# Accounting for Diradical Character through DFT. The Case of Vinyl Allene Oxide Rearrangement

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S *Supporting Information*

ABSTRACT: The transformation of vinyl allene oxides into cyclopentenones is key to the biosynthesis of a number of hormone-like molecules in plants. Two competitive paths are generally accepted for this transformation: a concerted S_N2-like mechanism and a stepwise path with a diradical oxyallyl intermediate. Recently, a new stepwise closed-shell path has been proposed that circumvents the key oxyallyl intermediate. In this work, we conduct a thorough computational investigation, including dynamic effects, to identify the most likely mechanism for this transformation.
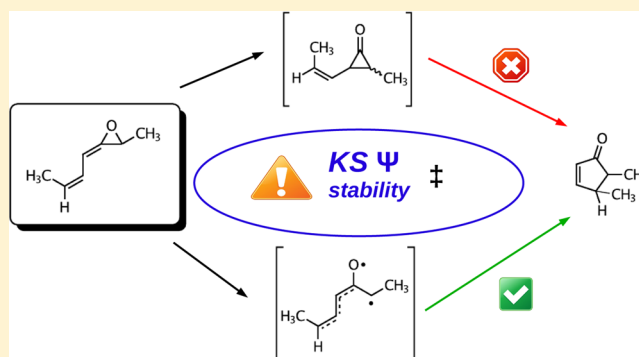
Diradical intermediates have been found to be key to a number of relevant reactions in organic chemistry.[1,2] Their fleeting nature and oftentimes uncontrolled reactivity limit the experimental exploration of the mechanisms in which they participate, thus making their computational exploration very appealing. One such case is the rearrangement of vinyl allene oxides to cyclopentenones (see Figure 1). This process is
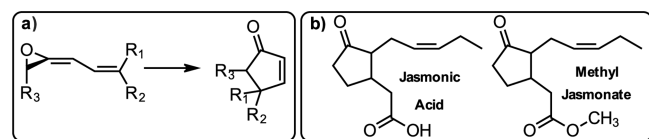
Figure 1. Vinyl allene oxide to cyclopentenone rearrangement and examples of plant hormone-like molecules exhibiting this structural motif.

responsible for the biosynthesis of a number of fatty acid derived hormone-like molecules that are related to plant defense and signaling mechanisms.[3-7] Similar hormones are ubiquitous also in the animal kingdom, but they are biosynthesized following a different route that circumvents the vinyl allene oxide intermediate.[8,9]

In 2004, de Lera and our group explored the enzyme-free mechanism of this transformation with the goal of clarifying a number of aspects: (1) to what extent the reaction is affected by solvation, (2) whether chirality transfer can occur for substituted vinyl allene oxides, and thus, (3) whether the role of the protein in the enzyme-catalyzed mechanism would be limited to reducing the activation energy and not inducing the chirality found in the jasmonate derivatives.[10] In that work, we built upon the computational work of Hess, which had described in detail the mechanism of the rearrangements of

allene oxide and unsubstituted vinyl allene oxide to cyclopropanone and cyclopentenone, respectively.[11-13]

When Hess and co-workers inspected the mechanism of the biologically relevant rearrangement of vinyl allene oxide to cyclopentenone (see Figure 2),[12] they found two possible pathways: a concerted one, described as an S_N2-like attack of the vinyl substituent onto the epoxide, and a stepwise one, involving a flat vinyl oxyallyl intermediate with diradical character. The concerted mechanism involves an inversion of the configuration of the epoxide terminus (and thus implies chirality transfer from reactant to product), whereas the planarity of the vinyl oxyallyl intermediate results in the loss of any chiral information in the reactant. In this work, Hess suggests that steric effects may play a role in the concerted pathway and that polar solvent effects may also be important from the stereochemical point of view since it would favor the stepwise process (Figure 2).

In this scenario, we extended in 2004 the previous work of Hess, considering several substitution patterns on the vinyl allene oxide and also accounting for the effect of solvation. We confirmed this hypothesis after finding very similar profiles for the substituted and unsubstituted systems and characterizing both concerted and stepwise alternatives, the latter involving a flat vinyl oxyallyl intermediate. We found that upon substitution at the epoxide and vinyl termini the two mechanistic alternatives are affected by steric effects and that solvation with water favors the stepwise pathway so that both mechanisms are competitive.

In later work, we showed that this chemistry is not restricted to allene oxides and their substituted derivatives, and in a series
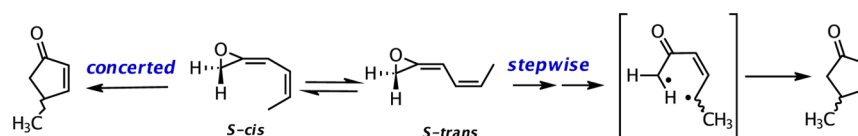
Figure 2. Mechanism proposed by Hess for the transformation of vinyl allene oxides into cyclopentenones.
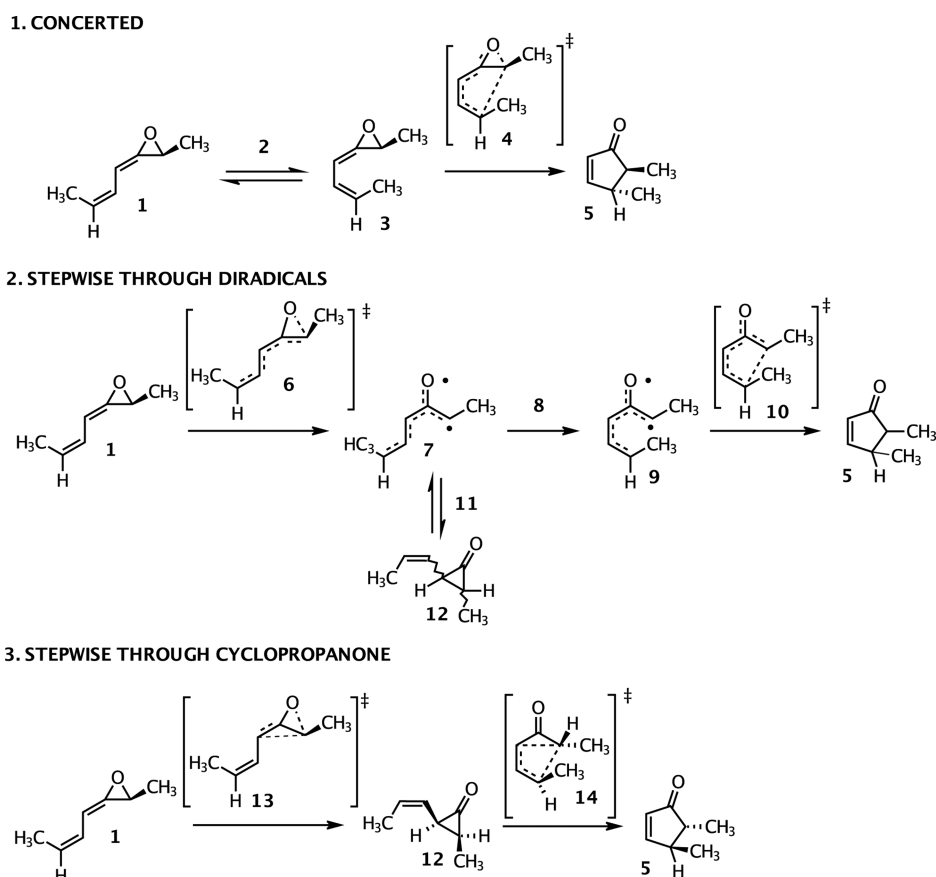

Figure 3. Mechanistic pathways for the transformation of vinyl allene oxides into cyclopentenones.

of papers, we have explored experimentally and computationally the diradical cascade of an aza isoelectronic derivative in the way to synthesize biologically active indoles.[14,15] The computational work provided enhanced control on the stereochemistry of this diradical cascade, which has been successfully used in the total synthesis of meloscine.[16,17] We found that these aza derivatives, isoelectronic to the oxyallyl species, share the same electronic structure features and reactivity. When computing the percentage of diradical character for the flat intermediate in these systems, we found a 41% value.[14,18] Our interest in the field was also fueled by our recent characterization of a possible Woodward−Hoffmann behavior in the cyclization of vinyl oxallyl and azallyl compounds.[19]

In 2014, de Lera published a revision on the rearrangement of vinyl allene oxides to cyclopentenones that proposed a new stepwise mechanism that circumvents the flat vinyl oxyallyl intermediate, ubiquitous in the previous work.[20] Thus, two mechanisms would be available for this transformation: the concerted S_N2-like path, found in all previous studies, and this new mechanism, involving a direct cycloisomerization from the vinyl allene oxide to a cyclopropanone and from that cyclopropanone to the final cyclopentenone, thus following a

closed-shell electronic structure all along the stepwise process (see Figure 3).[20]

Given the relevance and the impact of such findings on our and others' work on diradical species,[11,13−15,19,21−23] we decided to perform a new and thorough investigation of this mechanism on our own.

Reproducibility of the New Mechanism. We first set out to reproduce the new mechanism reported by de Lera et al.[20] For that we took the structures of the stationary points on the stepwise mechanism included in the Supporting Information of their paper and ran calculations at the level of theory reported therein (ω-B97XD/6-31++G(d,p)).[24] All of the structures were confirmed to be stationary points on the closed-shell potential energy surface and could also be correctly identified as minima or transition states in agreement with their report.

Interestingly, however, we found that all of the transition structures included in the stepwise pathways failed the wave function stability test (see the Supporting Information).[25] The stability check of the wave functions at the transition states yielded negative eigenvalues associated with orbital rotations that are typical to diradical species: they involve a transition strongly dominated by a HOMO−LUMO rotation and non-negligible triplet contamination (see Table S1). It is well-

known that the broken symmetry solutions of hybrid density functionals provide a reasonably accurate description of singlet diradicals through the reduction of the self-interaction error inherent to pure exchange functionals and that the admixture of the triplet state is a common side effect of these calculations.[26,27] The ability of broken symmetry DFT to account for diradical character does not imply, however, that the usual *black-box* treatment of these species is accurate and reliable. Actually, the need for a computational protocol that includes "*explicit computations demonstrating wavefuction stability*" has been claimed in the famous appeal by Hoffmann, Schleyer, and Schaefer entitled "Predicting Molecules—More Realism, Please!" but that particular item in their suggested protocol, although important, seems to have received insufficient attention.[28]

The instability of the wave functions associated with these transition structures is actually in good agreement with the results obtained by Hess on the same chemistry[11,12] and also with our work with de Lera on the same topic,[10] but they contrast with the authors' claim that "*we could not attribute radical character to the TSs leading to the vinylcyclopropanone 4 [at the (U)MP2/cc-pVDZ and (U)-B97XD/6-31++G(d,p) levels], and we determined that the wavefunction of these species is stable in all the stationary points characterized along the potential energy surface for the rearrangement of vinyl allene oxide. It appears that the presence of the additional substituents drives the conversion of the vinyl allene oxide to the cyclopentenone via the vinylcyclopropanone through closed-shell structures*".

We cannot explain what drove the authors to the conclusion that these structures do not have diradical character and that the closed-shell solution of the Kohn—Sham equations is an appropriate description of their electronic structure, but we can argue, however, about their statement suggesting that the presence of substituents may have, somehow, transformed these diradical species into closed shell species: (1) the electronic effect of methylation on π electron density is rather small, (2) the polarizing power of alkyl substituents, necessary for the stabilization of zwitterionic species is also quite modest, (3) diradicals, and other carbon based electron-deficient intermediates, are actually known to be stabilized through methylation,[29] not the other way around, and (4) the methylation pattern used in this work is exactly the same that we used in 2004, where the diradical character of the structures along the stepwise pathway for the conversion of vinyl allene oxide to cyclopentenone was thoroughly described.[10]

Geometry and Vibrational Normal Modes of the Key Transition States. From the results described above, it seems clear that the transition states described by de Lera and co-workers as involved in a diradical-free mechanism for the vinyl allene oxide to cyclopentenone conversion, are actually responsible for different chemistry.

By analyzing the normal mode associated with the imaginary frequency for these structures, we could not find a displacement responsible for either a cyclopropanone ring closure in **13** (in all the isomeric forms considered by de Lera, see the Supporting Information for more details on them) or a cyclopropanone ring opening in **14** (and its diastereomeric TS). In fact, these sets of transition states feature modes that we could readily associate with the oxirane ring opening **6** and the cyclopentenone ring closure **10**. This analysis suggests that transition states **13** and **14** are actually the starting and ending points of the stepwise mechanism (**6** and **10**) reported by Hess in 1999[12] and de Lera and us in 2004.[10]

To confirm this, we recovered the lowest energy transition structures reported in our work in 2004 (which are available in the Supporting Information of this paper) and performed a root-mean-square fit of the geometries to the presumably new transition states reported in 2014.

This procedure provided us with two pairs of transition structures which are almost superimposable (with RMS deviations of 0.05 and 0.18 Å, for the pairs **13**/**6** and **14**/**10**, respectively). The fitting is remarkably good if we take into account that different density functionals were used to optimize these pairs of structures (Figure S2). Intrinsic reaction coordinate calculations[30,31] were run on the correct (open shell and wave function stabilized) versions of the transition states **13** and **14**. These calculations confirmed that they are the same transition states proposed by Hess and us as starting and ending points of the diradical stepwise mechanism. Interestingly, despite the geometries and the normal modes associated with the imaginary frequency being quite similar between these two pairs of transition states, the dipole derivative unit vector is very different, which is a good indicator of substantial disparities in their electronic structures (open shell diradical vs closed shell zwitterionic, see Figure S2).

Dynamic Effects. One of the motivations to look for a new mechanism is the fact that experimental work has recently suggested that Z vinyl allene oxides, which cannot undertake the concerted mechanistic pathway, rearrange at room temperature to form a cyclopentenone[32] and that the traces of cyclopentenone being formed have optical activity. Therefore, it seems that chiral information is at least partially preserved in the product, which appears to be at odds with the existence of a planar oxyallyl diradical intermediate, where this information should be lost.[33]

We took into consideration that, although the stationary points described by de Lera et al. have been found not to be part of such a reaction path, the rearrangement from vinyl allene oxide **1** to cyclopentenone **5** via cyclopropanone **12** that they propose could nicely lead to the transfer of chiral information from reactant to product. For this, we explored the possibility of such a mechanism being a result of dynamic effects.[34−39] We therefore performed a study of the epoxide ring opening running pseudoclassical trajectories from transition state **6**, corresponding to the parent (S,Z,Z)-**1** vinyl allene oxide (see Figure 4).

Only five out of the 200 trajectories launched from the epoxide ring-opening transition state reach the cyclopropanone basin. These are a minor number of trajectories, but they represent a large enough percentage to justify the formation of a cyclopropanone ring through dynamic effects, given some plausibility to the mechanistic proposal by de Lera. In fact we also traced the chiral descriptors along the trajectories and found that, out of the five trajectories, four form a pair of enantiomeric trans cyclopropanones (leading to the 2R,3R and 2S,3S pairs) while one yields a *cis* product (2S,3R). Given the small number of trajectories arriving to the cyclopropanone, although consistent with only traces of the product being found experimentally, we cannot make statements on the chirality conserving capabilities of this process. A closer look at the set of trajectories leading to the cyclopropanone, however, shows that the reacting molecule spends a significant amount of time in the basin corresponding to the flat oxyallyl, so that it should have time to undergo conformational scrambling, thus resulting in loss of the chiral information. Figure 4 shows this set of five productive trajectories plus one trajectory leading back to the
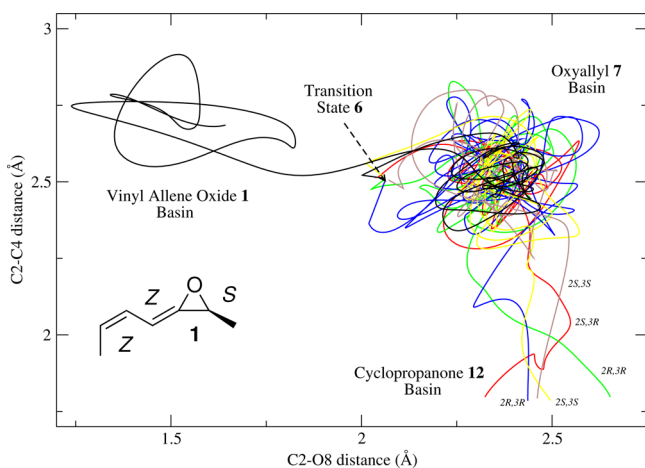
Figure 4. Quasiclassical trajectories reaching the cyclopropanone or vinyl allene oxide basins from TS **6** Trajectories arriving to the cyclopropanone from the vinyl allene oxide have stereochemical descriptors indicated in black. Only one trajectory recoiled to the vinyl allene oxide basin, which is conveniently employed to illustrate the location of the reactant basin.

Figure 5. Quasiclassical trajectories for the ring opening of vinyl allene oxide (S,Z,Z)-**1** and cyclopropanone $(2S,3S)$-**12** plotted as a function of relevant geometrical parameters. Trajectories arriving to the cyclopropanone from the vinyl allene oxide have stereochemical descriptors indicated in italics. Trajectories recoiling from the cyclopropanone opening transition state have the stereochemical descriptors in boldface.
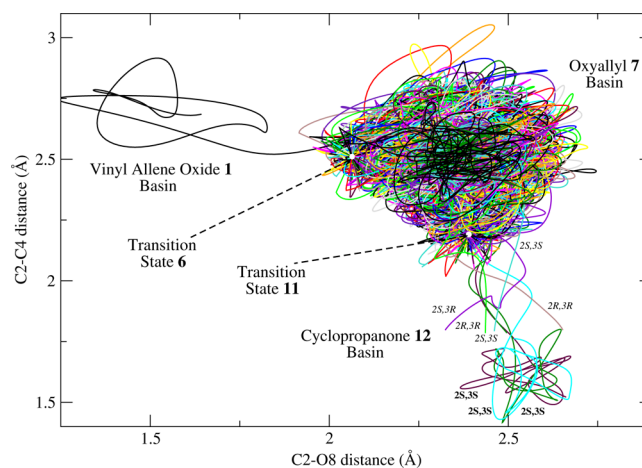
reactant. From a simple visual inspection of this plot the intermediate nature of the oxallyl diradical seems evident (see the SI for a cyclopropanone C−C bond formation versus time plot confirming this interpretation).

Despite the above results clearly suggesting that no trajectory arrives to the cyclopropanone ring without expending a significant time in the oxyallyl diradical basin and thus losing the original chiral information, we decided to run further simulations to confirm this.

In 2004, we had described the cyclopropanone as an unproductive intermediate that could be reached from the flat oxallyl **7** (see Figure 3). However, in the event that some of the trajectories that arrive to the cyclopropanone pass through the basin of the flat oxallyl intermediate with high kinetic energy in such a way that some of them preserve the chiral information contained in the initial vinyl allene oxide, a chirally enriched ensemble of cyclopropanone molecules would be formed. However, to furnish the final cyclopentenone these cyclopropanone molecules have to rearrange also in a chirality-preserving fashion. We therefore ran a second set of trajectories for the ring opening process of the cyclopropanone $(2S,3S)$-**12**. These results, together with the previous trajectories, are summarized in Figure 5.

None of the trajectories starting at the cyclopropanone ring-opening transition state **11** arrive to the cyclopentenone. All but three of the trajectories end up at the oxyallyl intermediate, and three recoil to the cyclopropanone basin. These results therefore confirm that it is not possible for the cyclopropanone to rearrange to the final cyclopentenone product avoiding the oxyallyl intermediate. As a consequence the cyclopropanone is only a nonproductive intermediate in the mechanism of the transformation of vinyl allene oxides into cyclopentenones. What was proposed in 2004 based only on the location of stationary points along the reaction pathway is now supported also on the grounds of molecular dynamics simulations.

Conclusions. In this work, we provide an example that DFT can be used as a cost-efficient tool to simulate reactions involving diradical intermediates, as already suggested by a number of previous studies.[26] However, care has to be taken that the wave function obtained from the self-consistent field

procedure actually represents the diradical structure. One robust way to confirm the validity of the wave function is to analyze its stability matrix.[25] Failure to do that may render the computational results unreliable and all the chemical information derived from the analysis of such results erroneous.[40,41]

This revision of the mechanism transforming vinyl allene oxides into cyclopentenones confirms the strong diradical character of the key intermediates involved. The possible formation of a cyclopropanone intermediate is validated and is also in good agreement with previous studies,[11,12] but it is found to be a nonproductive intermediate, unable to proceed to the final cyclopentenone unless it reverts back to the flat diradical oxyallyl intermediate **7**. Both mechanistic and dynamic studies agree with such conclusions.

The general features of the mechanism proposed by Hess[12] and studied in greater detail by de Lera and us[10] in 2004 are compatible with the dynamic study performed here. The proposed mechanism therefore still stands more than a decade after its publication. We have, however, provided a revised energy profile with a more modern density functional, including empirical corrections to account for dispersion and optimizing all the structures in the presence of solvation (through a continuum model). This revised reaction pathway is illustrated in Figure 6.

■ COMPUTATIONAL METHODS

Throughout this work, the Konh−Sham formulation of the density functional theory was employed.[42,43] A four-rung hybrid density functional including short and long-range dispersion effects, ω-B97xD,[44,45] has been used with the triple-ζ quality def2-TZVP basis set for all of the static calculations. All geometry optimizations have been carried out using *tight* convergence criteria in order to obtain accurate stationary points. Such accuracy in the geometries also required a pruned grid for numerical integration with 99 radial shells and 590 angular points per shell. Analysis of the normal modes obtained via diagonalization of the Hessian matrix was used to confirm the topological nature of each stationary point. The wave function stability for each optimized structure has also been checked.[25] Solvation effects have been taken into account variationally throughout
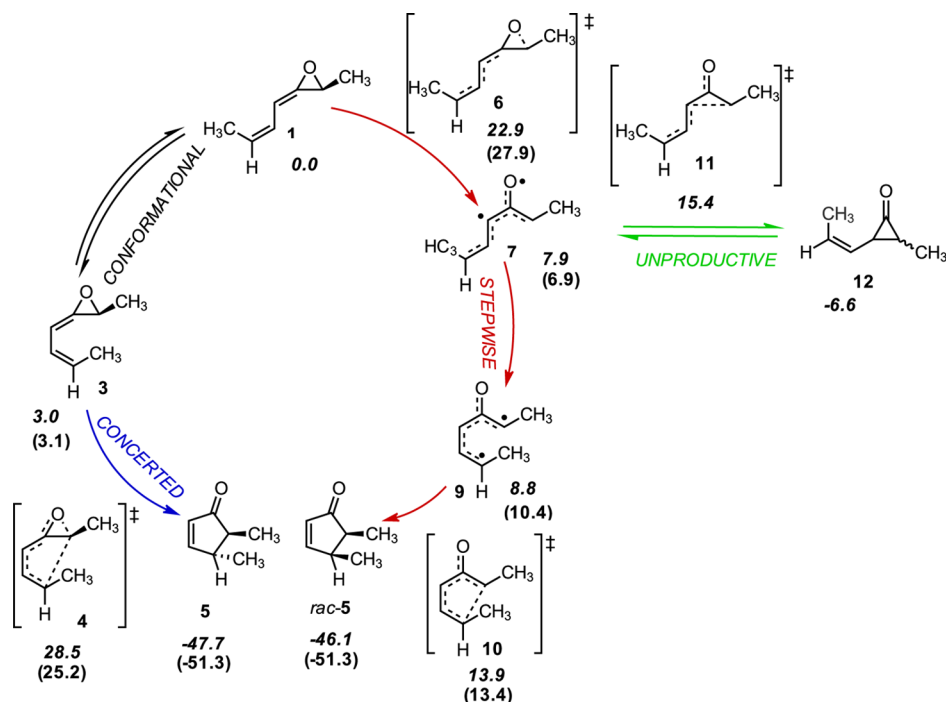
Figure 6. Relative free energies for the transformation of *S,E,Z* dimethylvinyl allene oxide into cyclopentenone (kcal/mol). For the sake of comparison, relative free energies reported by Hess in his seminal paper are provided in parentheses (for the unsubstituted vinyl allene oxide system).

the optimization procedures via the polarizable continuum model (PCM) and the smooth switching function by York and Karplus.[46,47]

Dynamic trajectory experiments within the Born−Oppenheimer approximation were run at the lower U-ω-B97xD/6-31G(d) level.[48−50] Due to the diradical nature of these species, a broken-symmetry initial guess was used at every point of the dynamic trajectories. We ran benchmark calculations at this level of theory which confirmed that the relative stability of intermediates and transition states do not suffer significant changes with respect to the U-ω-B97xD/6-31++G(d,p) results. Two sets of 200 trajectories were run from transition states **6** and **11**, respectively, with environmental conditions of 300 K and 1 atm. Initial velocities were assigned via random vibrational sampling. Four hundred true random numbers were obtained from atmospheric noise as provided by random.org.[51] All trajectories were integrated with a stepsize of 0.1 fs, and an initial phase was selected in the direction of products from the starting transition state. Trajectory steps were recorded every 0.25 amu$^{1/2}$Bohr and were stopped after 800 steps (ca. 480 ps) or when they arrived at the product basin.

All the calculations performed in this work have been carried out with the Gaussian 09 program.[52]

ASSOCIATED CONTENT

S **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02072.

    SCF energies; Cartesian coordinates; number of imaginary frequencies for all computed structures; detailed account of the stability of the transition states involved in the closed-shell mechanism, the geometry fitting, and the characterization of trajectories leading to cyclopropanone (PDF)

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Notes

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