it to PKR conditions. If the alkyne complex is not stable it can be formed in situ, either under stoichiometric or catalytic conditions. For catalytic PKRs it is more convenient to use the dicobalt alkyne complex as a catalyst (**1 c**/**A1** in Figure 1), since it is usually a more robust species than the rather unstable $Co_2(CO)_8$. This approach is definitely advantageous if accurate measuring of the catalytic loading is required. If the alkyne component of a desired PKR does not provide stable dicobalt alkyne complexes (this happens usually with alkynes bearing electron withdrawing substituents), a good practice is using known stable complexes such as **1 a** and **1 b** as pre-catalysts, with the only caveat that a small amount of an undesired cyclopentenone (**4 a–b)** will be formed in the first turnover (Scheme 1b). Complexes **1 a–b** can be stored in the fridge under nitrogen without apparent decomposition for months and are convenient equivalents of $Co_2(CO)_8$ in PKRs, in particular complex **1 b** derived from inexpensive 2-methyl-3-butyn-2-ol (**2 b**).[6] The next step of the reaction mechanism is the barrierless release of a CO ligand from **A1** to provide the unsaturated complex **A2**, to which the alkene coordinates leading to intermediate **A3** (Figure 1). The isolation and characterization of this intermediate has been a long-sought goal, since it would provide valuable mechanistic insight for the design of improved PKR manifolds. Gimbert and co-workers have detected such species by high resolution mass spectrometry under electrospray ionization (ESI-HRMS).[7] The use of alkenes with covalent or coordination tethers has been exploited as a strategy to obtain and isolate arrested η^2-alkene complexes akin to **A3**.[8] Unfortunately, none of these were productive towards the PKR reaction, providing limited insight. Recently, Uyeda and co-workers have isolated a catalytically active η^2-alkene complex using a formally Ni(I) dinuclear complex supported by a redox non-innocent ligand, setting an interesting precedent for further methodological improvements in the Co-mediated version.[9] Following alkene coordination, 1,2 insertion into one of the alkyne-Co bonds takes place from the same face where coordination occurred, and the regiochemistry and stereochemistry of the final product are defined in this key step. The term insertion has been extensively used in the specialized literature for this elementary step, although it is perhaps better understood as an oxidative coupling reaction akin to that postulated for the first C–C bond forming event in [2+2+2] cycloadditions.[10] The insertion step leads to an unsaturated dicobalt complex **A4** that incorporates a new CO ligand to provide **A5**. Next, one of the proximal CO ligands undergoes insertion into the cobaltacycle to obtain acyl-Co complex **A6**, and a new CO ligand enters the coordination sphere providing **A7**. Finally, a reductive elimination takes place, providing the dicobalt coordinated cyclopentenone **A8**, which furnishes the product upon turnover. Under stoichiometric conditions, it is a good practice to stir the reaction under air or in the presence of a mild oxidant to promote decomposition of the resulting low valent cobalt by-products, facilitating purification. From the theoretical point of view, the calculations of Pericàs identified the first decarbonylation step leading

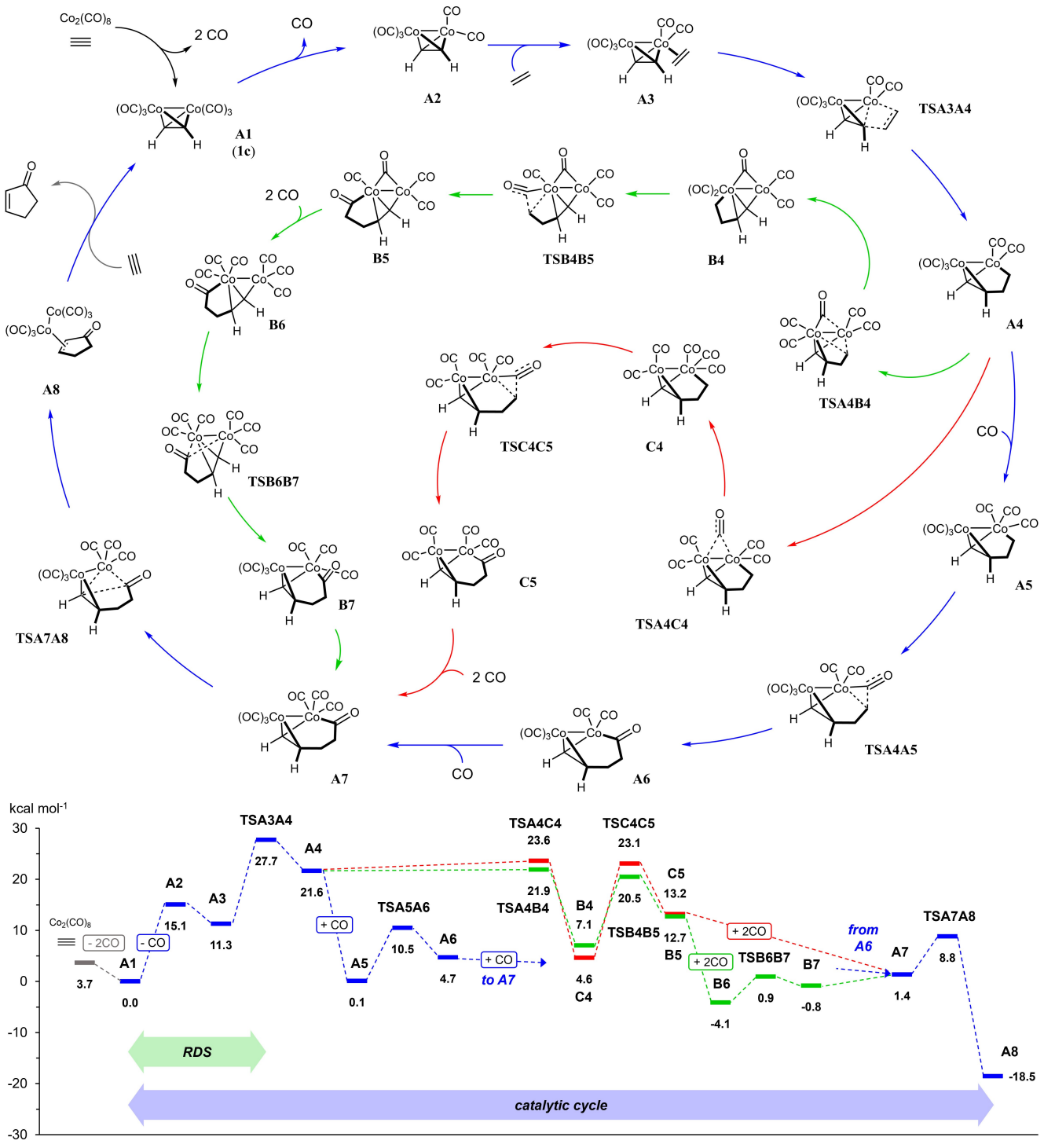


Figure 1. Integrated mechanistic cycle and associated free Gibbs energy profile of the catalytic PKR between acetylene and ethylene, catalyzed by **1c** (**A1**) in toluene. Pathway **A** (blue) depicts the original Magnus-Nakamura mechanism. Pathway **B** (green) involves additional cobalt to cobalt alkyl and CO migration steps. Pathway **C** (red) involves only additional cobalt to cobalt CO migration steps.

to **A2** as rate determining,[5a] but the seminal study from Nakamura reveals the transit from **A1** to **A4** (i. e. decarbonylation, alkene coordination and insertion) as the *rate determining span* (RDS)[11] of the PKR.[5b] For the purpose of the present review, we have reevaluated the Magnus-Nakamura mechanism for the PKR between acetylene and ethylene at the M06/cc-pvdz/cc-pvtz/GD3DJ level including implicit solvent effects of

a toluene solution (Figure 1).[12] The resulting reaction profile is qualitatively similar to the one in the Nakamura study and confirms the transit **A1**→**A4** as the RDS, albeit with a more feasible overall barrier and higher energy difference between **A2** and **TSA3A4**. Importantly, this finding is commensurate with the kinetic studies reported by Riera and Verdaguer, which found a negative experimental order rate of the reaction with respect to the CO concentration.[13] This study confirmed quantitatively an empirical observation that is common knowledge of the PKR aficionado: there is a sweet spot of CO pressure in catalytic PKRs; high CO pressures result in a dramatic slowdown of the reaction rate, while under low pressures the catalytic system is unstable and the reaction stops. This is a common feature of other carbonylation reactions mediated by metal carbonyl species, such as the Co(I) catalyzed hydroformylation of alkenes.[14] From the insertion intermediate **A4**, saturation of the cobalt coordination sphere with an additional CO ligand (**A4**→**A5**) is followed by CO insertion into the alkyl-Co bond (**A5**→**A6**), coordination of another CO ligand (**A6**→**A7**), and reductive elimination to release the product (**A7**→**A8**).

In 2014, Gimbert and co-workers challenged the last steps of the Magnus-Nakamura mechanism based on ESI-HRMS experimental evidence.[7a] These experiments (in the gas phase) suggested that the carbonyl group undergoing insertion into the cobalt-alkyl bond originates exclusively from the initial coordination sphere of **A1**, and not from extraneous CO that enters the catalytic cycle in the **A4**→**A5** carbonylation step. Two alternative pathways (**B** and **C**, Figure 1) were proposed that circumvent this early carbonylation event, involving additional alkyl and/or CO migration steps between cobalt centers. The complete reconstruction of both pathways converging at intermediate **A7** is also presented herein, depicting a more than plausible alternative mechanistic scenario. Still, under high CO concentration conditions (i.e. catalytic PKR conditions), the diffusion controlled carbonylation step leading to **A5** could occur at a reasonable rate, which may explain in part the complex kinetics observed in catalytic PKRs.[10] Notwithstanding, pathways **B** and **C** involve a series of events *following* the RDS, and are therefore of lesser importance vis a vis to developing more active catalytic systems. Finally, an alternative theoretically plausible mechanism has been reported that proceeds throughout the RDS without decarbonylation, but this proposal is hard to reconcile with the universally observed inhibition of the PKR by CO pressure/concentration.[15]

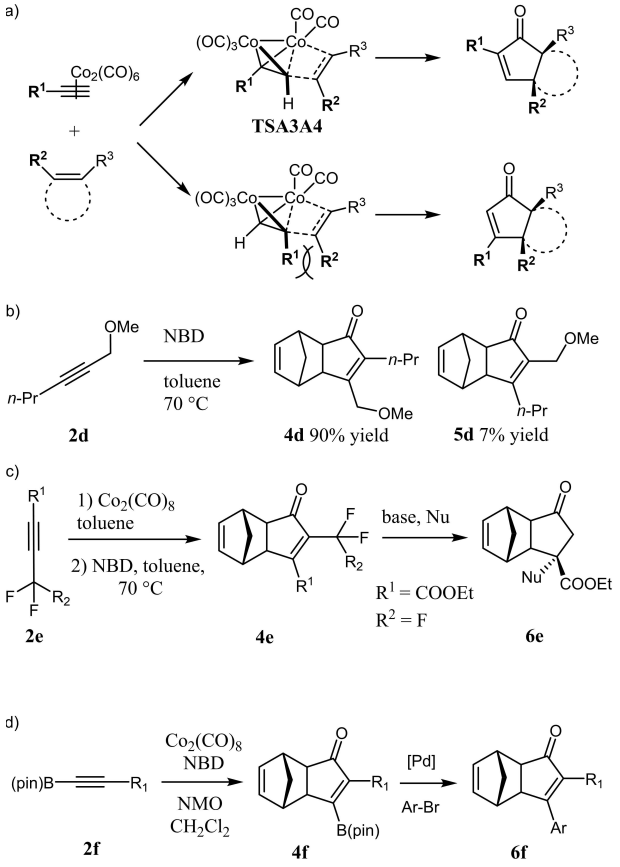
Given the previous considerations, it is now a good point to consider the three basic operation modes in which an intermolecular PKR can be run. Albeit a considerable number of diverse reaction conditions and promoters have been reported, three main scenarios exist that are significantly different from a mechanistic perspective: a) the thermally activated stoichiometric PKR, b) the tertiary amine *N*-oxide (or equivalent reagents) promoted stoichiometric PKR, and c) the thermally activated catalytic PKR (Scheme 1b). In a purely thermally activated PKR the reaction mixture has to be heated at temperatures sufficient to overcome the barrier of the RDS up to **A4**. While some alkenes (see Section 3) react at a significant rate at room temperature, heating is commonly required and reaction temperatures in the range 50–100 °C are more usual. Common solvents for this approach are toluene or 1,2-dimethoxyethane. When less reactive alkenes are used, the thermal activation is impractical, leading often to decomposition. The use of a tertiary amine *N*-oxide as a reagent, an approach first reported by Schreiber and co-workers,[16] allows the PKR to be run at low temperatures (−20 °C to room temperature typically). The *N*-oxide promotes the irreversible decarbonylation of the starting alkyne complex, releasing CO_2 and bypassing the reversible CO dissociation step that constitutes a significant fraction of the RDS (Figure 1). This protocol is the method of choice when the alkene is unreactive and/or the substrate has thermally unstable structure and functionalities. Trimethylamine *N*-oxide (TMANO)[17] and *N*-methylmorpholine *N*-oxide (NMO)[18] are the most common reagents for this approach. A significant improvement of the *N*-oxide protocol was first introduced by Baran[19] and later on developed by Verdaguer and Riera, consisting in the use of ethylene glycol and molecular sieves as additives.[20] A significant increase in the yields is observed under these conditions, particularly for the less reactive alkenes, thus broadening the scope of the PKR. The mechanistic origin of this improvement remains unclear. Nitrous oxide has also been used as a promoter of the PKR operating under the same principle as the *N*-oxide additives.[21] Finally, the PKR can be run under catalytic conditions by using a CO atmosphere. Although the use of CO may be perceived as inconvenient, especially in R + D environments, the PKR has the advantage to operate typically under low CO pressures, obviating the need of highly specialized equipment. In addition to the obvious benefits of catalysis from a sustainable chemistry perspective, the use of the cobalt complex in catalytic amounts is definitely advantageous for purification purposes since cobalt by-products are often difficult to remove chromatographically. The substitution of CO by ancillary ligands in the coordination sphere of the dicobalt complex or the use of mildly coordinating solvents or additives is advantageous from the synthetic point of view, providing enhanced yields and in some cases better stereoselectivity. However, the kinetic study by Riera and Verdaguer convincingly demonstrated that such additives and ligands actually *slow down* the reaction, and

probably provide only the beneficial effect of stabilizing the catalytic system. This effect is discussed further in the context of potential improvements in Section 6.

3. Scope and Selectivity

3.1. Alkyne

Most alkynes will readily form complexes by reaction with dicobalt carbonyl or analogous complexes, hence the scope of the intermolecular PKR is wide in this regard. Alkynes bearing a range of both electron withdrawing and electron donating substituents can be used, albeit in some cases finding optimal conditions may not be trivial. Terminal alkynes are by far the more synthetically useful, since steric effects are predominant in these substrates and furnish selectively the α-substituted cyclopentenone (Scheme 2a). The



Scheme 2. Regioselectivity of the PKR with respect to the alkyne. a) Steric interactions in **TSA3A4** dictate the preference for the α-regioisomer with terminal alkynes. b) Regioselectivity observed by Riera and Helaja, for electron-withdrawing substituents with *−I* effect. c) Selectivity with fluorinated internal alkyne derivatives and further elaboration described by Verdaguer and Riera. d) PKR of alkynylboronic esters and subsequent elaboration by Suzuki-Miyaura reaction. NBD: 2,5-norbornadiene. NMO: *N*-methyl-morpholine *N*-oxide.

prevailing hypothesis is that this selectivity is driven by steric interactions in the insertion step (**A3**→**A4**, Figure 1). The use of non-symmetrical internal alkynes is less synthetically useful because mixtures of regioisomers are obtained in most cases and the prediction of the selectivity is not straightforward. Nevertheless, some general trends can be observed. When the substituents are of similar electronic nature, the steric effect prevails and the major product is the one with the bulkier group in the α position. In strongly polarized alkynes, an electronic effect will dominate and the major cyclopentenone will feature the electron donating substituent at the α position (Scheme 2b). Although this outcome was rationalized on the basis of a *"trans* effect" by Gimbert and Greene, the current mechanistic understanding of the PKR does not support their postulates.[22] The hypothesis was that, in a polarized alkyne, the accumulation of electron density in one of the *sp* carbons ($C^{\delta-}$) translates, via π backdonation, to stronger Co-CO bonding. The extent of backdonation to the different CO ligands in the dicobalt cluster would not be the same, being the Co-CO bond *trans* to the $C^{\delta-}$ carbon the more reinforced. This would make the pseudo-equatorial carbonyl in relative *cis* orientation the most labile, and alkene insertion would take place from this same position yielding the cyclopentenone with the electron-donating substituent in the α position. However, this notion ignores the fact that there is no evidence supporting an associative mechanism for CO-alkene exchange. Alkene coordination takes place on intermediate **A2** *after* the CO dissociation step (Figure 1), and therefore the origin of the selectivity cannot be related to the relative lability of the CO ligands in **A1**. Regardless of the molecular basis for this effect, a good empirical correlation can be established between the degree of alkyne polarization and the regioselectivity observed. This effect was studied experimentally and with DFT calculations by the groups of Riera and Helaja (Scheme 2b).[23] Analyzing the regioselectivity of electronically different but sterically similar non-symmetric alkynes, the authors showed that electronic effects significantly affect the regioselectivity of the PKR. In addition, for diarylalkynes with the same steric demand at both sides, a quantitative correlation exists between C_{sp} charges obtained from natural bond orbital (NBO) analysis and the experimental regioisomer ratio, providing a good rational design tool for this particular set of substrates.[23b] Anyhow, the selectivity towards the alkyne is a delicate balance between steric and electronic effects. For example, the group of Verdaguer and Riera described that alkynes bearing fluoroalkyl substituents form PKR adducts leaving the fluorinated group in the α position.[24] The authors suggested that the electronic effect of the fluorine atoms is weaker than expected or somehow outweighed by steric effects (Scheme 2c). Importantly, for the PKR adduct of ethyl

4,4,4-trifluorobutynoate (R^1 = COOEt, R^2 = F) the conjugate addition of a nucleophile (cyanide or nitroalkanes) proceeds stereospecifically with concomitant loss of the trifluoromethyl group, providing a practical entry to cyclopentanones with β quaternary centers. Importantly, when using alkynylboronic esters with non-terminal alkyne moieties, the electronic effects predominate, placing the boryl group exclusively at the β position.[25] The resulting adducts can be further elaborated through Suzuki-Miyaura cross-couplings, allowing the preparation of a range of α,β-disubstituted cyclopentenones with precise control over the regioselectivity of the overall process (Scheme 2d).

3.2. Alkene

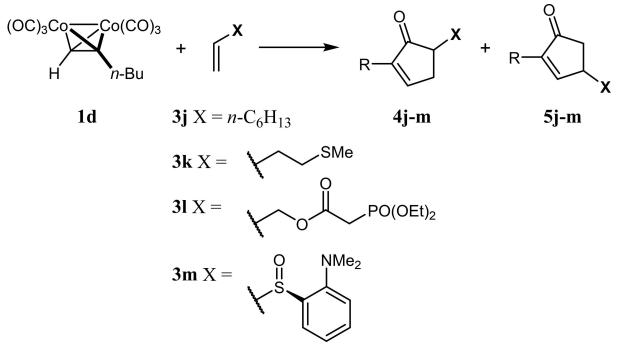
The main limitation of the intermolecular PKR in relation to the intramolecular variation is the limited range of alkenes that can be used. In general, two main classes of alkene partners can be delineated: a) alkenes with attached coordinating groups, which operate under *pseudo*-intramolecular conditions through a chelated alkene-cobalt intermediate, and b) alkenes containing a significant degree of ring strain as illustrated by the norbornene derivatives featured in the seminal work of Khand and Pauson.[1b]

Although numerous examples of alkenes with coordinating ancillary groups have been described,[26] the state-of-the-art is defined by the (2-dimethylaminophenyl)-sulfoxide group developed by Carretero (Table 1), which furnishes good yield with a range of different alkyne components.[26c,d]

With respect to strained alkenes, derivatives delivering good yields consistently in a range of conditions typically have double bonds embedded in small cycles or polycyclic systems (Scheme 3).[27] Within this family, norbornadiene derivatives stand out as synthetic equivalents for ethylene via a PKR/retro-Diels-Alder sequence (see Section 5). Alkene **3c** in particular allows the more challenging retro-Diels-Alder step to be carried out under milder conditions.[28] Similarly, the tricyclic alkene **3d** developed by Gibson and coworkers serves as a cyclobutadiene equivalent for the PKR.[27a] Another family of reactive alkene partners comprises strained *trans*-alkenes embedded in medium-sized rings as reported by Riera and Lledó (**3g–i**).[29] This approach is complementary to the use of small cyclic alkenes in the sense that it provides access to *trans*-fused rather than *cis*-fused polycyclic cyclopentenones. Competitive reaction studies demonstrated that *trans*-cyclooctene has the same reactivity than norbornene in a PKR.

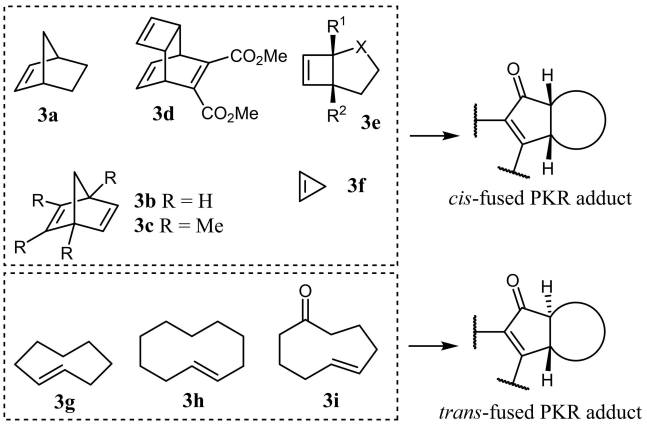
Finally, ethylene has also been successfully used in a number of applications (see Section 5). While being less reactive than strained alkenes, it is definitely more reactive than the average non-functional alkene. Most importantly though, ethylene can be used in large excess/pressure and easily removed from the reaction medium, providing a synthetic competitive advantage. Alkenes not belonging to the main typologies previously described display sluggish reactivity in the PKR. However, the combined use of *N*-oxide activators and ethyleneglycol previously discussed provides synthetically useful yields even with the less reactive alkenes, significant expanding the scope in stoichiometric PKRs.[19–20] Unfortunately, the *N*-oxide activation is not compatible with catalytic PKR conditions, and only a very moderate beneficial effect of ethyleneglycol is observed in PKRs of norbornene (NBN) and norbornadiene (NBD).[30] Therefore, the scope remains restricted to strained alkenes for the catalytic PKR, which is the more appealing variation from the perspective of economy and sustainability.

Table 1. Effect of coordinating functionalities on the regioselectivity of the PKR.



Alkene	Conditions	Yield	Ratio **4**:**5**	Ref.
3j	toluene, 100 °C	41%	1:1	26e
3k	toluene, 100 °C	60%	8:1	26e
3l	CH_3CN, 82 °C	47%	7:1	26a
3m	NMO[a] (6.0 eq.), CH_3CN, 0 °C	74%	13:1	26d

[a] NMO: *N*-methyl-morpholine *N*-oxide.

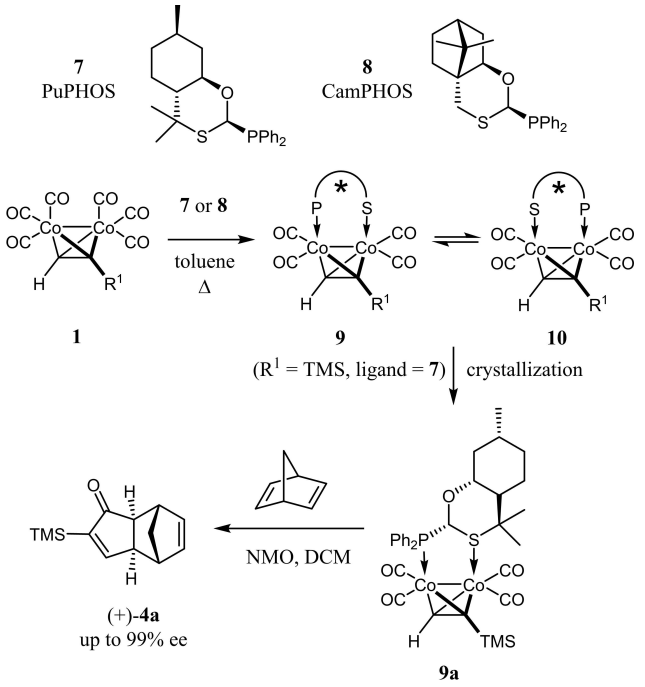


Scheme 3. Strained alkenes of different typologies used as reactive partners in the PKR.

An added problem of the alkene counterpart is the lack of regioselectivity when non-symmetrical alkenes are used. Only when alkenes with coordinating functionalities are used, useful and – more importantly – predictable levels of selectivity can be achieved (Table 1).[26]

4. Enantioselective Intermolecular PKRs

The PKR reaction furnishes up to two new stereocenters originating from the alkene double bond. In order to control the enantioselectivity of the reaction the use of chiral auxiliaries in the alkene[26c,d] or the alkyne[31] has been employed. In this sense, the use of auxiliaries with chelating capability, such as thioethers, improve the diastereoselectivity in the formation of the complex.[32] The studies in the Pericàs and Riera group demonstrated that the reversible coordination of the sulfur atom is highly selective towards one cobalt center.[33] Sulfur/alkene ligand exchange directs the reaction towards this atom, yielding the PKR adducts with excellent stereocontrol. Nevertheless, a much more practical and elegant approach is the use of chiral ligands. Coordination to the cobalt-alkyne complex leads to mixtures of diastereomers that, once isolated, can lead to enantiopure PKR adducts. This strategy reduces the synthetic cost of introduction and removal of the chiral auxiliary and, as we will discuss later, can lead to a catalytic asymmetric version of the reaction. Early reports include the use of phosphines such as GLYPHOS,[34] but the lack of selectivity in the coordination leads to the formation of two complexes in poor diastereomeric ratio (60:40). Moreover, at high temperatures the complexes isomerize to this ratio therefore limiting the conditions (and substrates) that can be used in the PKR. The use of diphosphines such as BINAP in a bridged coordination mode avoid equilibration, but inhibit the reaction as developed in Section 6.[35] Accordingly, the development of hemilabile, bidentate ligands featuring a phosphine ligand and a thioether functionality that can reversibly bond to the metal center allowing the creation of a coordination vacant was an important breakthrough. Verdaguer, Riera and Pericàs reported the synthesis of difuntional ligands synthesized from (+)-pulegone (PuPHOS, **7**) and (+)-camphorsulfonic acid (CamPHOS, **8**) (Scheme 4).[36] These ligands coordinate in a bridged manner, giving rise to two diastereoisomers (**9**/**10**) that can be separated by crystallization or chromatography. Once isolated, the reaction with norbornadiene proceeds with excellent enantioselectivities, especially when using amine *N*-oxides as activators. To this end, it is important to have pure diastereomers as somehow when using mixtures, the diastereomeric ratio of the complexes is not conserved in the PKR adducts, losing optical purity (an important limitation in order to develop catalytic versions). The



Scheme 4. Top) PuPHOS and CamPHOS ligands. Bottom) Schematic representation of the formation of alkyne dicobalt bridged complexes with PuPHOS and CamPHOS and use in the PKR.

diastereomeric ratios (dr) range between 1:1 and 4.5:1 for PuPHOS and 1:1 to 2:1 for CamPHOS. However, as the dr is the result of a thermodynamic equilibrium, in the case of PuPHOS, after crystallization of the major diastereomer it is possible to thermally re-equilibrate the mother liquor to obtain a new batch of the complex. For (trimethylsilyl)acetylene (TMS-acetylene, **2a**), it is possible to repeat the cycle up to 4 times to obtain the major diastereomer in a 70% overall yield.[37] Substrate **2a** is the most synthetically valuable, as the removal of the TMS groups makes the optically pure adduct **4a** a useful chiral cyclopentadienone synthon. Importantly, the diastereomeric ratio of the complexes formed with PuPHOS and CamPHOS can be improved if an attractive, non-conventional, hydrogen bond interaction can be established between the substrate and the ligand.[38] This leads to diastereomeric excesses up to 99%, translating into improved yields of isolated optically pure complexes. A step further was the investigation of these ligands in a catalytic process both in metal and ligand (Figure 2).[39] The usual conditions in the catalytic reaction involve the use of a carbon monoxide atmosphere. Under these conditions, carbon monoxide displaces the labile sulfur ligand, yielding a pentacarbonylic complex as ascertained by in-situ FT-IR. The formation of these pentacarbonylic species is responsible for the low enantioselectivities obtained in the process, due to the

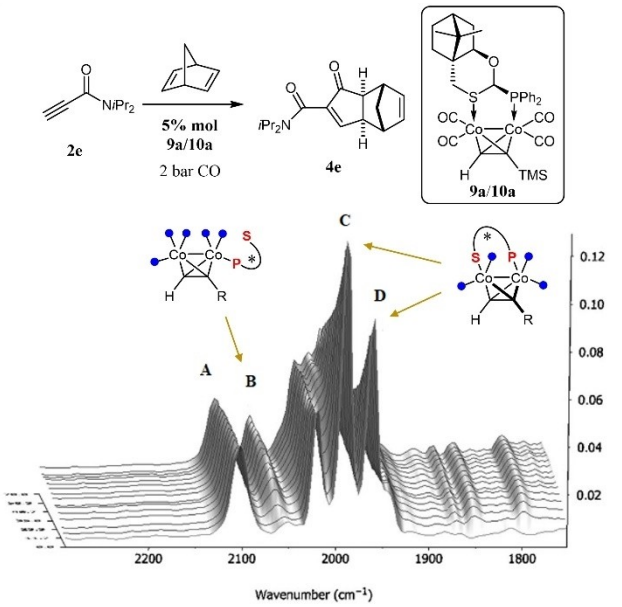
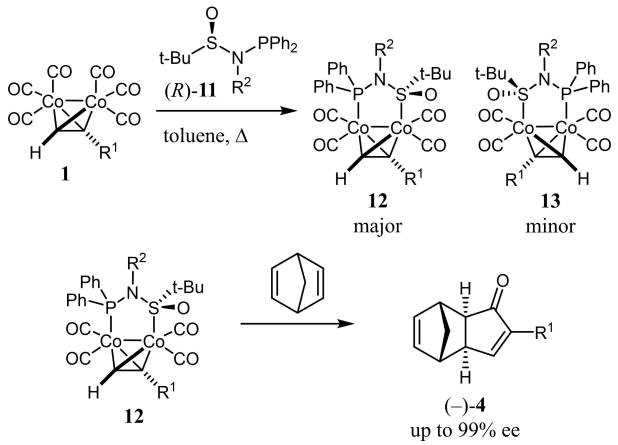


Figure 2. FT-IR time course monitoring of the PKR of alkyne **2e** catalyzed by complexes **9a**/**10a**. A: Alkyne C–C stretching band at 2104 cm^{-1}. B: CO stretching band at 2063 cm^{-1} of the pentacarbonylic complex. C, D: CO stretching bands at 1991 cm^{-1} and 1960 cm^{-1} of the tetracarbonylic complex, which decrease during the course of the reaction due to displacement of the sulfur atom by CO, giving rise to the pentacarbonylic complex.



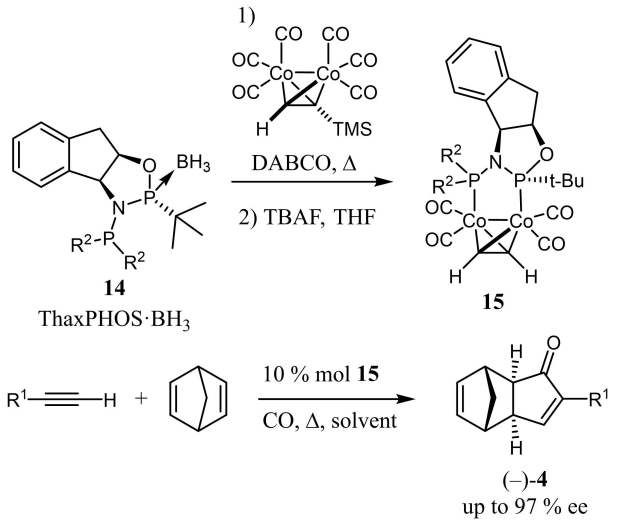
Scheme 5. Coordination of the PNSO ligands to hexacarbonyldicobalt alkyne complexes and subsequent enantioselective PKR, as described by Verdaguer and Riera.

lack of selectivity in the formation of the diastereomeric non-bridged complexes (the phosphorus ligand can easily migrate between cobalt centers). Only in the cases when the ligand and the substrate establish a hydrogen bonding interaction (as mentioned above), a certain degree of stereocontrol is retained in the catalytic intermolecular reaction. Yet, low to modest enantiomeric excesses (up to 40%) were obtained.

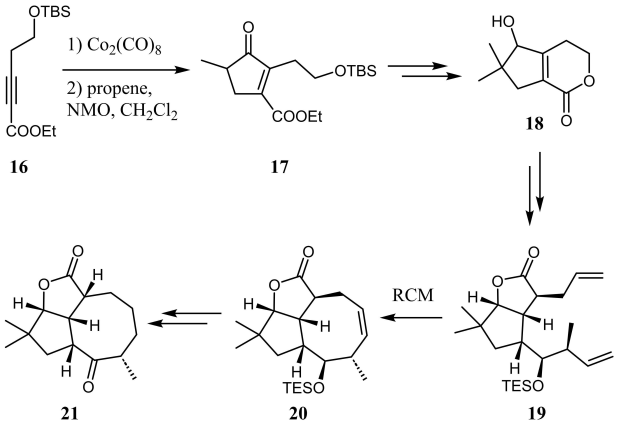
A novel class of ligands was later described by Verdaguer and Riera. They reported the synthesis of *N*-phosphinoyl-*tert*-butylsulfinamides (PNSO, **11**) that are easily available in a two step synthesis from commercially available compounds (Scheme 5).[40] This new class of ligands ingeniously combines the coordinative properties of phosphines with sulfur-centered chirality, as opposed to ligands used until then in the PKR that featured stereogenic elements on the carbon backbone alone. The coordination of the new PNSO ligands to the dicobalt hexacarbonyl complexes resulted in good to excellent selectivities. Again, it was possible to obtain the major diastereomer of the corresponding dicobalt-alkyne complex in pure form by crystallization, which was in turn reacted with norbornadiene to yield the corresponding PKR adducts with good to excellent enantioselectivities. It is important to notice that in this case both enantiomers of the PNSO ligands are synthetically feasible (both (*R*)- and (*S*)-*tert*-butyl sulfinamide are commercially available), allowing access to both enantiomers of the PKR adducts. On the contrary, only one enantiomer of the adduct is available when using ligands derived from natural products such as PuPHOS or CamPHOS, where the chirality is fixed by their natural source.

Later, the same group reported the related *N*-phosphinoyl-*p*-tolylsulfinamides, which provided inferior selectivity both in the coordination and the reaction steps.[41] Nevertheless, the *p*-tolyl derivatives provide good results in the enantioselective PKR with symmetrical alkynes, given the fact that the coordination step furnishes a single isomer in good yields for these substrates.[42]

In order to overcome the labile nature of all the above mentioned ligands, which prevents their use in catalytic asymmetric versions of the reaction, the group of Riera and Verdaguer developed a new family of family of bridging diphosphanes (ThaxPHOS) derived from *cis*-1-amino-2-indanol (Scheme 6).[43] The ThaxPHOS ligands feature a stereogenic phosphorus atom, following the design principle previously introduced in the PNSO ligands consisting on introducing stereogenic elements as close to the cobalt cluster as possible. Notably, *P*-chiral ligands had not been used in the enantioselective PKR up until then. The coordination of this new family of ligands to alkyne hexacarbonyl complexes furnished several chiral derivatives that were then tested as catalysts. This effort led to the first catalytic system delivering useful yields and enantioselectivities, albeit at the expense of a poor substrate scope. The ThaxPHOS system is efficient exclusively when using TMS-acetylene (**2a**) as substrate. The same group also investigated other diphosphines such as QuinoxP*, originally developed by Imamoto.[44] In this case the coordination proceeded exclusively yielding chelated complexes, with diaster-



Scheme 6. Coordination of ThaxPHOS ligands to hexacarbonyldicobalt alkyne complexes and their use in the catalytic asymmetric PKR.



Scheme 7. PKR reaction used by the group of Krafft in the route towards the synthesis of (±)-asteriscanolide (**21**).

eomeric ratios highly dependent on the substrate (from 1.3:1 to 10:1). The complexes were then studied in the PKR, resulting in good activities in some cases (depending on the substrate), but obtaining poor enantioselectivities.

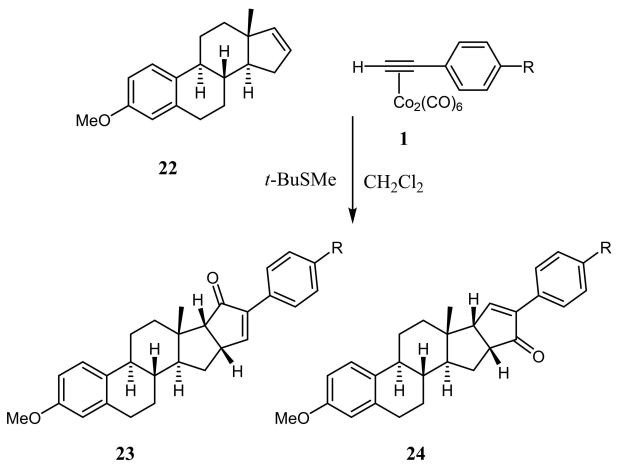
5. Synthetic Applications of the Intermolecular PKR

The intermolecular PKR reaction has been used as a strategic transformation in the preparation of cyclopentenones either in their racemic form or as homochiral starting materials. Here, we present a selection of synthetic routes that have been employed for the preparation of relevant natural products in the last 20 years. We make emphasis on the role that the PKR plays in the synthetic strategy, but we refer the readers to the original works for details concerning the other synthetic transformations.

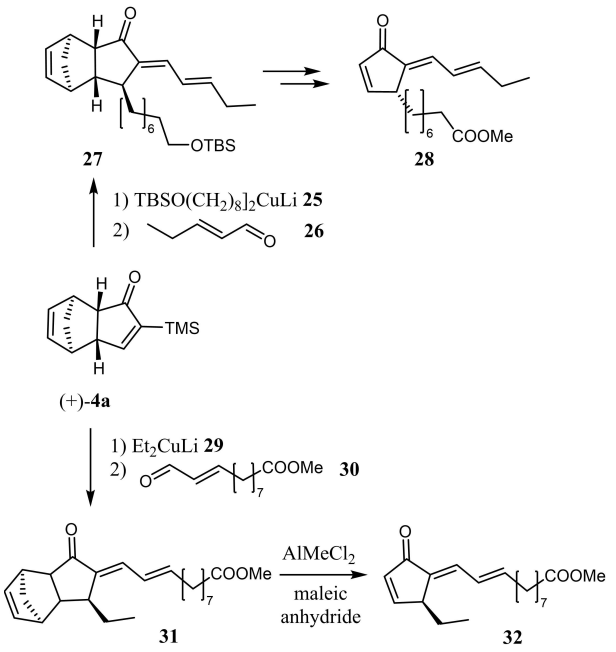
In 2001, Krafft and co-workers reported the total synthesis of (±)-asteriscanolide starting with the formation of cyclopropenone **17** by a PKR between **16** and propene (Scheme 7).[45] This compound is then cyclized to yield lactone **18** and further elaborated to furnish intermediate **19**, which will provide the tricyclic compound **20** through a RCM reaction. A series of additional steps conduct to (±)-asteriscanolide (**21**).

The possibility of forming fused polyciclic compounds using cyclic alkenes is one of the strengths of the PKR. Thus, Laschat described the formation of pentalenes (bicyclo[3.3.0]octanes) by reaction of the cobalt complex of functionalized acetylenes with norbornadiene.[46] Addition of organocuprates to the corresponding PKR adducts followed by reductive ozonolysis of the resulting norbornene leads to bis(hydroxymethyl)pentalenones, which are interesting materials for further manipulation. An intermolecular PKR was also used by the group of Helaja for the preparation of several E-ring extended estrone analogues (Scheme 8).[47] In this case, compound **22** was reacted with a series of phenylacetylene cobalt complexes using *t*-butyl methyl sulfide as promoter, giving rise to cyclopentenone isomers (**23**/**24**) with ratios ranging from 1.6:1 to 1:1.5 depending on the substrates. NMR studies provided evidence that these isomers were regioisomers and not stereoisomers. Steric effects rather than electronic explain the lack of regioselectivity in this particular case.

In collaboration with the laboratory of Mueller, the group of Verdaguer and Riera reported the asymmetric synthesis of prostaglandin-like, phytoprostane metabolites (Scheme 9). As stated above, using the PuPHOS

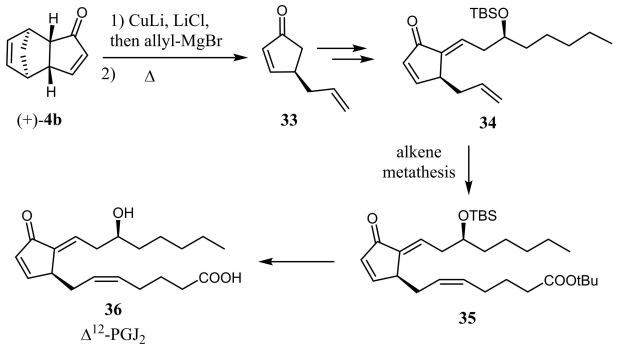


Scheme 8. PKR E-ring formation in estrone derivatives described by Helaja.



Scheme 9. Synthesis of 13,14-dehydro-12-oxo-phytodienoic acids from PKR adduct (+)-**4a**.

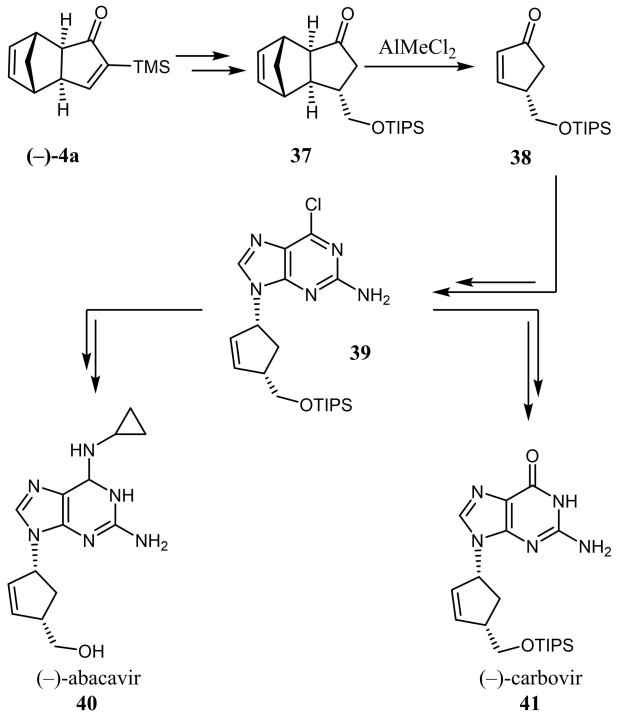
auxiliary the key intermediate (+)-**4a** is easily accessible in multi-gram scale.[23] From **4a**, using a series of transformations it is possible to reach the deoxy-J_1-phytoprostane **28**. The key steps of the synthesis are a 1,4-addition followed by Peterson olefination to form **27** and the retro-Diels-Alder reaction to furnish the cyclopentenone **28**.[48] Following a similar but more convergent route the related (+)-12-oxo-phytodienoic acid **32** was also obtained. Later on, a comprehensive study of the one-pot conjugate addition-Peterson olefination sequence starting from **4a** was carried out.[49] The geometry of the exocyclic alkene can be controlled depending on the organometallic reagent used. Thus, following this sequence other phytoprostane scaffolds can be accessed. More recently, the group of Nicolaou developed the synthesis of Δ^{12}-prostaglandin J_2 and a series of analogues, including several oligomeric macrolactones, also starting from compound (+)-**4a** (Scheme 10).[50] Cyclopentenone **4b** is easily available by treatment of **4a** with TBAF.[37] Then, a stereoselective Michael addition of an in situ generated allyl-copper reagent followed by a retro-Diels-Alder reaction generates cyclopentenone **33**. From there, it is possible to introduce the requisite exocyclic double bound by aldol reaction followed by crotonization. Finally, olefin metathesis of **34** and final deprotection yields Δ^{12}-PG J_2 (**36**). The macrolactonization of **36** was also explored, furnishing the cyclic monomer or mixtures of cyclic oligomers depending on the concentration. The synthesis of non-natural prostaglandin analogues with different side chains was



Scheme 10. Total Synthesis of Δ^{12}-prostaglandin J_2 reported by Nicolaou.

also investigated, including α-halo ketone functions and CF_3 groups in the terminal alkyl position.

Taking advantage of the PNSO ligands developed in their group, Verdaguer and Riera employed the asymmetric intermolecular PKR as key step in the synthesis of carbanucleosides (Scheme 11).[51] Starting from (−)-**4a** addition a d^1 synthon (either by cyanide addition or, more conveniently, using a photoinduced addition of the hydroxymethyl radical) and further functional group manipulation leads to intermediate **37**, which is then submitted to the retro-Diels-Alder reaction to furnish cyclopentenone **38**. Further trans-



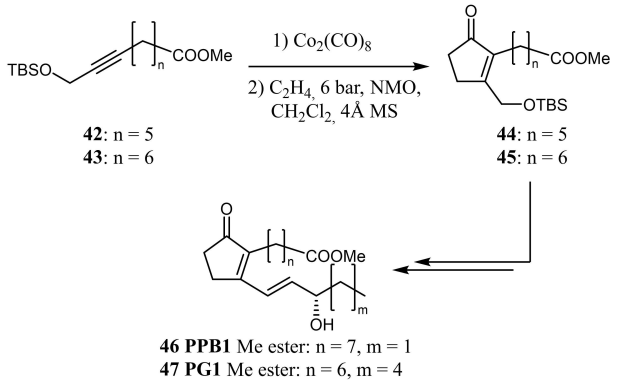
Scheme 11. Synthesis of (−)-abacavir and (−)-carbovir described by the group of Verdaguer and Riera starting from PKR adduct **4a**.

formations lead to compound **39**, which can then be easily manipulated to yield nucleosides (−)-abacavir **40** and (−)-carbovir **41**.

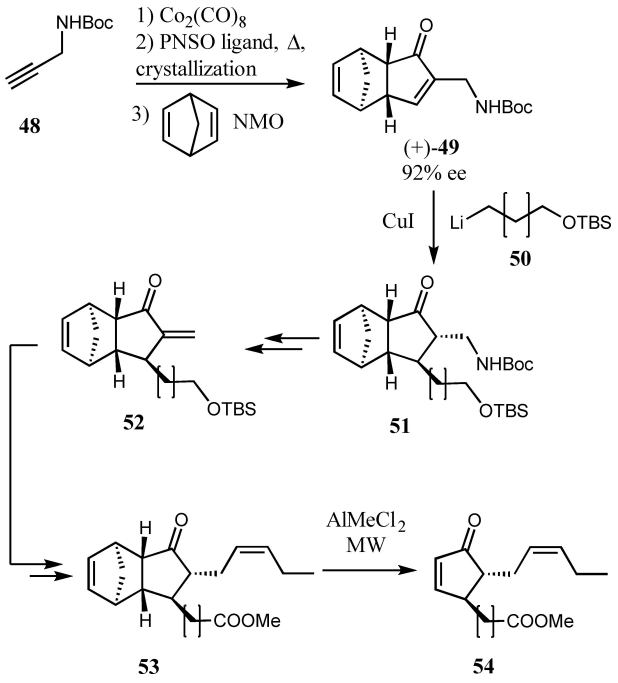
Using ethylene as the source of alkene, the same group addressed the synthesis of prostaglandin and phytoprostane B1 (Scheme 12). In this case, the careful optimization of the reaction conditions, involving the use of 6 bar of ethylene, NMO and 4 Å molecular sieves, was essential to reach the key achiral intermediates **44** and **45** in good yields and complete regioselectivities.[52] The electron withdrawing nature of the silyloxymethyl group is sufficient to control the regioselectivity, providing the adducts with this substituent in the β position as previously discussed (see Section 3). After alcohol deprotection and Swern oxidation, the resulting aldehydes were subjected to Julia olefination with the appropriate sulfones to yield, after the final deprotection steps, the corresponding PPB_1 **46** and PGB_1 **47** as methyl esters. The same research group also took advantage of *N*-Boc-propargylamine **48** as a masked allene equivalent for the PKR, leading to cyclopentenones with an exocyclic double bound that could be used to introduce additional sidechains through conjugate addition reactions (Scheme 13). After further elaboration, 13-epi-12-oxo-phytodienoic acid (13-*epi*-12-oxo-PDA) methyl ester **54** was synthesized, demonstrating once more the value of the PKR in the synthesis of prostanes.[53]

More recently, starting with a PKR between *N*-Boc-propargylamine **55** and ethylene, the preparation of (*R*)-sarkomycin was achieved after introducing chirality by means of an asymmetric Ir-catalyzed isomerization followed by elimination of the amino group (Scheme 14).[54]

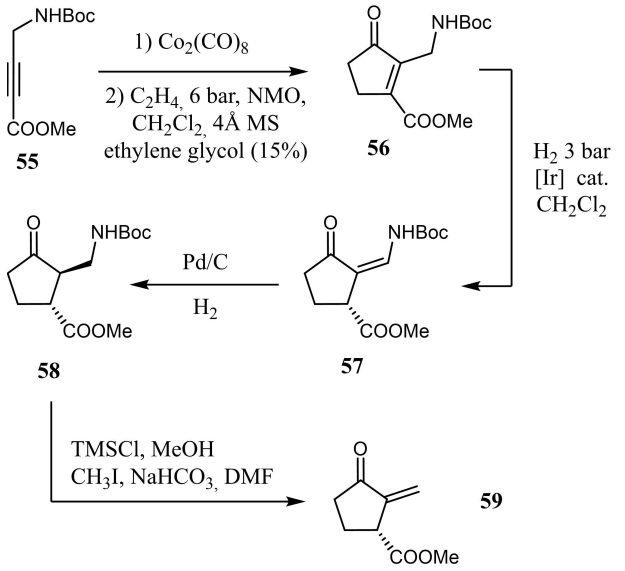
In 2011 the group of Baran reported the synthesis of a series of natural products within the bioactive pyrrole-imidazole marine alkaloid (PIA) family (Scheme 15). Very importantly, they identified intermediate **63** as common precursor of axinellamines (A and B), massadines (massadine and massadine Cl) and palau'amine. The synthesis begins with a multi-gram (6.2 g scale) PKR between the bis-allylic trimethyl silyl ether **60** and *N*-Boc-propargylamine **61** to yield the cyclopentenone **62** in up to 58% yield.[19] Additional steps including a chemoselective Barbier-type reaction and a chlorination-spirocyclization lead to **63**,



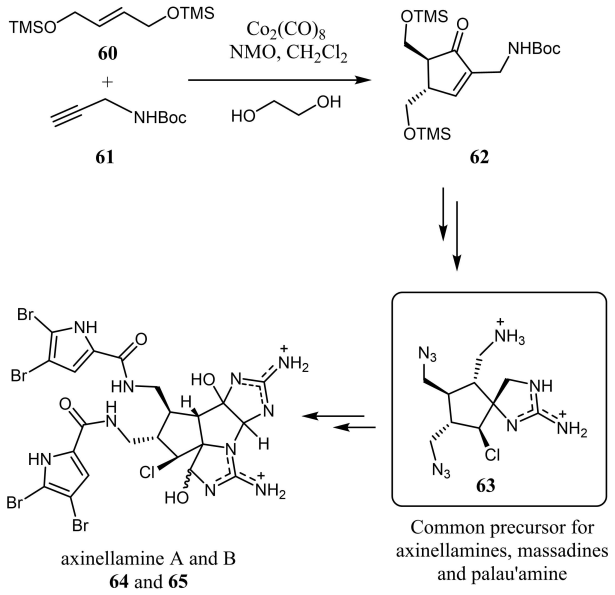
Scheme 12. Synthesis of prostaglandin and phytoprostane B_1 described by Verdaguer and Riera starting from a PKR of internal alkynes **42** and **43**.



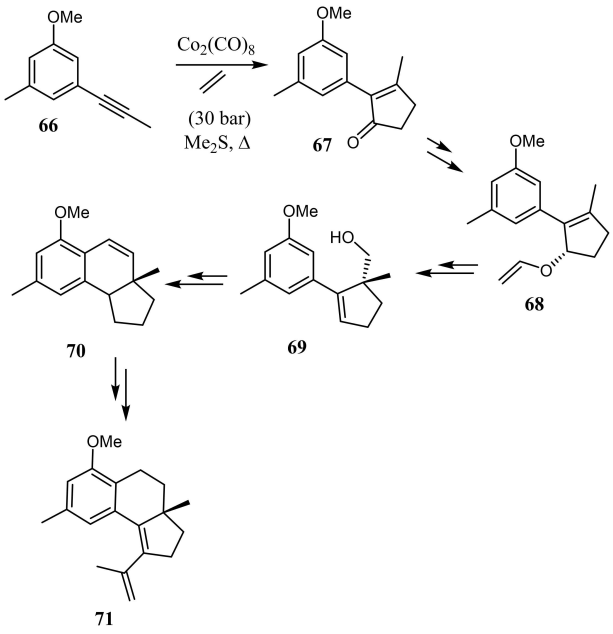
Scheme 13. Synthesis of prostane **54** by addition to an *exo*-cyclic double bound and posterior retro-Diels-Alder reaction.



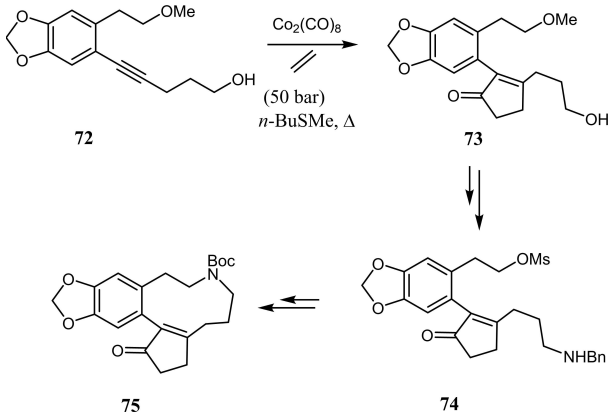
Scheme 14. Synthesis of (*R*)-sarkomycin methyl ester (**59**) using a PKR and an Ir-catalyzed isomerization developed in the group of Verdaguer and Riera.



Scheme 15. Synthesis of compound **63** described by Baran and co-workers. This compound can then be further functionalized to several natural products including axinellamines A and B. A multi-gram PKR to yield compound **62** is placed at the beginning of the synthetic route.



Scheme 16. Formal total synthesis of (−)-hamigeran B described by Jiang et al. The synthesis starts with a PKR between compound **66** and ethylene.



Scheme 17. Formal total synthesis of (±)-cephalotaxine carried out by Jiang et al. The cyclopentenone fragment is introduced using an intermolecular PKR between **72** and ethylene.

which is a common ancestor of the above mentioned compounds. From **63**, the group completed the total synthesis of axinellamines A and B.

The PKR was also the starting point for the formal synthesis of (−)-hamigeran B, reported by Jiang and co-workers (Scheme 16).[55] Their synthesis starts with the construction of the cyclopentane moiety by the reaction of compound **66** with ethylene in the presence of octacarbonyl dicobalt and dimethylsulfide. Later, reduction of the carbonyl and kinetic resolution of the alcohol followed by vinylation furnished intermediate **68**. This compound was subjected to a reductive Claisen rearrangement to yield **69**, which was oxidized and then treated with $BF_3 \cdot Et_2O$ to form the tricyclic compound **70**. Further manipulations allow the formal total synthesis of (−)-hamigeran B, as compound **71** was known previously converted to this natural product in 5 steps.[56]

The same group also made use of the PKR to accomplish the formal total synthesis of (±)-cephalotaxine (Scheme 17).[57] In this case, a fundamental step was the intermolecular PKR between compound **72** and ethylene to furnish cyclopentenone **73**. Standard functional group manipulations and a final cyclization conducted to compound **75**, which can be transformed to cephalotaxine in 5 steps.

Finally, is worth noting that the intermolecular PKR as also attracted industrial interest, as demonstrated in several patents. In addition to earlier examples describing the synthesis of simple cyclopentenones by industry giants such as BASF[58] or Firmenich,[59] a few recent examples demonstrate the potential of the PKR for the assembling of pharmacologically relevant compounds containing five membered carbon rings (Figure 3).[60]

6. Limitations and Challenges of the Intermolecular PKR

Despite its synthetic potential, it is clear that the current methodological limitations of the intermolecular PKR reduce its appeal as a versatile and efficient

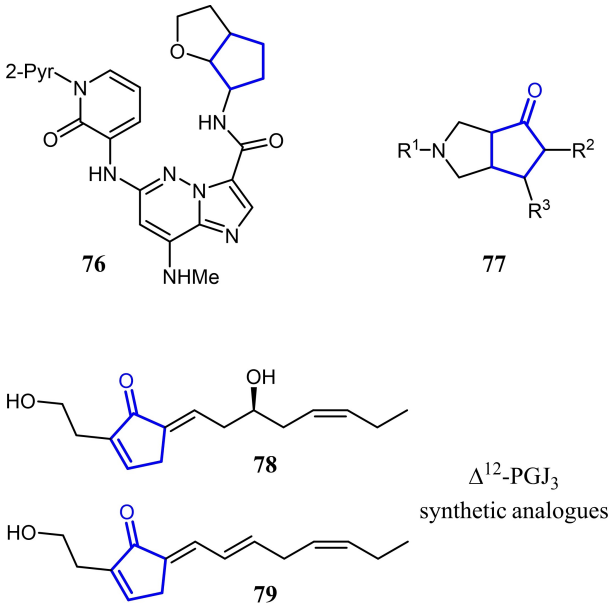


Figure 3. Compounds of industrial interest synthesized through intermolecular PKRs.

assembly method for cyclopentenones. Arguably, the key downsides of the reaction are a) the limited scope with regards to the alkene, and b) the lack of a generally applicable catalytic enantioselective version. In this section, we will develop the idea that both limitations are intimately related to the lack of a ligand-accelerated version of the reaction and provide hints on how to address it.

The seminal mechanistic study by Riera and Verdaguer convincingly demonstrated that sigma donor ligands do not accelerate the PKR under catalytic conditions, and rather provide a way to stabilize the catalytically active species and avoid catalyst deactivation.[13] The inhibiting effect of phosphane ligands and other σ-donor ligands can be rationalized in terms of π-back donation to the carbonyl ligands. The introduction of σ-donors in the coordination sphere increases the electron density on Co, which in turn enhances π-back donation to the π* orbitals of the CO ligands. This reinforces the Co-CO bond, increasing the barrier to CO dissociation that constitutes a significant portion of the RDS energy difference as previously discussed. Additionally, a weakening of the C–O triple bond should be expected. Indeed, this effect is reflected in the IR spectra of dicobalt-alkyne carbonyl complexes, which feature decreased wave numbers (ν) of the associated C–O stretching bands when σ-donor ligands are introduced. It is reasonable to postulate that a catalytic system displaying a lower CO dissociation barrier would facilitate the coordination of the alkene, and would probably represent a step forward in terms of reactivity and scope. However, the overall barrier of the RDS needs to be considered, which also includes the alkene insertion step. An intuitive idea to address the lack of ligand acceleration is to introduce ligands that are poor σ-donors and better π-acceptors. This is extremely challenging conceptually, since this hypothetical ligand would need to surpass the superior π-accepting character of the carbonyl ligand. To gain insight into this question, we evaluated computationally the RDS of the PKR between acetylene and ethylene with three different ligands: triphenylphosphine (**L1**) and two of the most electron-deficient phosphanes available, tris(hexafluoroisopropyl)phosphite (**L2**)[61] and tris[2,6-bis(trifluoromethyl)-pyridin-4-yl]phosphine (**L3**, Figure 4).[62] As expected, the introduction of a PPh_3 ligand results in an increase in both the CO dissociation step and the overall RDS barrier with respect to the parent reaction without ancillary ligand (L=CO).

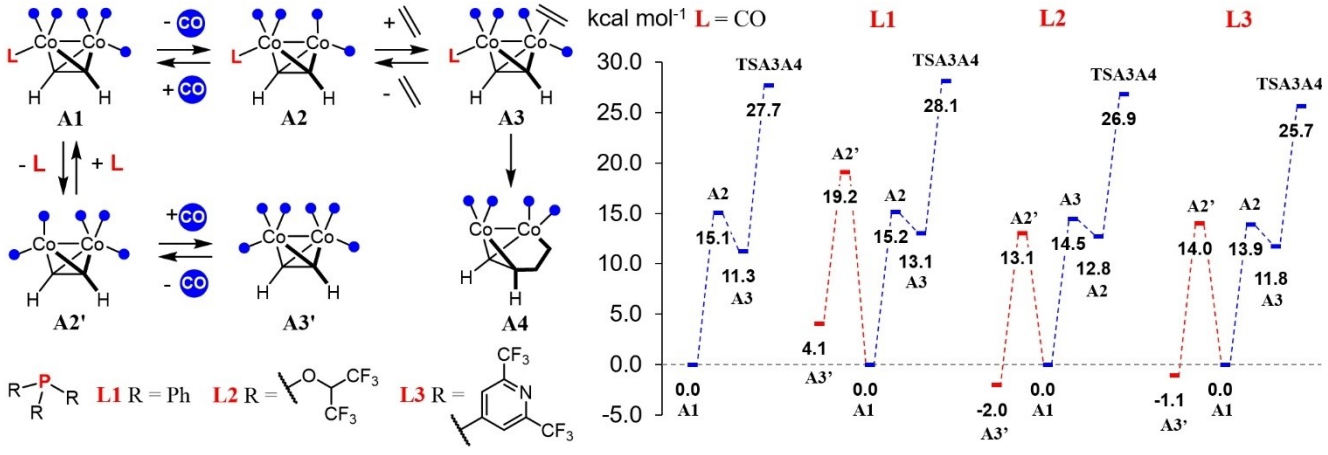
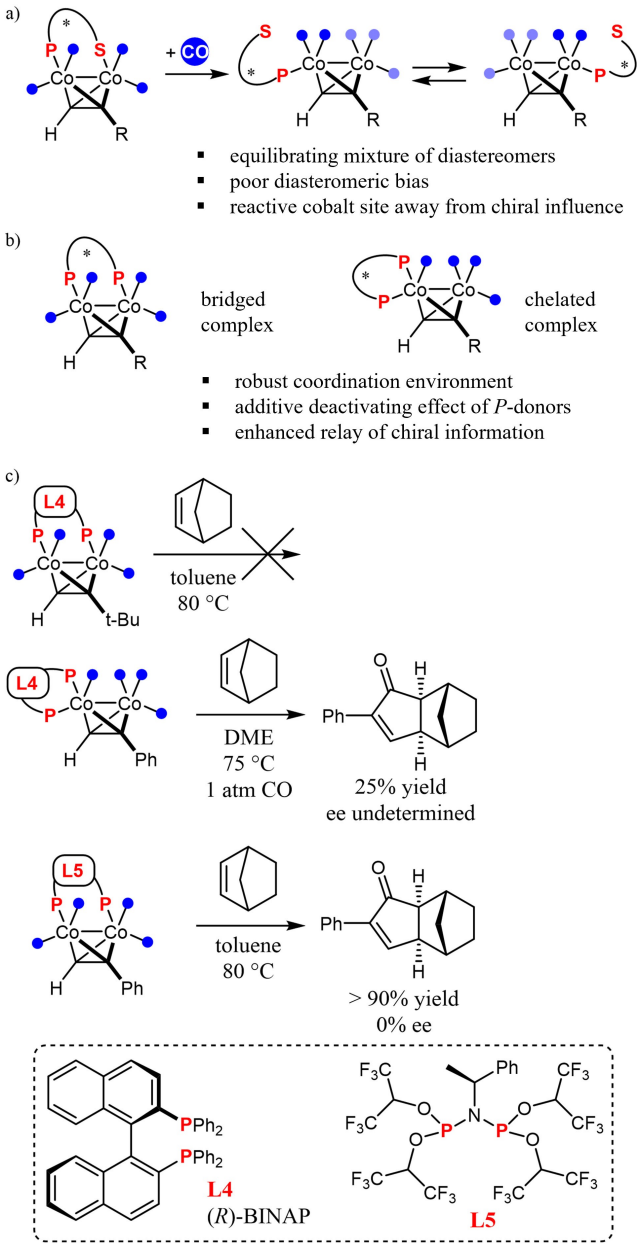


Figure 4. Effect of different phosphane ligands on the outcome of the critical reaction barriers of the PKR. Relative Gibbs energy differences are shown for the RDS of the PKR with different ligands (**A1**→**TSA3A4**, blue pathways), and for the ligand exchange equilibria leading to hexacarbonyldicobalt acetylene (**A1**→**A3'**, red pathways).

Interestingly though, there is a slight decrease in the insertion barrier (15.0 vs 16.4 kcal mol^{-1}). Notably, the introduction of electron deficient ligands **L2** and **L3** results in a net decrease of the dissociation step, the insertion step and the overall RDS barriers with respect to the reference reaction, establishing a promising design rationale for developing ligand-accelerated versions of the PKR. These results must however be taken with caution, because for these "privileged" monodentate ligands, the ligand displacement by CO takes place with barriers way below that of the PKR RDS, and the corresponding equilibria favor the hexacarbonyl dicobalt complex (Figure 4, red pathways). In other words, under catalytic PKR conditions (CO atmosphere) it is likely that complexes featuring ligands **L2** or **L3** will rapidly dissociate from cobalt, and the PKR will proceed through the hexacarbonyl-alkyne complex, superseding any putative accelerating effect. A possible solution to this problem would be the integration of electron poor phosphane donors into a bidentate scaffold (see below).

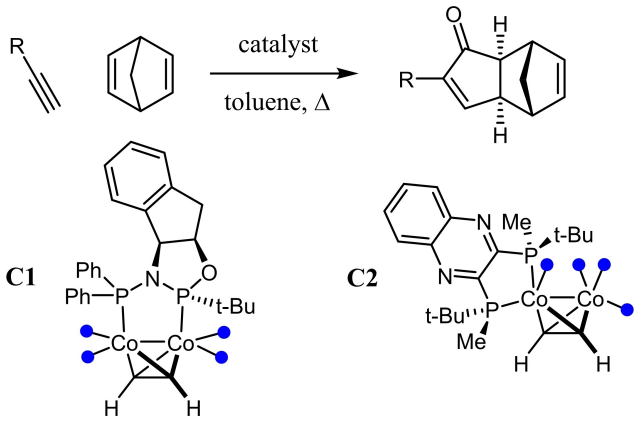
The lack of ligand-accelerated reaction manifolds is also the main impediment towards catalytic enantioselective PKRs. It has been demonstrated that chiral bidentate ligands are required to provide good levels of enantioinduction in the PKR (see section 4). However, the privileged (*P*,*S*) chiral ligands previously discussed underperform under catalytic conditions due to their inherent design: the hemilabile Co–S linkage that facilitates the formation of a vacancy for alkene coordination will also favor displacement by extraneous CO, resulting in monocoordinated species (Scheme 18a). These catalytically active species deliver poor enantioinduction for two reasons: a) monodentate ligands provide poor selectivity in the formation of the diasteromeric alkyne-dicobalt complexes, and b) coordination and insertion of the alkene is favored at the distal Co atom with respect to the ligand, hindering the relay of stereochemical information. To address this problem, diverse research groups have resorted to (*P*,*P*) bidentate chiral ligands looking for a more robust coordination environment (Scheme 18b).[8a,43,63] However, the additive effect of two deactivating *P*-donor ligands is manifested in the harsher reaction conditions typically required, which limit the scope of this approach (Scheme 18c). This lower reactivity is manifested more clearly in bridged complexes, as illustrated with the case of BINAP. While both bridged and chelated dicobalt-alkyne complexes of BINAP can be accessed, only the chelated complex has been proven to be reactive under standard PKR conditions.[35,63a] Either in bridged or chelated complexes, the reduction of electron donating character of the *P*-donors through the ligand backbone is required to unfold significant reactivity. However, combing this design feature with efficient relay of chiral information from the ligand to the metal cluster



Scheme 18. Challenges for the development of catalytic enantioselective PKRs. a) Hemilabile (*P*,*S*) bridging ligands behave as monodentate ligands under CO atmosphere and provide poor stereoinduction. b) (*P*,*P*)-bidentate ligands offer robust coordination environments but display sluggish reactivity. c) Comparative reactivity of dicobalt-alkyne complexes with different (*P*,*P*)-bidentate ligands and coordination modes.

is far from trivial. So far, only *P*-chiral ligands have been proven effective to provide good yields and enantioselectivities in catalytic PKRs (Table 2).

Table 2. Comparative performance of dicobalt-alkyne complexes with (*P*,*P*)-bidentate ligands as catalysts for enantioselective PKRs.[a]



R	Catalyst	Conditions	Yield	ee	Ref.
n-Bu	**C1** 10 mol%	100 °C CO 1 barG	54%	3%	43
n-Oct	**C2** 5 mol%	95 °C CO 1.5 barG	99%	41%	44
TMS	**C1** 10 mol%	130 °C CO 1 barG	77%	89%	43
TMS	**C2** 5 mol%	120 °C CO 1.5 barG	12%	< 5%	44

[a] Relative stereochemistry indicated for the reaction product.

7. Outlook

The PKR introduces a high degree of molecular complexity in a single reaction step that few organic reactions can accomplish. The improvements developed over the years now allow a good control of the intermolecular reaction in terms of stereoselectivity and regioselectivity, allowing the synthesis of valuable starting materials and advanced intermediates. Recent advances addressing the scope of the transformation and the advent of catalytic enantioselective variations hold a promising future for the use of the PKR as an early-stage multicomponent reaction for the synthesis of chiral, densely functionalized cyclopentenones of high added value. In this regard, the main challenge is the generalization of the intermolecular catalytic version of the reaction. Ligand engineering towards this goal will have to address two inseparable facets of the bisphosphane scaffolds that have so far proven useful. While the ThaxPHOS and QuinoxP* ligands provide the well-structured and robust coordination environment that is necessary for (good) enantioinduction, their strongly electron-donating nature is detrimental for the reaction rate, which limits in turn the alkene scope. In addition, *P*-chiral phosphanes are synthetically challenging and available mostly as electron-rich *P*-(*t*-Bu) derivatives.[64] A possible alternative to this dilemma could be the exploitation of non-covalent supramolecular interactions as described for propynamide substrates.[38,39] A speculative idea in this direction could be reclaiming monodentate phosphanes (to alleviate the electron donation to cobalt) in combination with confinement effects (provided by large aromatic panels) akin to those operating in imidodiphosphorimidate Brønsted acid catalysis.[65] The ultimate goal in this context would be to achieve reaction acceleration by the ligand or additives, but a clear design rationale in this direction has not been developed so far.

Computational Details[12]

Geometries of all stationary points were optimized without symmetry constraints with the Gaussian 16 program[66] using the DFT M06 hybrid exchange-correlation functional[67] in conjunction with the all-electron cc-pVDZ basis set.[68] The electronic energy was improved by performing single point energy calculations with the same functional and the cc-pVTZ basis set. All calculations were carried out including solvent effects corrections for toluene computed with the polarizable continuum model (PCM), and D3 Grimme energy corrections for dispersion with the original damping function.[69] Analytical Hessians were computed to determine the nature of stationary points (one and zero imaginary frequencies for TSs and minima, respectively) and to calculate unscaled zero-point energies (ZPEs) as well as thermal corrections and entropy effects. The reported Gibbs energies contain electronic energies calculated at the M06/cc-pVTZ/D3 level together with gas phase thermal

and entropic contributions computed at 298.15 K and 1 atm with the M06/cc-pVDZ/D3 method. Starting geometries for previously reported stationary points in the general mechanism (Figure 1) were obtained from the respective original contributions.[5b,7a] Pathways B and C including previously unknown stationary points were unambiguously confirmed by IRC calculations. Starting geometries for dicobalt cluster intermediates with coordinated ancillary phosphane ligands were constructed from the original Nakamura geometries.[5b]

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