

## Toward the understanding of the mechanism and enantioselectivity of the Pauson–Khand reaction. Theoretical and experimental studies\*

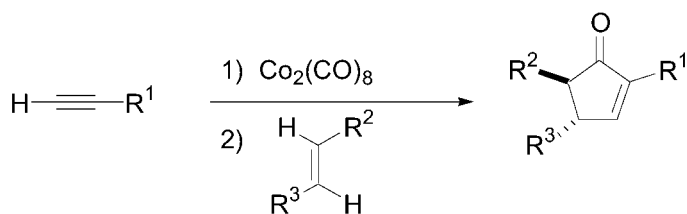
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**Abstract:** Semiempirical and density functional theory (DFT) calculations have been performed on the key steps of the commonly accepted mechanism of the Pauson–Khand reaction (PKR). In this context, the high reactivity of ynamine complexes in the cycloaddition process has been rationalized on the basis of an anomerically assisted dissociation of CO. Moreover, an explanation has been provided for the correlation between olefin strain and reactivity in the PKR. Inspired by these results, new selective syntheses of cyclopentanones and phenols based on PKR with cyclopropene have been developed. On the other hand, the theoretical analysis of phosphine-substituted dicobalt carbonyl complexes of alkynes has helped in the development of efficient chelating (P,N) and bridging (P,S) ligands for the stereochemical control of the reaction and in the understanding of their action modes.

### INTRODUCTION

The Pauson–Khand reaction (PKR), a process first disclosed in 1973 [1], which joins an alkyne, an alkene, and a CO group into a cyclopentenone (Scheme 1) [2], has evolved over the years into a powerful and well-established procedure for the synthesis of this type of compounds.

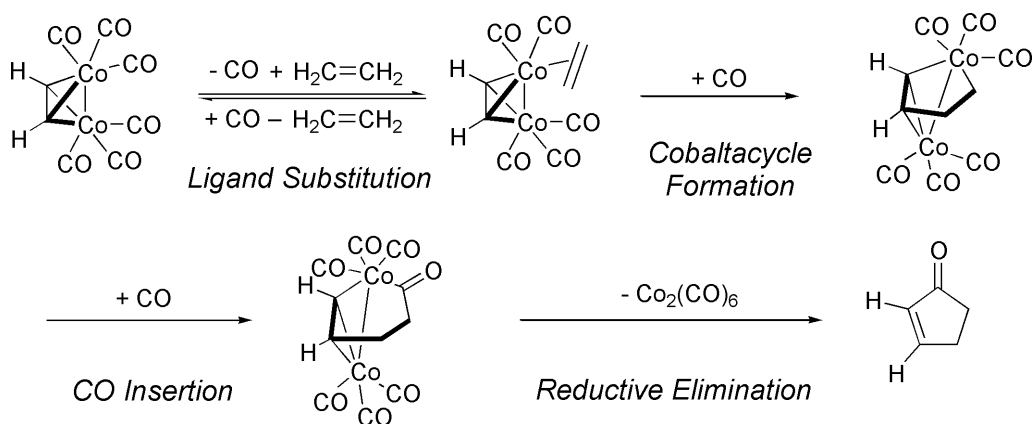


**Scheme 1**

A mechanistic sequence for the reaction was proposed by Magnus in 1985 (Scheme 2) [3]. Although no experimental studies have been devoted to the elucidation of this sequence, and no intermediates have been detected or characterized, this proposal has the virtue of accommodating the known experimental facts of the reaction and has gained universal acceptance.

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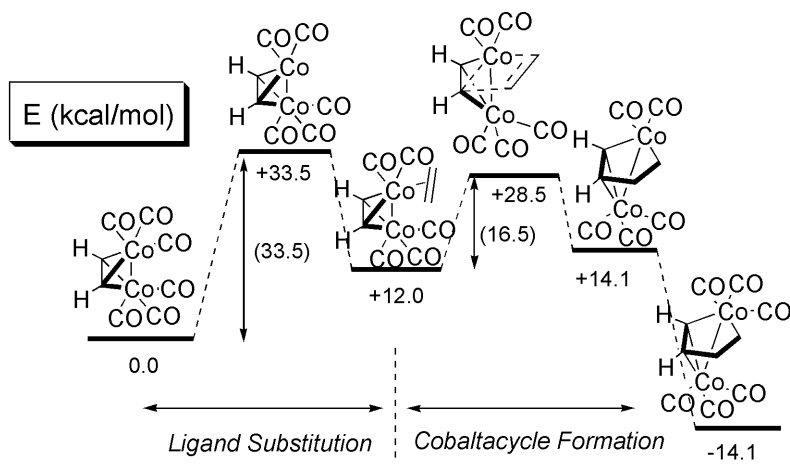
Scheme 2

Ligand substitution, leading to coordination of the reacting olefin, is probably rate-determining, while cobaltacycle formation is the product-determining step, since (with adequately substituted substrates) both the regiochemistry and the stereochemistry of the product cyclopentenone are fixed in it. We report in this paper theoretical calculations on these two steps of the Pauson–Khand reaction, putting emphasis on how the results of these calculations have inspired the development of useful synthetic applications of the reaction, both in its racemic and in its enantioselective versions.

### LOWERING THE ACTIVATION ENERGY OF PAUSON–KHAND REACTIONS

To get a deeper understanding of the process, we have studied the prototypical PKR between acetylene and ethylene using DFT (VWN/PW91xc) methodology [4]. A related DFT study has been recently published [5].

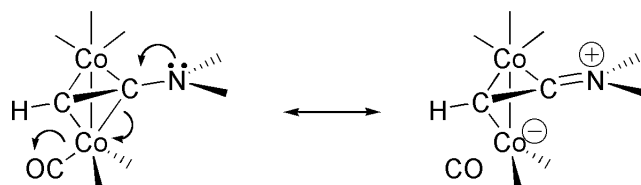
If we center our attention on the relevant steps of the reaction (Scheme 3), the calculations predict that the dissociative loss of CO will be strongly endothermic and will represent the rate-determining step of the reaction. The so-generated coordinatively unsaturated species finds an important stabilization through complexation with the reacting olefin, thus completing the ligand substitution stage. The cobaltacycle formation stage taking place next has interesting characteristics: The olefin insertion stage has moderate activation energy and is almost thermoneutral. However, a subsequent coordination



Scheme 3

of CO on cobalt is strongly exothermic, so that the overall cobaltacycle formation is predicted to be strongly exothermic and, hence, irreversible when the reaction is performed in a CO-rich environment.

According to these results, practical rate increase in PKR can be achieved through facilitation of the initial dissociative step. In fact, the most popular approach to chemical activation of the PKR is based on the use of amine oxides [6]. In it, the oxidation of a CO ligand leads to its irreversible detachment, allowing the reaction to proceed at highly increased rate. We have explored a different possibility, based on the effect that strongly electron-donating substituents on the alkyne molecule can exert on the ease of dissociation of the initial hexacarbonyl complex through the combined effect of anomeric and *trans* effects as shown in Scheme 4.



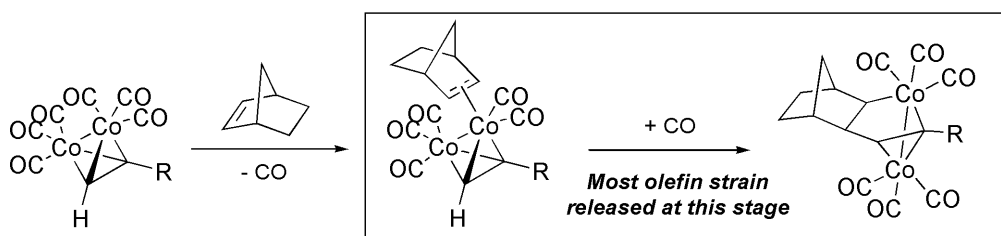
**Scheme 4** Substrate-assisted dissociation in cobalt carbonyl complexes of electron-rich alkynes.

In fact, DFT calculations on the dicobalt hexacarbonyl complex of dimethylaminoacetylene indicate that the anomeric interaction is operating: The nitrogen atom is almost perfectly planar, with the lone pair antiperiplanar to one of the carbon–cobalt bonds. Interestingly, this bond is predicted to be significantly elongated relative to the one that is free of the anomeric interaction (2.166 vs. 2.014 Å) [7]. We next studied the different possibilities of dissociative loss of CO from the dicobalt hexacarbonyl complex of dimethylaminoacetylene. For comparison purposes, the same study was done on the complex of propyne. The most favorable dissociation corresponds in both cases to the loss of a distal equatorial CO ligand. Interestingly, the dissociation of the dimethylaminoacetylene complex is predicted to be much more easy than that of the propyne (8.8 vs. 18.6 kcal.mol<sup>-1</sup>) [8].

Cobalt complexes of ynamines were practically unknown, so that to study their behavior in the PKR we had to develop first a convenient preparation for them. In agreement with theoretical prediction, they are thermally unstable and lose CO spontaneously. In fact, they have to be stored in the cold under a CO atmosphere [7].

Quite interestingly, the ynamine complexes were extremely reactive toward strained olefins. For instance, the complex derived from methoxymethyl-pyrrolidine reacted instantaneously (2 min) with norbornadiene at room temperature, and the reaction even proceeded at -21 °C. Most remarkably, the complex derived from *trans*-2,5-bismethoxymethylpyrrolidine underwent **thermal** reaction with norbornadiene at -35 °C, thus defining a new paradigm of reactivity in PKR.

However, the same complex failed to react with cyclohexene, clearly showing that the easy dissociation of the initial complex is not a sufficient condition for the observation of Pauson–Khand reac-

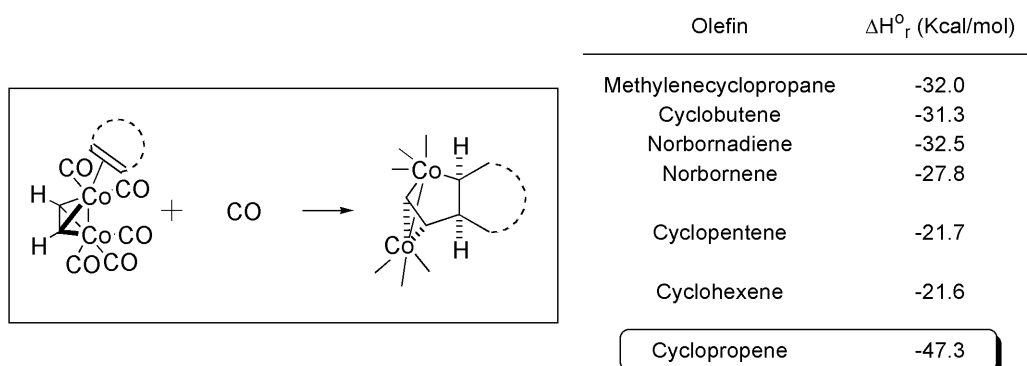


**Scheme 5**

tivity. This observation, together with the well-known relationship between strain and reactivity in cyclic olefins, led us to think that for strained olefins, cobaltacycle formation could be facilitated (Scheme 5) and that this condition should be simultaneously fulfilled for the observation of high reactivity.

### WHY STRAINED OLEFINS SHOW HIGH PAUSON–KHAND REACTIVITY?

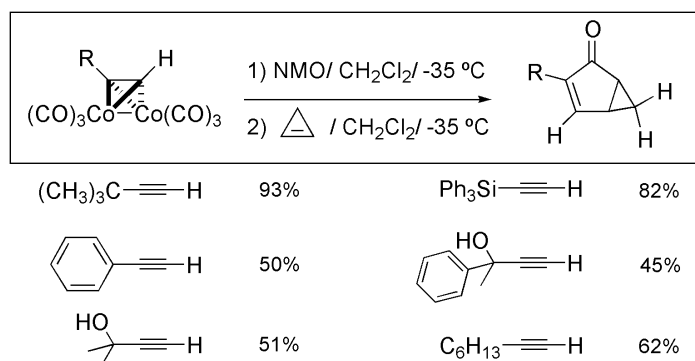
A possible explanation for this behavior could be found in the cobaltacycle formation step, since most of the olefin strain is liberated at this stage due to the change in the hybridization of the double bond carbons. Since this possibility had not been explored before, a theoretical study of the cobaltacycle formation step was undertaken for a variety of cyclic olefins covering different degrees of strain. Due to the size of the molecules involved in the study, a combined semiempirical [PM3(tm)] and DFT [VWN/PW91xc] approach was used. Gratifyingly enough (Scheme 6), a clear correlation between exothermicity of the cobaltacycle formation step and olefin strain was observed, thus providing an answer to the question of why strained olefins are more reactive in PKR [9].



Scheme 6

Cyclopropene, which had never been studied in the reaction, would present in theory the best enthalpic characteristics in the cobaltacycle formation step. In view of that, we decided to explore its Pauson–Khand reactivity.

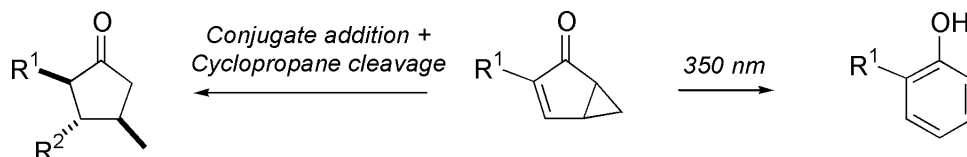
The reactions of cyclopropene need to be performed at low temperature, since polymerization of the olefin becomes fast at  $-30$  °C. It was necessary to perform a careful optimization of reaction conditions, and we could finally establish that the best reaction conditions involve performing the reaction at  $-35$  °C in dichloromethane, with simultaneous activation with *N*-methylmorpholine *N*-oxide (NMO).



Scheme 7

As shown in Scheme 7, good-to-excellent yields of bicyclo[3.1.0]hex-3-en-2-one adducts are obtained with a variety of alkyne complexes [10].

The bicyclo[3.1.0]hex-3-en-2-one adducts have been shown to possess an important synthetic potential, and processes have been developed for their efficient conversion into polysubstituted cyclopentanones and *ortho*-substituted phenols (Scheme 8).



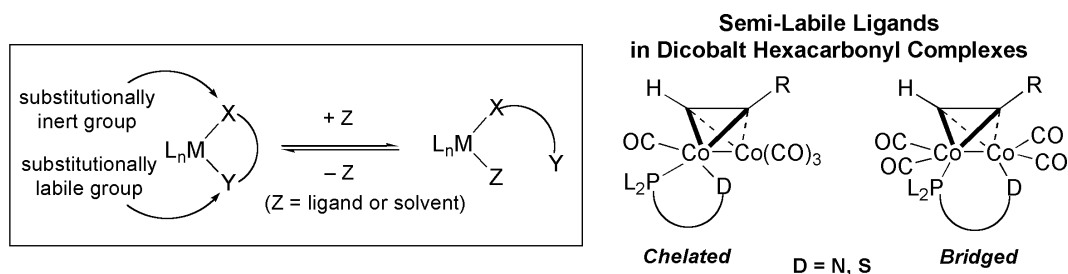
Scheme 8

### CONTROLLING THE ENANTIOSELECTIVITY OF PAUSON–KHAND REACTIONS WITH CHIRAL LIGANDS ON COBALT

Besides the control of reactivity, control of the enantioselectivity of the PKR is another topic of fundamental importance. Among the different methodologies implemented to this end, the use of chiral ligands on cobalt, introduced by Pauson and Brunner in 1988 [11], has the advantage of starting from immediately available precursors and that the adducts do not require further elaboration aimed at the removal of chiral auxiliaries. However, the initial versions of this approach, based on the use of phosphine ligands, presented some limitations (poor diastereoselectivity in complex formation, difficult separation of diastereomeric complexes, diminished reactivity) that have hampered their use in synthesis.

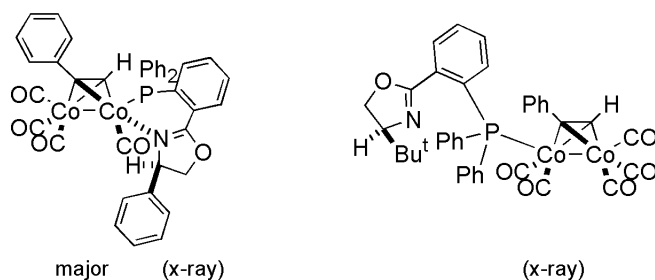
We wanted to understand the effect of a phosphine ligand on a cobalt carbonyl cluster and then try to generate more practical alternatives to this approach. There are some fundamental questions relative to phosphine-substituted cobalt carbonyl complexes, like the preferred site (axial or equatorial) for CO/PR<sub>3</sub> substitution, the overall effect on reactivity of CO/PR<sub>3</sub> substitution, and the directing effect on CO dissociation of an existing phosphine ligand, that theoretical calculations could answer. We decided to study by theoretical means the triphenylphosphine-substituted complexes of acetylene. Due to the size of these systems, a combined PM3(tm)/DFT approach was used. In agreement with previous experimental knowledge, the calculations predict that axial substitution is most favorable ( $\Delta E_{\text{eq/ax}} = 4.5 \text{ kcal.mol}^{-1}$ ) and that the overall effect of substitution will be a decrease in reactivity. Interestingly, the calculations also predict that further CO dissociation (and, hence, PK reactivity) is directed toward the unsubstituted Co(CO)<sub>3</sub> moiety.

For our experimental studies on ligand-enantiocontrolled PKR, we decided to explore the use of semi-labile ligands (Scheme 9) which should act similarly to the *chelating auxiliaries* we had introduced for diastereocontrol of the reaction some years ago [12].



Scheme 9

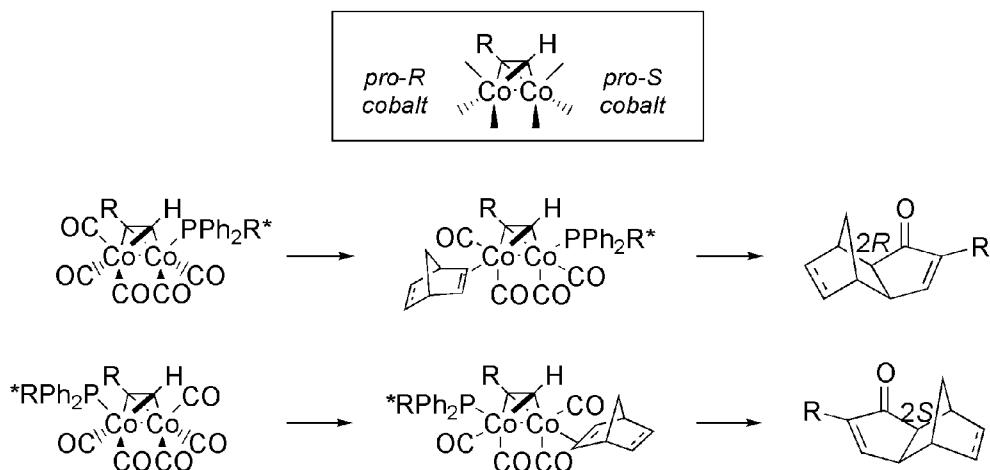
We started using phosphinoxazolines as semi-labile ligands. With the one derived from phenylglycinol, a remarkably diastereoselective complexation (85:15 d.r.) took place, and the diastereomeric complexes could be very easily separated. Interestingly, X-ray analysis of the major diastereomer showed that coordination in a chelated mode had taken place (Scheme 10). In any case, when this diastereomerically pure complex was treated with norbornadiene, a slow reaction took place, and the tricyclic adduct was obtained with 51% ee [13].



Scheme 10

With the phosphinoxazoline derived from *tert*-leucinol, readily separable complexes were again obtained. Probably because of the increased steric hindrance near the nitrogen atom, the ligand in these complexes act as monodentate (Scheme 10). For all the studied examples, the diastereomeric complexes exhibited pseudo-enantiomeric behavior in their CD spectra, thus indicating that they differ in the cobalt atom onto which the phosphine has coordinated. Since the X-ray structure could be determined in one case, a simple rule could be derived for the establishment of the absolute configuration of phosphine-substituted cobalt complexes from their CD spectra [14].

When the pseudoenantiomeric complexes participated in PKR, the existence of a stereospecific relationship was observed. Since we were able to correlate the absolute configuration of the product cyclopentenones with products of known stereochemistry, a correlation between the stereochemistry of the reacting complexes with that of the product cyclopentenones was also established (Scheme 11).



Scheme 11

According to the accepted mechanism of the reaction, this relationship means that the reacting olefin has coordinated to the cobalt atom do not bearing the phosphine ligand, and that the reaction has taken place at that precise cobalt atom, in complete agreement with the results of theoretical calculations discussed above.



tions on phosphine-substituted cobalt carbonyl complexes provide explanation for the mechanism of enantiodiscrimination in the PKR of these species. New chiral ligands for the efficient enantiocontrol of PKR have been developed and shown to act according to theoretical prediction.

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