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A Qualitative Molecular Mechanics Approach to the Stereoselectivity of Intramolecular Pauson-Khand Reactions

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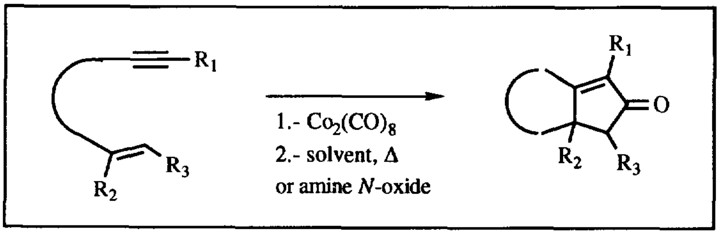
Abstract: Molecular mechanics calculations on the proposed cobaltacycle intermediates of the Pauson-Khand bicyclization of substituted 6-heptenynes are reported, providing the first theoretical evidence supporting the currently accepted mechanism for the Pauson-Khand reaction. In all instances, the experimentally observed configuration of the predominant bicyclo[3.3.0]oct-1-en-3-one product can be correlated with that of the most stable putative product-determining cobaltacycle, which contains a *trans*-fused five-membered ring Co-metallocycle.

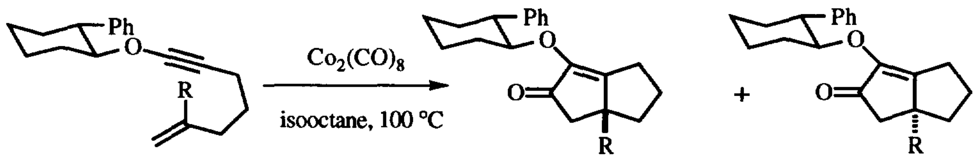
Introduction

The intramolecular version of the Pauson-Khand reaction,[1] which was first reported more than a decade ago by Schore,[2] constitutes a powerful method for the one-step construction of cyclopentenone-containing polycyclic systems from acyclic or monocyclic precursors, and has provided the key step in synthetic approaches to several complex natural[3] and non-natural[4] products (Scheme 1).



Scheme 1

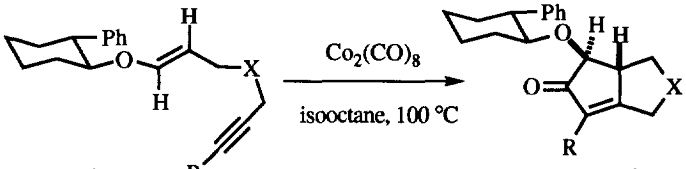
In the past few years, we have been involved in the development of reliable, practical asymmetric approaches to the Pauson-Khand reaction, either in the intramolecular[5,6] or in the intermolecular[7,8] version, by the use of covalently-linked external chiral auxiliaries. Among these chiral auxiliaries, *trans*-2-phenylcyclohexanol, which is readily available in both enantiomeric forms,[9] exhibits the broader applicability in the intramolecular Pauson-Khand reaction, either when attached to the acetylenic (Scheme 2, enynes **1a-b**)[5a] or the ethylenic (Scheme 3, enynes **4a-f**)[5b,c] ends of the enyne:



R = H **1a** **2a** 3.2 : 1 **3a**

R = CH_3 **1b** **2b** 1 : 1.2 **3b**

Scheme 2



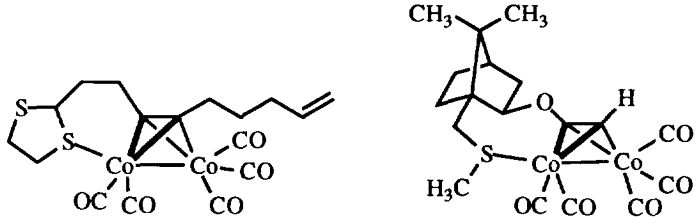
4 **5** (major)

entry	R	X	d.r.
a	H	$-CH_2-$	7 : 1
b	CH_3	$-CH_2-$	3.5 : 1
c	H	$-(CH_2)_2-$	10 : 1
d	CH_3	$-(CH_2)_2-$	11 : 1
e	H	-O-	4.5 : 1
f	CH_3	-O-	4 : 1

Scheme 3

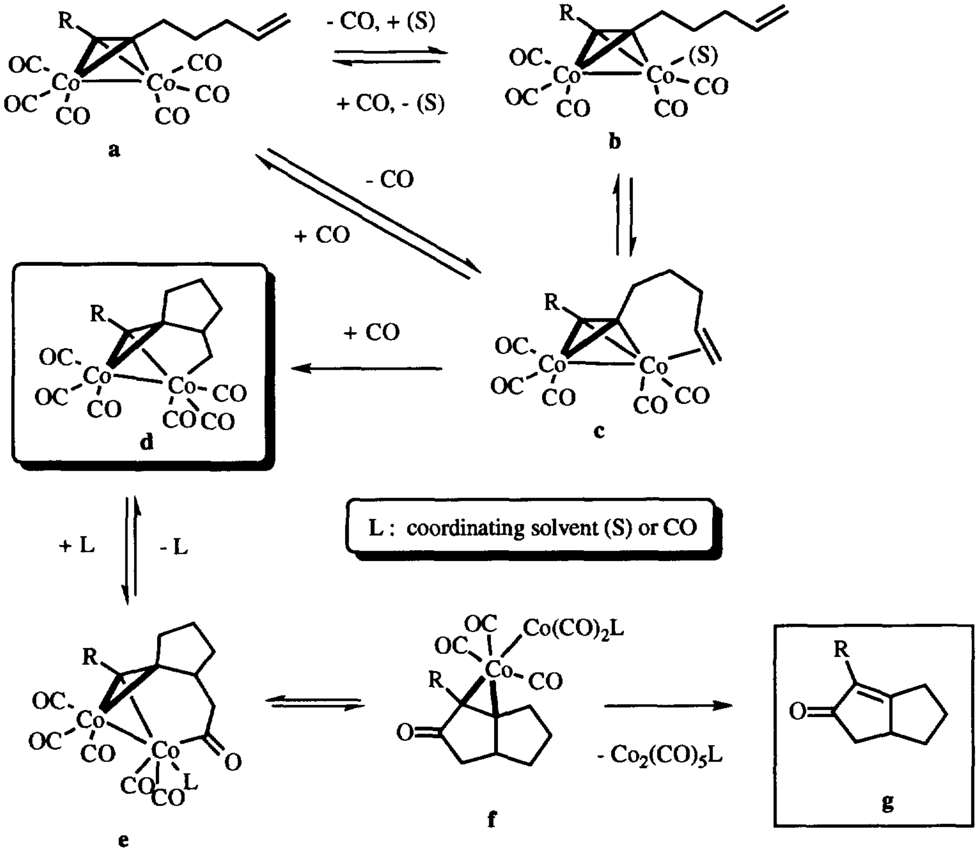
In sharp contrast with its amply recognized synthetic utility, practically nothing is known regarding the mechanism of the Pauson-Khand cyclization, excepting the fact that a previous stage of the reaction involves the initial formation of an hexacarbonyldicobalt-alkyne complex.[1]

The currently accepted mechanistic pathway for the transformation of this complex into the cyclopentenone product, initially proposed by Magnus,[10] is as follows (see Scheme 4 for the suggested cyclization mechanism of 6-heptenyne): The first step (from **a** to **c**) is a ligand exchange (olefin for CO) at one of the two stereoheterotopic cobalt atoms of the initial alkyne complex **a**. The necessary dissociative process can be induced either thermally or chemically, by means of a tertiary amine *N*-oxide.[11] Moreover, it is probable that a solvent-coordinated complex (**b**) is also involved in this stage of the reaction. Recently, support to this dissociative pathway has been provided by the identification of the pentacarbonyl complexes **6**[12] and **7**,[7] which can be regarded as intramolecularly trapped forms of the transient species **b** (Figure 1).



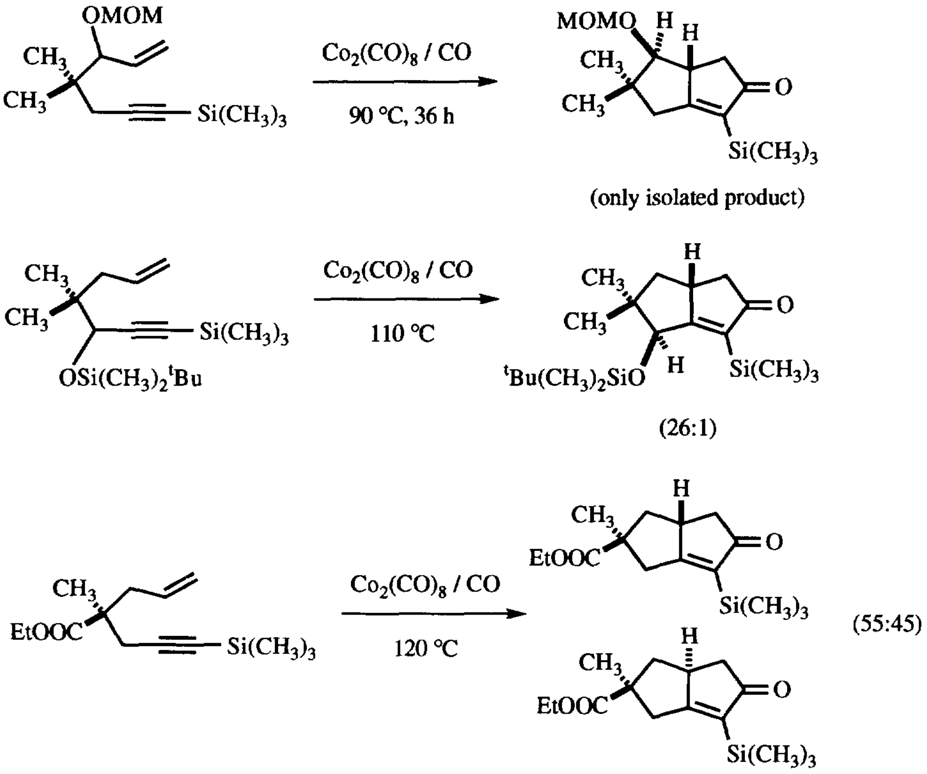
6 **7**

Figure 1: Chelated pentacarbonyldicobalt-alkyne complexes



Scheme 4

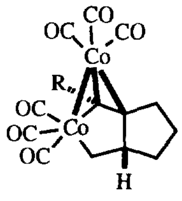
The second step (from **c** to **d**) is an insertion reaction of the π-complexed olefin into a cobalt-carbon bond, which results in the formation of the cobaltacycle **d**. This important step, in which the first of the three new single carbon-carbon bonds formed in the reaction is created, is usually assumed to be both rate-limiting and product-determining. The third step (from **d** to **e**) involves an insertion of carbon monoxide into a cobalt-carbon bond and generates the acyl complex **e**, which is irreversibly transformed into the final bicyclic enone **g** through reductive cobalt elimination from **e** to the complexed cyclopentenone **f**. This working mechanistic hypothesis has allowed the rationalization of diverse experimental facts, such as the regioselectivity of the intermolecular Pauson-Khand reaction,[1,13] the acceleration of the intramolecular process by substrate-attached ligands,[12,14] or the stereochemical outcome of the cyclization of 6-heptenynes possessing stereogenic carbon atoms at the allylic or propargylic positions (Scheme 5):[3c,10]



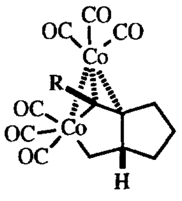
Scheme 5

Magnus[10] explained the observed preferential formation of bicyclooctenones in which the substituents at C_6 (corresponding to an allylic position of the precursor enyne) or at C_8 (propargylic position of the enyne) are *cis* to the hydrogen atom attached to C_5 by qualitatively analyzing the steric requirements of the transient cobaltacycle **d** (Scheme 4), whose formation from **c** is presumed to be the rate-determining step. In doing so, however, he introduced an additional assumption, which we shall examine presently.

A closer look at the bicyclic intermediate **d** reveals that it contains a cobaltacycle moiety that can be either *cis-* or *trans*-fused to a five-membered carbocyclic ring, so that we have in principle two possible diastereomeric cobaltabicyclo[3.3.0]octanes, which we shall call **d**-*cis* and **d**-*trans*:

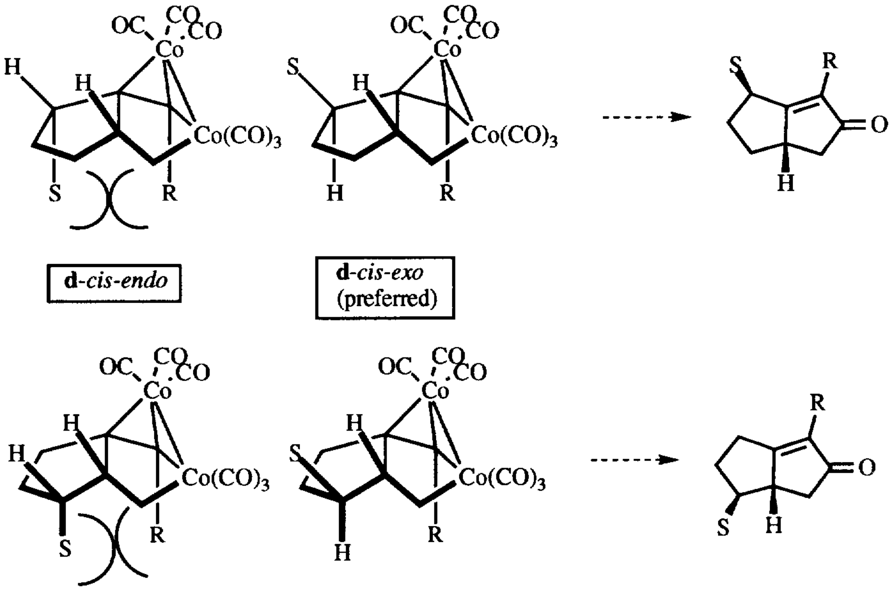


d - *cis*



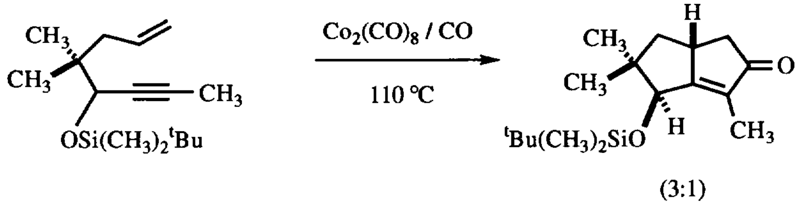
d - *trans*

The additional assumption introduced by Magnus is that the *cis*-fused cobaltacycle **d**-*cis* is thermodynamically more stable than the **d**-*trans*, and is exclusively (or at least majoritarily) formed by olefin insertion from **c**; if this is so, the triple-bond terminal substituent R lies necessarily in the concave (*endo*) face of the U-shaped **d**-*cis* intermediate (see Scheme 4), and its steric repulsion with the allylic or propargylic substituents (S) determines that in the preferred intermediates (which we are referring to as **d**-*cis-exo*) these substituents are located in the convex (*exo*) face, and lead to the predominant formation of an 6- or 8-*exo* substituted bicyclooctenone (Scheme 6). On the other hand, substituents at C_7 have only marginal stereodirective effects (last example in scheme 5).



Scheme 6

Reasonable support to this assumption comes from the fact that the steric bulk of the alkyne substituent R has an important effect on the diastereoselectivity of the reaction, so that a methyl group is much less effective than a trimethylsilyl (*Cf.* Schemes 5 and 7):[10]



Scheme 7

However, as recently demonstrated by Schore,[15] in the Pauson-Khand cyclization of 3,4-disubstituted-1-hepten-6-ynes the normal stereoselectivity of the reaction is greatly diminished (and can be even reversed in the case of bulky olefinic 4-substituents), a fact that cannot be adequately explained on the sole basis of steric interactions within an intermediate substituted *cis*-cobaltacycle. Moreover, the results of a recent theoretical study on bis(cyclopentadienyl)-3-zirconabicyclo[3.3.0]octanes[16] show, at various levels of theory (MM, ZINDO, DFT), that the *trans* isomer is 2.5-3.6 kcal mol^{-1} more stable than the *cis*.

In order to clarify the important issue of the relative stability of *cis* and *trans* cobaltacycles **d**, we decided to investigate from a theoretical point of view the cobaltacycles leading to each one of the two possible diastereomeric products in the cyclization of some key 6-heptenynes. Our main aim in this study was the search of a firmly grounded rationalization of the sense of the asymmetric induction observed in the Pauson-Khand bicyclization of (*trans*-2-phenylcyclohexyloxy)enynes.

We report in this paper our initial results in this area, which allow the rationalisation of diverse experimental facts relative to the stereochemistry of intramolecular Pauson-Khand reactions.

Results and Discussion

Given the size and complexity of the systems intended for study, we decided to use the MMX force field as implemented in the interactive molecular modelling program PCMODEL,[17] which we had found to give sensible results when applied to the search of conformational minima of the hexacarbonyldicobalt complexes of alkoxyacetylenes.[5a,6] In Figure 2 and Table 1, we show the most relevant geometric parameters of the cobalt-carbon cluster of the complexes as given by PCMODEL calculations, and we compare them to experimental values extracted from X-ray diffraction studies.[18] As it can be readily seen, the agreement is quite good, with the only exceptions of the carbon-carbon and cobalt-cobalt distances in the cluster which are systematically overestimated in PCMODEL by 0.10 and 0.07 Å, respectively.

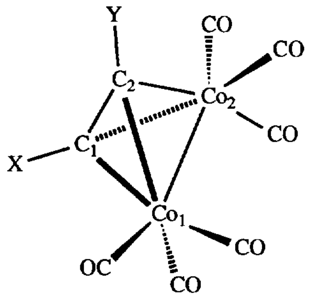


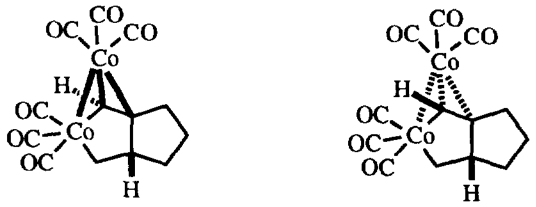
Figure 2: General structure of an (alkyne)hexacarbonyldicobalt complex

Table 1: Selected calculated (PCMODEL)[17] and experimental[18] geometrical parameters of the $C_2Co_2(CO)_6$ cluster (See Fig. 2).

Bond length or angle	PCMODEL	Experimental
C_1–C_2	1.466-1.477 Å	1.335-1.380 Å
Co_1–Co_2	2.541-2.546 Å	2.463-2.473 Å
$C_{(1,2)}$–$Co_{(1,2)}$	2.008-2.036 Å	1.970-2.011 Å
$Co_{(1,2)}$–CO	1.842-1.861 Å	1.798-1.830 Å
CO	1.135-1.154 Å	1.118-1.141 Å
Co_1–$C_{(1,2)}$–Co_2	77.8-78.1°	76.1-77.9°
$C_{(1,2)}$–$Co_{(1,2)}$–$Co_{(2,1)}$	50.3-51.3°	51.2-52.4°
C_1–$CO_{(1,2)}$–C_2	42.5-42.7°	38.9-39.2°
OC–$Co_{(1,2)}$–CO	99.6-104.7°	97.6-104.8°

A) Stereoselectivity in the Formation of 6-Substituted Bicyclooctenones

As an starting point in our study, we calculated the relative stabilities of the four possible cobaltacyclic intermediates involved in the first reaction shown in Scheme 5, in order to see if, as assumed by Magnus,[10] the **d**-*cis-exo* cobaltacycle was significatively more stable than the other three. As a preliminary step, we obtained the MMX-optimized structures corresponding to the unsubstituted *cis*- (**8**) and *trans*-cobaltacycles (**9**) (Figure 3).



8 (*cis*) $E_{rel} = +3.46$ kcal mol^{-1}

9 (*trans*) $E_{rel} = +0.00$ kcal mol^{-1}

Figure 3: Relative energies of diastereomeric cobaltacycles **8** and **9**.

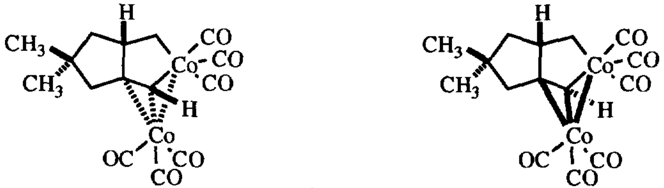
Contrary to our initial expectations, the MMX-energy value for the *trans* isomer **9** was *circa* 3.5 kcal mol^{-1} lower than that of the *cis*-cobaltacycle **8**. Interestingly, this same behaviour was observed for several pairs of substituted cobaltacycles; irrespective of the number and position of the substituents, the *trans* cobaltacycle exhibited a lower (by 2-4 kcal mol^{-1}) MMX-energy value than the *cis* (Figure 4).

trans $E_{rel} = +0.00$ kcal mol $^{-1}$

cis $E_{rel} = +1.60$ kcal mol $^{-1}$

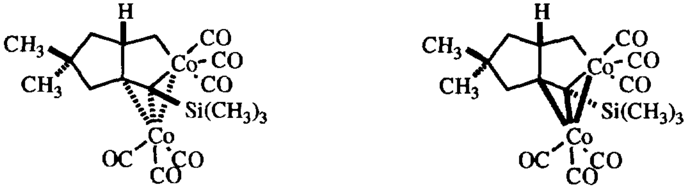
trans $E_{rel} = +0.00$ kcal mol $^{-1}$

cis $E_{rel} = +2.82$ kcal mol $^{-1}$



trans $E_{rel} = +0.00$ kcal mol $^{-1}$

cis $E_{rel} = +3.60$ kcal mol $^{-1}$

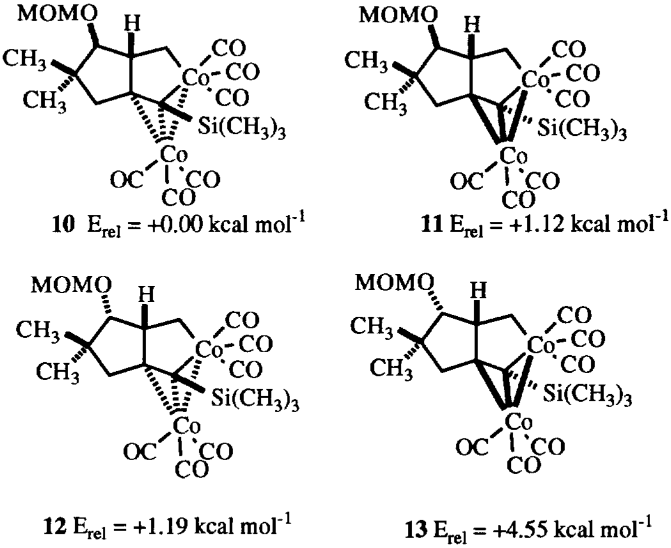


trans $E_{rel} = +0.00$ kcal mol $^{-1}$

cis $E_{rel} = +2.07$ kcal mol $^{-1}$

Figure 4: Relative energies of *cis/trans* pairs of substituted cobaltacycles

Finally, the MMX optimization of the four intermediate complexes (**10**-**13**) presumably involved in the first of the intramolecular Pauson-Khand cyclizations depicted in Scheme 5 produced the energy ordering shown in Figure 5. In the two most stable cobaltacycles, **10** and **11**, the relative stereochemistry between the methoxymethyl substituent and the bridgehead hydrogen is *cis*, as in the major diastereomer isolated from the reaction. Thus, the preferential formation of the bicyclooctenone depicted in Scheme 5 can be explained by the kinetically controlled passage through either the *trans*-cobaltacycle **10** or the *cis*-cobaltacycle **11**.



10 $E_{rel} = +0.00$ kcal mol^{-1}

11 $E_{rel} = +1.12$ kcal mol^{-1}

12 $E_{rel} = +1.19$ kcal mol^{-1}

13 $E_{rel} = +4.55$ kcal mol^{-1}

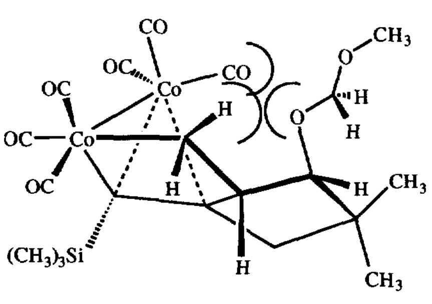
Figure 5: Relative energies of diastereomeric cobaltacycles **10**-**13**.

A detailed analysis of the geometric characteristics of the four cobaltacycles **10**-**13** reveals two important points (see Figure 6):

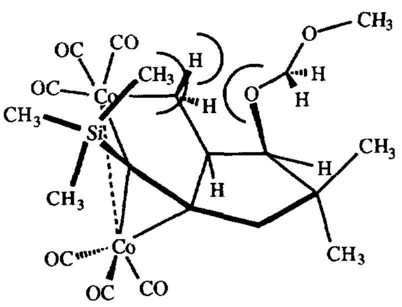
i) As first suggested by Magnus, the origin of the energetic preference of the *exo-cis* cobaltacycle **11** over the *endo-cis* cobaltacycle **13** is largely determined by the steric repulsions experienced by the allylic substituent when disposed in the concave face of the molecule.

ii) However, and more unexpectedly, the *trans*-cobaltacycle **12** is also substantially destabilized with respect to its epimer **10** by means of steric interferences of the allylic substituent with other portions of the rather twisted molecule.[19]

In conclusion, the calculated stabilities of the cobaltacyclic intermediates allow a qualitative interpretation of the stereochemical outcome of the Pauson-Khand reaction in a real case. However, the intermediacy of *trans*-cobaltacycles cannot be ruled out for stability reasons, at variance with the currently accepted Magnus' mechanistic hypothesis. At the light of these results, we undertook the molecular mechanics study of the intermediate cobaltacycles involved in the intramolecular Pauson-Khand reaction of the (1*S*,2*R*)-2-phenylcyclohexanol-derived enynes **1a**, **1b** (Scheme 2) and **4a** (Scheme 3), in order to see if also in this case the relative stabilities of the cobaltacycles allowed a qualitative rationalization of the experimental results obtained by us.



12

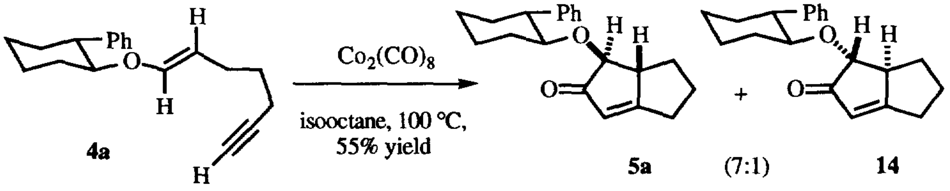


13

Figure 6: Schematic representation of the most important repulsive interactions experienced by the allylic enyne substituent in cobaltacycles 12 and 13.

B) Stereoselectivity in the Cyclization of Enol Ether type 6-Heptenynes Derived from trans-2-Phenylcyclohexanol

Let us consider in the first place the bicyclization of enyne **4a**, which leads to a readily separable 7:1 mixture of the 4-alkoxybicyclo[3.3.0]oct-1-en-3-ones **5a** and **14** (See Scheme 8).



Scheme 8

As a working model, we have shown that the absolute configuration of the major diastereomer **5** obtained in all of the reactions performed within this approach (Scheme 3) can be predicted by assuming an extended *s-trans* conformation of the enol ether moiety of the alkoxyenyne complex, so that the ($C\alpha$)-*si*, ($C\beta$)-*re* face of the double bond is appreciably shielded by the phenyl group of the chiral auxiliary and the attack by the cobalt cluster is preferentially directed towards the ($C\alpha$)-*re*, ($C\beta$)-*si* face of the alkene.[5b,c] However, at the light of the results described in the preceding section, it is clear that a more satisfactory rationalization of the observed stereoselectivity should involve the calculation of the relative stabilities of the product-determining intermediates.

Turning therefore our attention to the intermediate cobaltacycles, and bearing in mind the stereospecificity of the Pauson-Khand reaction with respect to the olefin moiety, we have again in this case four possible diastereomeric cobaltacycles **15-18**, two of them (**15** and **17**) leading to the major product **5a** and the other two (**16** and **18**) leading to the minor product **14**. The most stable conformations and the relative energies of the cobaltacycles, according to the PCMODEL results, are shown in Figure 7:

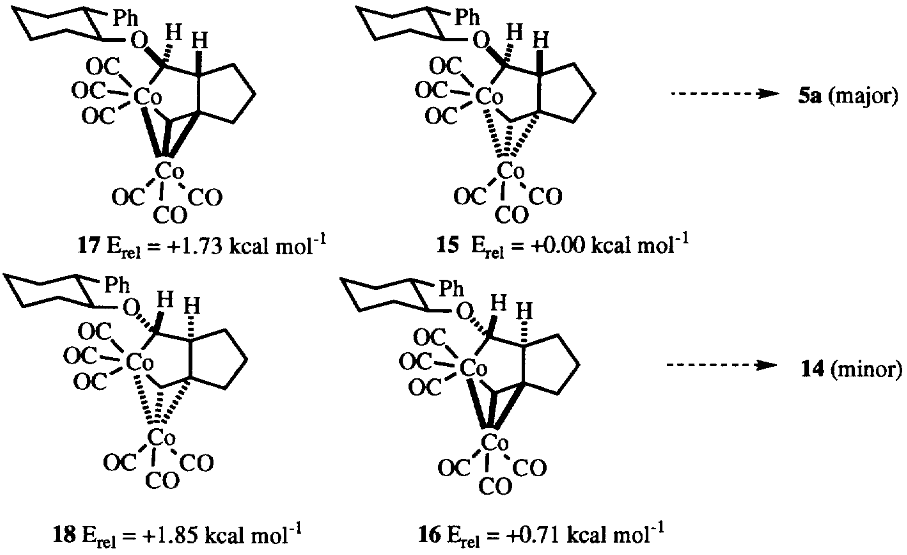


Figure 7: Relative energies of diastereomeric cobaltacycles **15-18**.

As observed in the case of intermediates **10-13**, the *trans*-cobaltacycles **15** and **16** are more stable than the *cis* (**17**,**18**); within each pair, the most stable (**15** and **17**) are those leading to the major product (**5a**). It is also worth noting that in this case the *trans*-cobaltacycles appear to be more stereodiscriminating than the *cis*, since the energy differences are higher in the former. While these results are in qualitative agreement with the observed stereoselectivity of the reaction, it is more difficult to find an easy explanation for them. An inspection of the geometrical features of the intermediates shown in Figure 7 reveals however that both "stable" cobaltacycles **15** and **17** adopt a very similar *staggered* conformation for the connecting CH-O-CH moiety, in which the endocyclic cobalt-tricarbonyl moiety occupies and almost *antiperiplanar* position with respect to the carbon atom of the auxiliary bearing the phenyl group (see Figure 8); on the other hand, one can see that for both "unstable" intermediates **16** and **18** the bulky cobalt and phenyl groups occupy closer positions in space. Thus, the preferred configuration of the stereogenic center adjacent to the cobalt atom will be that in which the tricarbonylcobalt group is disposed as far as possible from the phenyl ring. It is worth noting that in fact, an MM2 calculation on *trans*-1-isopropoxy-2-phenylcyclohexane shows that in the energetically more stable conformer the CH-O-CH moiety exhibits an *staggered* conformation almost identical to that of the present cobaltacycles, with a dihedral angle value of 46° between the two CH bonds (42.5° for **15**; 45° for **17**).

In summary, the relative energies of the cobaltacycles **15-18** can be rationalized on the basis of the conformational bias imparted to them by the *trans*-2-phenylcyclohexyloxy substituent, and lead to the correct prediction of the relative configuration of the major diastereomers obtained in the intramolecular Pauson-Khand cyclizations of enynes **4a-f**.

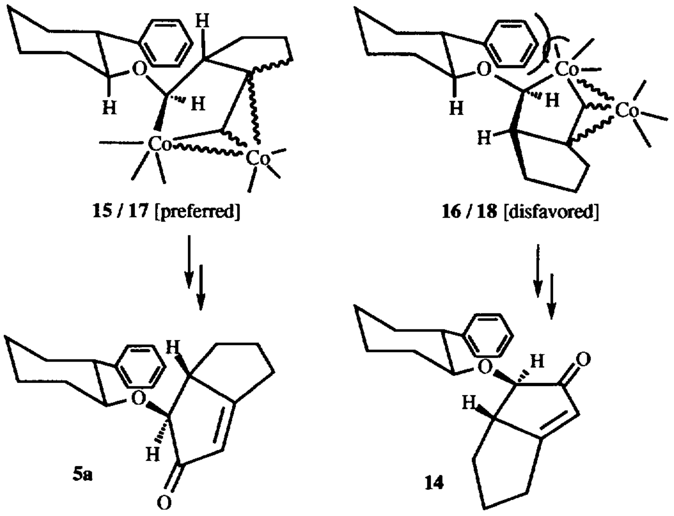
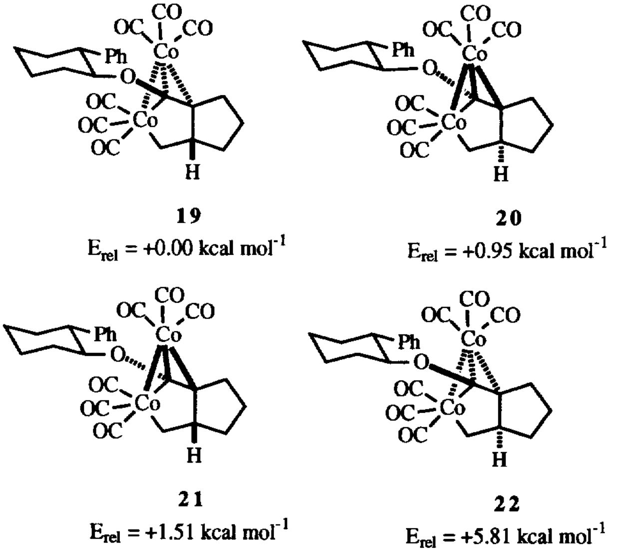


Figure 8: Schematic representation of the discriminating steric interactions in cobaltacycles **15-18**.

C) Stereoselectivity in the Cyclization of Ynol Ether type 6-Heptenynes Derived from trans-2-Phenylcyclohexanol

Our next goal was to investigate if the relative stabilities of the intermediate cobaltacycles could also account for the observed stereochemical preference of the reaction when the (1*S*,2*R*)-2-phenylcyclohexyloxy auxiliary was linked to the acetylenic portion of the enyne (Scheme 2). In the cyclization of enyne **1a**, we have again two pairs (*trans*, *cis*) of possible metallacycles **19-22**. These are shown in Figure 9, together with their relative MMX energies.



19
E_{rel} = +0.00 kcal mol^{-1}

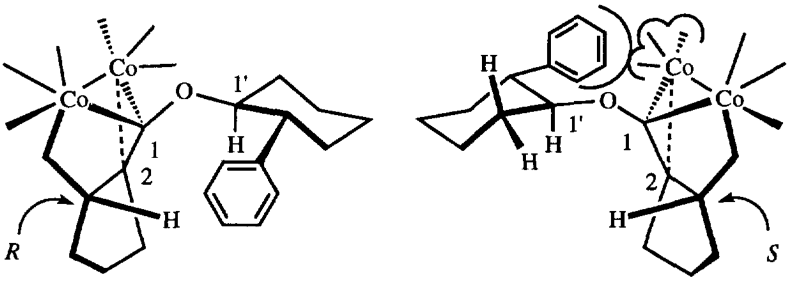
20
E_{rel} = +0.95 kcal mol^{-1}

21
E_{rel} = +1.51 kcal mol^{-1}

22
E_{rel} = +5.81 kcal mol^{-1}

Figure 9: Relative energies of the diastereomeric cobaltacycles **19-22**.

In this case, the experimental results are also in accordance with the calculated stabilities of the cobaltacycles **19**-**22**, since within each pair the most stable cobaltacycles (**19** *vs.* **20** for the *trans* and **21** *vs.* **22** for the *cis*) are those who correlate with the major bicyclooctenone **4a**, having *R* configuration at C_5 (see Scheme 2). The origins of the energy order are however difficult to discern, since it is not possible, upon inspection of the optimized structures, to select a single dominant steric interaction between the cobaltacyclic and cyclohexyl moieties that is common to both *cis* - and *trans*-cobaltacycles. It is interesting to note, nevertheless, that if we restrict ourselves to the *trans*-cobaltacycles **19** and **20**, they both adopt a very similar conformation, in which the $C_{1'}$-H bond of the alkoxy group is approximately eclipsed with the C_1-C_2 bond of the cobaltacycle (See Figure 10); in this way, the intermediate **20** is destabilized with respect to **19** by means of a repulsive contact between the exocyclic tricarbonylcobalt and phenyl groups.

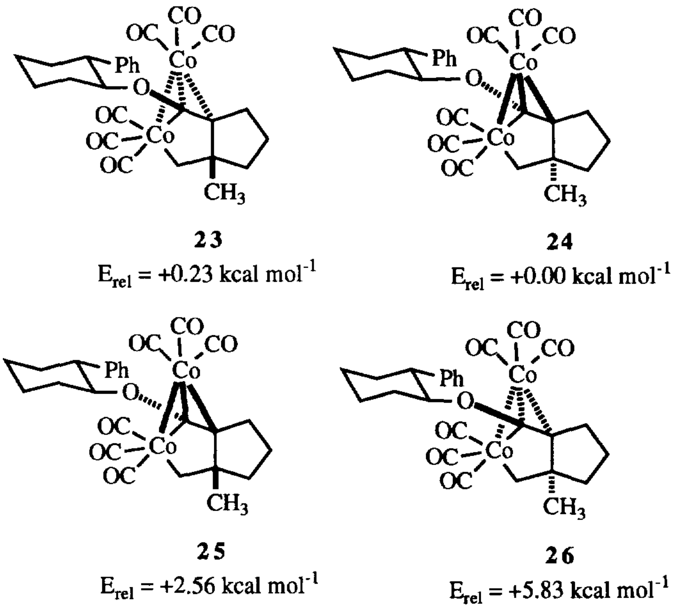


19 [preferred] **20** [disfavored]

Figure 10: Schematic representation of the discriminating steric interactions between diastereomeric cobaltacycles **19** and **20**.

An intriguing experimental observation concerning the Pauson-Khand bicyclization of chiral alkoxyenynes lies in the fact that the diastereoselectivity of the reaction is greatly diminished upon increasing substitution at C_2 of the enyne. Thus for instance, while the cyclization of **1a** gives predominantly the (5*R*)-bicyclooctenone **2a**, the cyclization of **1b** transcurs with almost no selectivity (Scheme 2).[5a] As a final and more stringent test of the reliability of our approach, we set out to calculate the relative stabilities of the four possible methyl-substituted cobaltacycle intermediates **23**-**26** corresponding to the intramolecular Pauson-Khand reaction of alkoxyenyne **1b** (Figure 11).

Interestingly enough, the results of the calculation reveal that in this case the *cis*-cobaltacycles **25** and **26** are not likely intermediates of this particular reaction, since they are both of relatively high energy; moreover, the energy difference between the two *trans*-cobaltacycles **23** and **24** is much less than that between the unsubstituted cobaltacycles **19** and **20**, in perfect agreement with the small diastereoselectivity observed in the cyclization of **3b**. In addition to that, the assumption that the conformational preferences of **23/24** are very similar to those of **19/20** offers a simple explanation for the diminished energy difference between the **23/24** pair.



23
$E_{rel} = +0.23$ kcal mol^{-1}

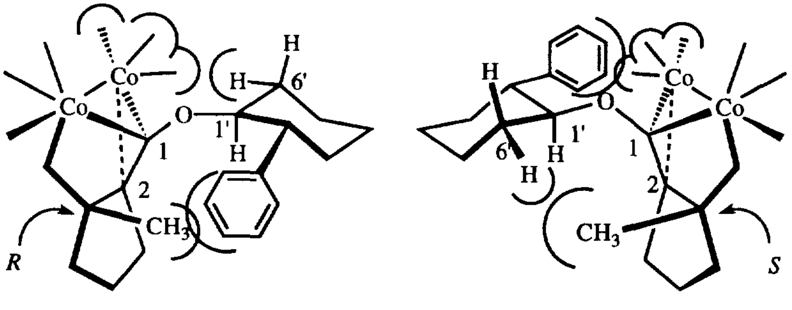
24
$E_{rel} = +0.00$ kcal mol^{-1}

25
$E_{rel} = +2.56$ kcal mol^{-1}

26
$E_{rel} = +5.83$ kcal mol^{-1}

Figure 11: Relative energies of the diastereomeric cobaltacycles **23-26**.

In effect, one can easily see (Figure 12) that in the cobaltacycle **23**, the conformation in which the bulky exocyclic tricarbonylcobalt and phenyl moieties lie in opposite sides of the molecule, leads to a destabilizing interaction between the C_5-methyl and the phenyl group. It is worth noting that any attempt to diminish this repulsive interactions within the cobaltacycle **23** would increase the close contacts between the auxiliary and tricarbonylcobalt moieties. Similarly, the repulsive interaction between the exocyclic tricarbonylcobalt and phenyl groups in cobaltacycle **24** cannot be lessened by rotation around the C_1-O bond, since this would lead to a close contact between the C_5-methyl and the $C_{6'}$-hydrogens. We can thus see that both cobaltacycles **23** and **24** are subject to quantitatively similar destabilizing interactions, and accordingly have very close steric energy values.



23 **24**

Figure 12: Schematic representation of the repulsive interactions in cobaltacycles **23** and **24**.

Conclusions

We can thus summarize the main conclusions of the present work as follows:

i) Simple, qualitative molecular mechanics calculations on the putative product-determining cobaltacycle intermediates of the Pauson-Khand bicyclization of several chain-substituted 6-heptenynes allow a rationalization of the experimentally observed diastereoselectivities, in the sense that *the configuration of the major bicyclo[3.3.0]oct-1-en-3-one product can always be correlated with that of the more stable cobaltacycle.* This constitutes the first theoretical evidence supporting the mechanism of the Pauson-Khand reaction proposed by Magnus.[10]

ii) At the same time, and at variance to what is currently accepted, the most stable stereochemistry of the newly formed cobaltacyclopentane ring appears to be *trans*.

The present findings pave the way for computationally more advanced calculations, which would both expand our knowledge of the mechanism of the Pauson-Khand reaction and increase our predictive power on the regio- and stereochemical issues of this synthetically important process.

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19.- It is worth noting that in the *trans*-cobaltacycles, the substituent at the alkyne terminus plays only a minor role in the stereochemical control of the reaction, at variance with the commonly accepted model depicted in Scheme 6. It should be pointed out however that while the importance of the steric bulk of the terminal alkyne substituent is well documented for the case of 8-substituted bicyclooctenones, the available experimental data do not support the existence of such an effect in intramolecular Pauson-Khand cyclizations leading to 6-substituted bicyclooctenones.[1e] In fact, replacement of the trimethylsilyl by a methyl substituent in the cobaltacycles **10, 11, 12** and **13** led to the following energy ordering (E_{rel}, kcal mol^{-1}): **10**, +0.00; **11**, +1.43; **12**, +1.18; **13**, +3.11, which shows that the bulk of the terminal alkyne substituent alone does not determine the relative stability of the diastereomeric cobaltacycles.

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