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On the mechanism of rhodium-catalyzed [6+2] cycloaddition of 2-vinylcyclobutanones and alkenes

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ABSTRACT

The intramolecular [6+2] cycloaddition mechanism of 2-vinylcyclobutanones and alkenes catalyzed by the $[Rh(CO)_2Cl]_2$ rhodium dimer has been studied using density functional theory, comparing this multistep process with the one-step reaction in the absence of catalyst. According to our results the calculated mechanism agrees with what was previously experimentally suggested. Calculations have also allowed to explain the reaction selectivity.

1. Introduction

Cycloadditions are usually described as pericyclic reactions characterized by two molecules (or two parts of the same molecule) coming together to form two new σ-bonds at the end of both components, joining them to form a ring. However, not all cycloadditions are pericyclic. When in a cycloaddition charged or radical intermediates are involved or when the cycloaddition result is obtained in a series of reactions steps, they are sometimes called *formal cycloadditions*.[1] In particular, *carbocyclations* are ring-forming processes that involve the formation of new carbon–carbon bonds via carbometallation. The rhodium-catalyzed [6+2] cycloaddition of 2-vinylcyclobutanones can be described with these two terms.[2]

Transition metals like cobalt, iron, molybdenum, nickel, palladium, rhodium, ruthenium, titanium, and zirconium are used in carbocyclizations.[3,4] Rhodium(I) complexes have been employed in the last decade in intra and intermolecular [m+n] cycloadditions. Their versatility allowed them to be used also in multicomponent [m+n+o+…+x] reactions.[5] There are many rhodium catalyst that can be used in these kind of cycloadditions; in concrete, the $[Rh(CO)_2Cl]_2$ rhodium dimer is an efficient catalyst for [5+2], [6+2] or [5+2+1] reactions.[6]

A way to obtain intramolecular carbocyclic ring enlargement reactions in organic synthesis would be the fusion of two small rings into a single larger one. This is possible due to the ability of some transition metals like rhodium to insert into strained rings. Huffman and Liebeskind[7] described an intramolecular variant of this strategy for synthesis of seven- and eight-membered ring dienones. This strategy was used by Wender and co-workers[2] to report a new [6+2] cycloaddition of 2-vinylcyclobutanones and alkenes for the synthesis of eight-membered rings (see Fig. 1). They proposed the most probable mechanism considering some

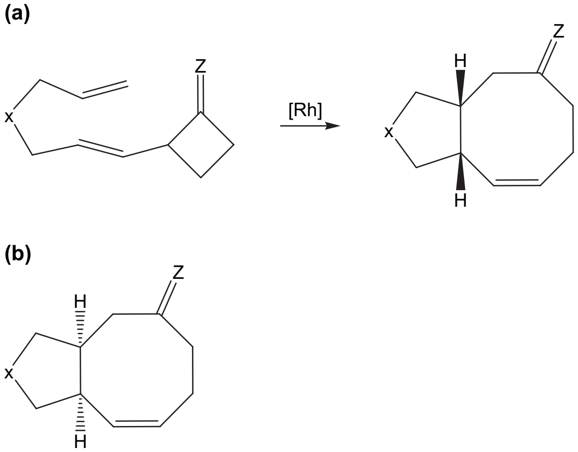

Figure 1. (a) General [6+2] intramolecular cycloaddition between vinylcyclobutanones and alkenes ([6+2] cycloaddition studied in this job: X=O, Z=O). The obtained diastereomer was labeled as **Pcis1**. (b) Diastereomer **Pcis2**.

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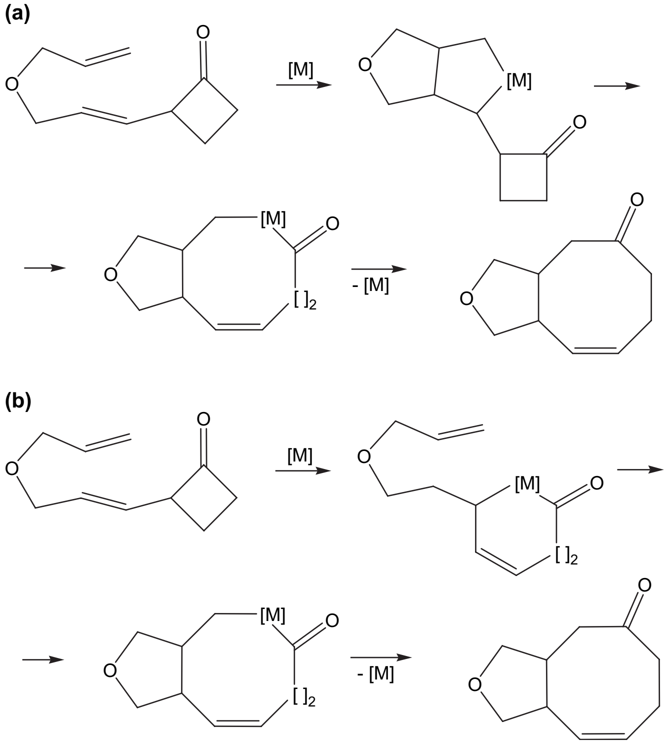

Figure 2. Two possibilities for the reaction mechanism of the [6+2] intramolecular cycloaddition of vinylcyclobutanones and alkenes.

experimental evidences, although there are several mechanistic hypotheses for this transformation.[8] Making an analogy between other similar cycloadditions and the [6+2] case, there are two main possibilities (see Fig. 2). It is important to remark that in the studied cases, cis products are formed exclusively or preferentially.

In this work, density functional theory calculations were performed in order to study the mechanism of this [6+2] cycloaddition and to analyze the role of the rhodium catalyst comparing with the same reaction in absence of catalyst. The reaction selectivity was also explained.

2. Computational details

Calculations were done with DFT (*density functional theory*) employing B3LYP hybrid functional. B3LYP[9] combines the Slater exchange functional corrected by Becke with the correlation potential of Vosko, Wilk, and Nusair corrected by Lee, Yang, and Parr. 6-31G(d,p) Pople's basis set was used for C, O, H, and Cl atoms, and the *effective core potential* LANL2DZ[10] was used for Rh atom. IRC[11] (*intrinsic reaction coordinate*) were obtained at the same level. All the stationary points were characterized as minimum or transition state by the vibrational frequency analysis, using analytical second derivatives. All calculations were carried out with Gaussian03 program.[12]

3. Results and discussion

3.1. Rhodium-catalyzed [6+2] cycloaddition in gas phase

In the first studies of the catalyzed intramolecular [5+2] cycloaddition of alkenes and vinylcyclopropanes[8c,d] the authors proposed two main options for the reaction mechanism, analogues to those shown in Figure 2. For [5+2] intermolecular cycloaddition of the alkynes and vinylcyclopropanes[8b] the same options were analyzed from a theoretical point of view. Basically, the two formulated mechanisms are based on the expectation that transition metal catalyst could form a metallacyclo in this kind of systems.[13] The difference between them is where the rhodium catalyst prefers in first place to form an intermediate, with the π-system or with the vinylcyclopropane. Attending to the obtained results based on very different reasons, it seems that in the intramolecular case rhodium prefers to react first with the alkene and in the intermolecular case rhodium prefers to interact with the vinylcyclopropane. Translating this discussion to our [6+2] case, the most probable way seems to be the initial formation of a metallacyclopentene with the π-system and then to form a bicyclo interacting with the cyclobutanone (a-pathway in Fig. 2). The reason is that the product is obtained as a single diastereomer, because as we commented above, in the studied reaction cis product was formed exclusively. In concrete, we have labeled the obtained cis-diastereomer as **Pcis1**. The other possible cis product (**Pcis2**) was not obtained, and we will discuss this result later.

Figure 3 shows the intermediate and transition state geometries for the rhodium-catalyzed [6+2] cycloaddition in gas phase to obtain the diastereomer **Pcis1**. The $[Rh(CO)_2Cl]_2$ dimer is in equilibrium with two monomeric units and the rhodium atom bonded to two ligands, CO and Cl, is the active species.[14] The complex **I1** shows an arrangement in which the transition metal is coordinated to the two parallel double bonds. Considering those multiple bonds as two different ligands, rhodium adopts a planar-square geometry. From the point of view of the transition metal, **I1** is a $16e^-$ complex. In spite of the known '$18e^-$ electron rule', it is usual in Rh(I) and in other d^8 metals from the 8–11 groups to adopt $16e^-$.[15]

Through the transition state **TS2**, **I3b** is obtained. **I3b** is a structure with two five-membered cycles, one of them is the mentioned metallacyclopentene. The disposition of the cyclobutanone is parallel to the metallacyclopentene's plane. This situation is more stable than in **I3a**, another conformer, in which the cyclobutanone's plane is perpendicular to the metallacycle's plane. From **I3b** to **I8b** the reaction goes through smaller barriers than from **I3a**. The metallacyclopentene is transformed into an eight-membered one, more strained in the case of **I5b** than in the **I5a** one, and the **I5c** conformer connects the two pathways. In the intermediates **I7a** and **I7b** the rhodium was already almost eliminated; the main difference between these two conformers is the angle between the rhodium ligands. The rhodium atom is far away from the bicyclo in **I8a**, but the most stable complex is **I8b**, where it can interact with the two oxygen atoms of the **Pcis1** product. A new molecule of vinylcyclobutanone **VCBcis1** will interact with the rhodium catalyst beginning the catalytic cycle again. The rhodium trend of forming strong bonds with oxygen is well known.

Taking a look in to the energy barriers obtained with the B3LYP/6-31G(d,p)+LANL2DZ calculations (see Table 1 and Fig. 4) it is obvious that the reaction will probably go through the b-pathway, since the rate-limiting steps (RLS)[16] of a and b pathways are really different. It is not only that in the a-pathway **I5a** is more stable than the product; moreover, the energy barrier of **TS6a** from **I5a** is almost 50 kcal/mol. The highest barrier in the b-pathway is less than 32 kcal/mol (the first transition state of the path) and the RLS corresponds with the way from **I3b** to **TS6b**. However, this [6+2] cycloaddition is an expensive process from the energetic point of view, even going through the most favorable pathway. This is in agreement with the experimental conditions to achieve the product. We have also checked that B3LYP method is appropriated for these kind of reactions, because another specific DFT functionals for organometallic chemistry (MPWLYP1M) have been proved for us in other similar rhodium-catalyzed cycloadditions giving similar results but with more computational cost.[17]

The alternative mechanism is to form first a rhodacycle with the vinylcyclobutanone. Note that if the first intermediate of the reaction was a structure of this type (see Fig. 5) then it would be

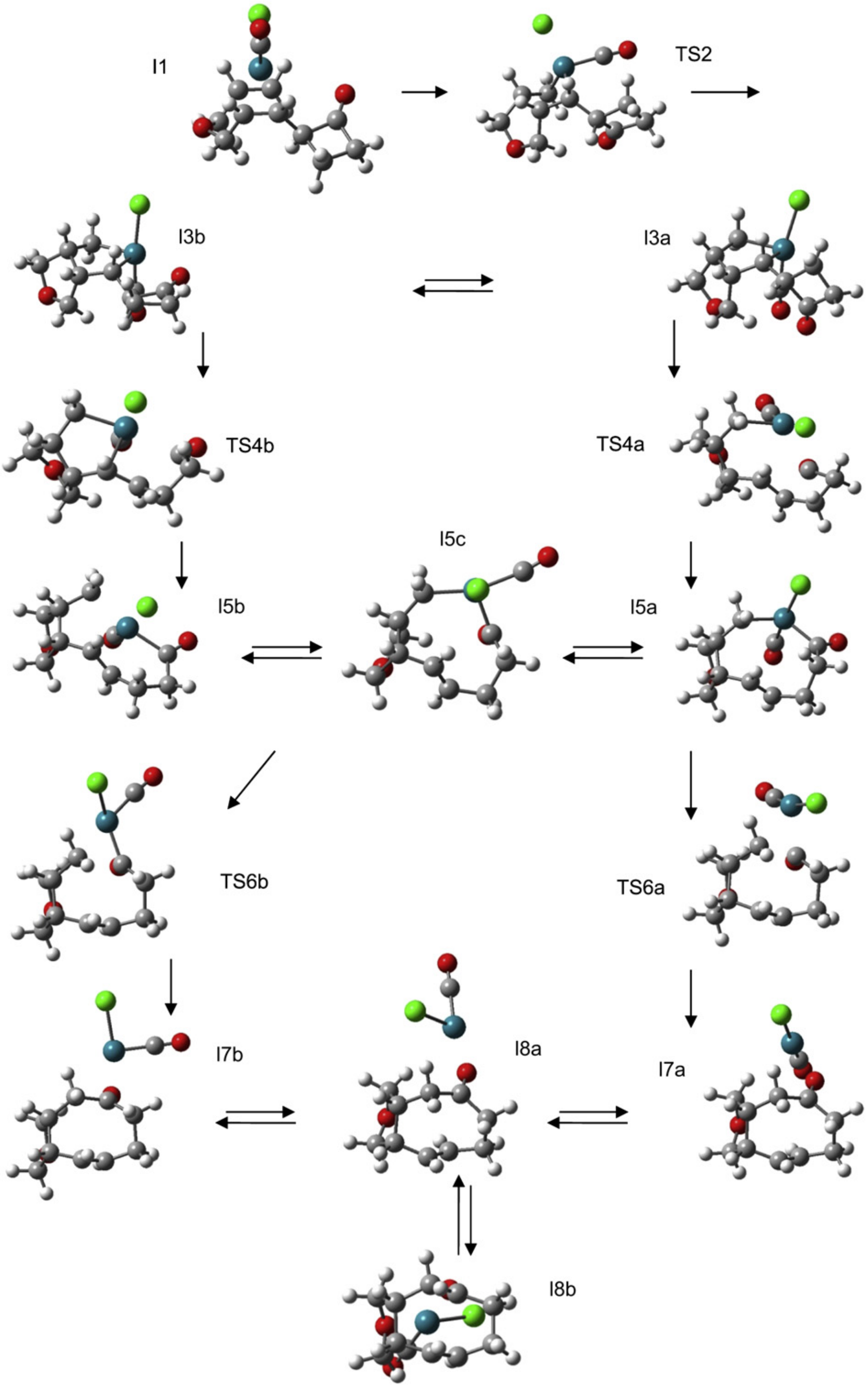

Figure 3. Intermediate and transition state geometries for the intramolecular [6+2] rhodium-catalyzed cycloaddition in gas phase at B3LYP/6-31G(d,p)+LANL2DZ level.

possible to form at least a certain amount of the trans-diastereomer product. In the other mechanism rhodium interacts over or below the plane of the two double bonds, but here the olefin is free for bonding in different ways. Nonetheless, only the cis-diastereomer is observed, then the conclusion is that this alternative mechanism does not take place.

We have also seen that in this cycloaddition only the diastereomer **Pcis1** is obtained as product. We performed the cis2-pathway at the same level to compare with the cis1-pathway and to analyze the diastereoselectivity of the reaction. Table 2 shows the energies for the calculated structures. At a glance, it seems that the energy barriers are similar or lower than in the cis1 case. A more detailed analysis reveals that although the cis2 product **I8a** is more stable than the **I1** starting complex, the **I5a** (for the a-pathway) and **I3b** (for the b-pathway) energies are below the energy of the product. That is, the last steps of the reaction are endothermic in the cis2-pathway. Moreover, attending to thermodynamics, **Pcis2** is 3.70 kcal/mol less stable than **Pcis1** (see absolute energies in Supplementary data).

Figure 6 shows the structures of the last complex in cis1 and cis2 pathways, which are **I8b** for cis1 and **I8a** for cis2. Note that in **I8b**-cis1 the rhodium atom adopts a planar-square geometry bonding

Table 1
Relative electronic energies in kcal/mol for the catalyzed reaction in gas phase at B3LYP/6-31G(d,p)+LANL2DZ level to obtain the Pcis1 product

	Δ*E* (kcal/mol)	ΔE_{ZPE} (kcal/mol)
I1	0.00	0.00
TS2	32.33	31.78
I3a	−2.97	−1.50
I3b	−7.25	−5.64
TS4a	33.04	32.96
TS4b	21.74	22.01
I5a	−9.22	−7.89
I5b	9.67	10.67
I5c	7.24	7.71
TS6a	41.13	41.82
TS6b	28.45	29.10
I7a	5.03	7.57
I7b	2.15	4.24
I8a	1.63	1.14
I8b	−10.72	−7.50

ZPE=zero point energy correction.

with the two oxygen atoms of the bicyclo and in the **I8a**-cis2 case this possibility does not exist. The oxygen of the ether group is far away from the catalyst and rhodium can only bond with the oxygen of the carbonyl group.

3.2. Non-catalyzed [6+2] cycloaddition in gas phase

It is interesting to analyze the particular problems of this [6+2] cycloaddition. The first attempts to achieve this eight-membered rings using vinylcyclobutanes were unsuccessful[2] and it was necessary to modify by substitution the cyclobutane unit to obtain the desired ring. We have compared the cycloaddition of vinylcyclobutanone in absence of catalyst with the catalytic process, and the vinylcyclobutane cycloaddition in absence of catalyst was also performed. Figure 7 and Table 3 show the reactant, transition state, and product energies for the non-catalyzed [6+2] cycloaddition in gas phase using B3LYP functional with 6-31G(d,p) basis set in three different cases: (1) to obtain the **Pcis1** product starting from **VCBcis1**; (2) to obtain the **Pcis2** product starting from **VCBcis2**; and (3) to obtain the analogue to **Pcis1** but with vinylcyclobutane.

The comparison between these hypothetical reactions shows that the barrier increases more than 13 kcal/mol changing the functional group of the reactant. Vinylcyclobutane is clearly a poorer reactant than vinylcyclobutanone, even adding a catalyst.

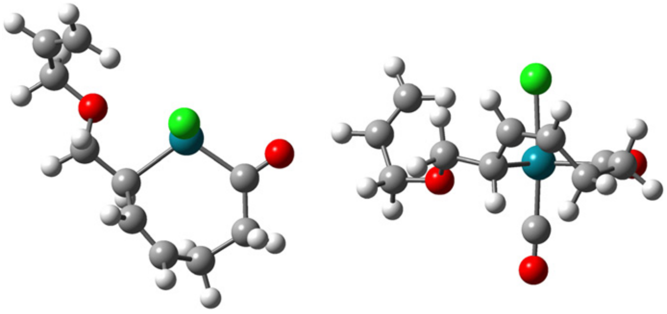

Figure 5. Two views of a possible intermediate in which rhodium interacts first with the vinylcyclobutanone (Fig. 2, b-pathway).

Table 2
Relative electronic energies in kcal/mol for the catalyzed reaction in gas phase at B3LYP/6-31G(d,p)+LANL2DZ level to obtain the Pcis2 product

	Δ*E* (kcal/mol)	ΔE_{ZPE} (kcal/mol)
I1	0.00	0.00
TS2	21.39	20.26
I3a	−17.49	−16.99
I3b	−21.67	−20.84
TS4a	8.18	7.70
TS4b	17.68	17.79
I5a	−26.05	−25.49
I5b	−6.89	−6.85
TS6a	19.49	19.30
TS6b	9.28	9.18
I7a	6.17	6.44
I7b	−15.84	−14.42
I8a	−20.15	−18.11

ZPE=zero point energy correction.

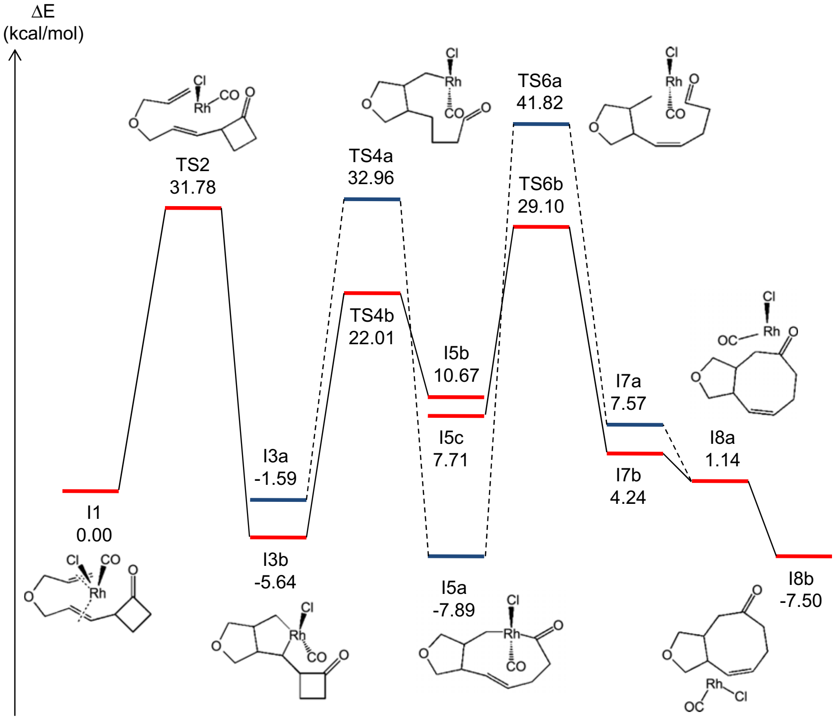

Figure 4. Relative energies in kcal/mol for intermediate and transition state geometries at B3LYP/6-31G(d,p)+LANL2DZ level (ZPE included).

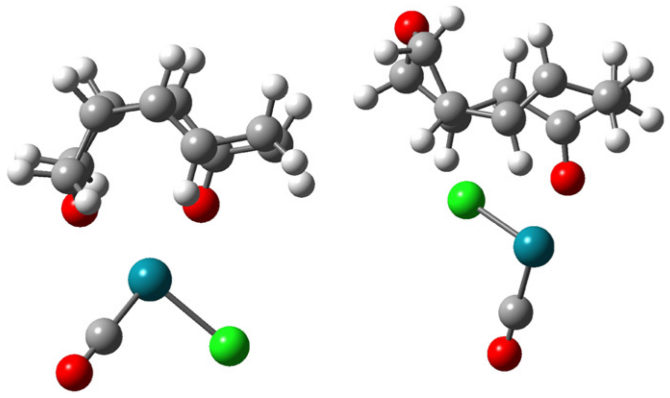

Figure 6. **I8b** of the cis1-pathway (left) and **I8a** of the cis2-pathway (right). Due to the oxygen atoms positions in the bicycle it is not possible to have an analogue to **I8b** in the cis2-pathway; in **I8a** of the cis2 product the rhodium cannot interact with the ether group.

For the vinylcyclobutanone cycloaddition, the transition state geometry is very similar for the two isomers. While the cyclobutanone is opening to give the eight-membered ring, the five-membered ring is closing. But the most interesting is to check that in absence of catalyst, products **Pcis1** and **Pcis2** obtained by the intramolecular cyclization of vinylcyclobutanone have the same order of magnitude energy barriers, around 44–45 kcal/mol in the two cases. That means, the rhodium catalyst not only transforms a one-step reaction in a multiple-step reaction with much lower barriers, but also in a completely selective process for sterical reasons.

Table 3
Relative electronic energies for the non-catalyzed [6+2] cycloaddition in gas phase at B3LYP/6-31G(d,p) level: (a) to obtain **Pcis1** product, labeled as 'Pcis1a'; (b) to obtain the **Pcis2** product, labeled as 'Pcis2a'; (c) to obtain an analogue to **Pcis1**, labeled as 'Pcis1b', but using as reactant vinylcyclobutane instead of vinylcyclobutanone

	ΔE (kcal/mol)	ΔE_{ZPE} (kcal/mol)
VCBcis1a	0.00	0.00
TScis1a	45.38	45.29
Pcis1a	−22.28	−18.24
VCBcis2a	0.00	0.00
TScis2a	43.86	43.79
Pcis2a	−21.25	−17.28
VCBcis1b	0.00	0.00
TScis1b	58.68	58.60
Pcis1b	−22.64	−18.89

ZPE=zero point energy correction.

4. Conclusions

The theoretical studies about the [6+2] rhodium-catalyzed cycloaddition of 2-vinylcyclobutanone and alkene point to a reaction mechanism in which the rhodium catalyst interacts first with the π-system, forming then a metallacyclopentene intermediate. This five-membered ring reacts to give a nine-membered metallacycle.

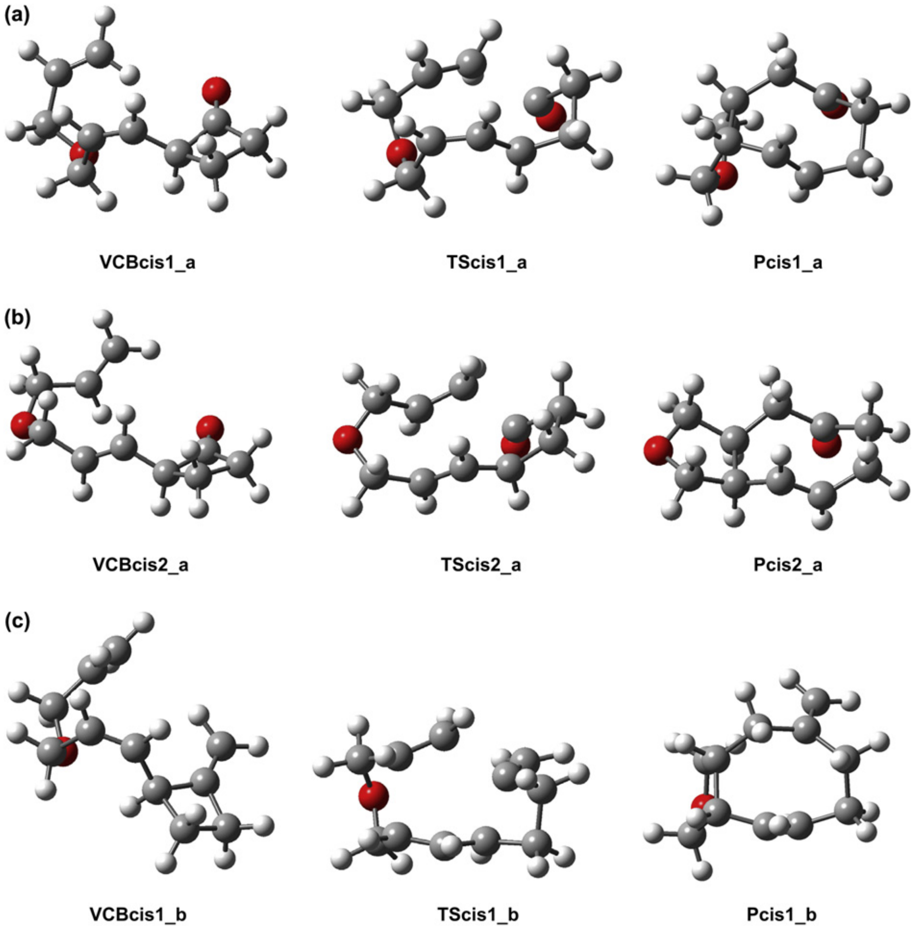

Figure 7. Reactant, transition state, and product structures for the non-catalyzed [6+2] cycloaddition in gas phase at B3LYP/6-31G(d,p) level: (a) cycloaddition to obtain the **Pcis1** product, labeled as Pcis1_a; (b) cycloaddition to obtain the **Pcis2** product, labeled as Pcis2_a; (c) cycloaddition with vinylcyclobutane instead of vinylcyclobutanone to obtain a product labeled as Pcis1_b.

The eight-membered ring of the final product is obtained by elimination of the rhodium catalyst. The reaction mechanism in which the rhodium catalyst interacts first with the vinylcyclobutanone is ruled out for experimental and theoretical results. Calculations show why in this reaction cis1-product is formed exclusively. Comparison of the catalyzed and non-catalyzed cycloaddition shows how a non-viable pericyclic cycloaddition is transformed into a viable *formal cycloaddition* by using a transition metal catalyst.

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Supplementary data

Optimized geometries of reactants, products, intermediates, and transition states for the reactions and absolute energies of all these species are listed. Some of the IRC and transition structures with d normal mode eigenvectors are also included. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.118.

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