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On the Mechanism of Gold(I)-Catalyzed Ring Expansion of Cyclopropanols: Theoretical Calculations Uncover a Bottle-Neck 1,4-H Shift and Suggest Adequate Reaction Conditions

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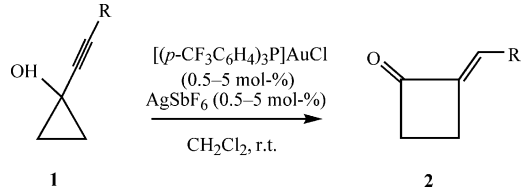
The mechanism of the one-carbon ring-expansion reactions of 1-(1-propynyl)cyclopropanol (**1**; R = Me), (1*R**,2*R**)-1-ethynyl-2-isopropylcyclopropanol (**3**), and (1*R**,2*S**)-1-(phenylethynyl)-2-isopropylcyclopropanol (**4**) catalyzed by $[AuP(Ph)_3]^+$ to yield the corresponding 2-alkylidenecyclobutanones was theoretically investigated by B3LYP-PCM calculations by using the LANL2DZ relativistic effective core potential for Au and the 6-31G(d) basis set for the remaining atoms. The most favorable route for these rearrangements in dichloromethane solution is a two-step mechanism involving as the first step the coordination of the gold(I) complex to the alkyne moiety with subsequent evolution through a 1,2-alkyl shift. Activation of the reactive C–C bonds takes place mainly through hyperconjugative interactions of these bonds with the oxygen atom and the alkyne moiety; this latter interaction is reinforced by the presence of the cationic gold(I) complex. The second step is the rate-determining one and consists of a 1,4-H shift, which requires the assistance by a second molecule of cyclopropanol to become readily accessible. This second molecule plays a very efficient bifunctional catalytic role, which cannot be played by a dichloromethane molecule. The use of methanol, water, and HFIP as assisting molecules was also investigated. Calculations suggest that the process would run most favorably in water. In agreement with experimental data, we found that the most favorable ring expansion of **3** takes place through migration of the substituted carbon atom. The only product to be expected from the rearrangement of **4**, however, is that corresponding to the migration of the nonsubstituted carbon atom.

Introduction

Nucleophilic additions to C–C multiple bonds are the most common gold-catalyzed organic reactions.[1] Gold catalysts are powerful soft Lewis acids that coordinate to C–C multiple bonds, which thus activates them for attack of a nucleophile. Alkynes have been so far the substrates most frequently activated in this way toward nucleophilic attacks. A series of nucleophilic additions to alkynes catalyzed by Au^I have been reported: hydroamination,[2] hydroalkoxylation and hydration,[3–11] hydrocarboxylation,[12–14] and addition of ketones[15] and C–C double bonds.[16–19]

Toste et al.[20] have shown that $[L\text{-}Au]^+$-type cations are capable of promoting migrations of nucleophilic σ-bonds to alkynes, which thus catalyzes ring-expansion reactions. Thus, these authors have reported the catalyzed ring enlargement of several 1-alkynylcyclopropanols to give the corresponding 2-alkylidenecyclobutanones (see Scheme 1).



Scheme 1.

Two possible mechanisms have been envisioned for these kinds of reactions[20] (see Scheme 2). On one hand, mechanism *a* involves coordination of the cationic gold(I) complex to the alkyne moiety with subsequent evolution into a four-membered ring cycloalkanone through 1,2-alkyl shift. On the other hand, in mechanism *b* the cationic gold(I) complex activates the cycloalkanol to give an alkyl gold(I) complex, which then undergoes insertion into the alkyne to yield the final expanded ring product.

The observed (*E*)-olefin geometry of the obtained alkylidene cycloalkanones and the migratory selectivity resulting from substituted cycloalkanols are most consistent with mechanism *a*. For example, the experimental results obtained by Markham et al. for the gold(I)-catalyzed rearrangements of substituted cyclopropanols **3** and **4** (see Scheme 3) can be rationalized by means of this mechanism

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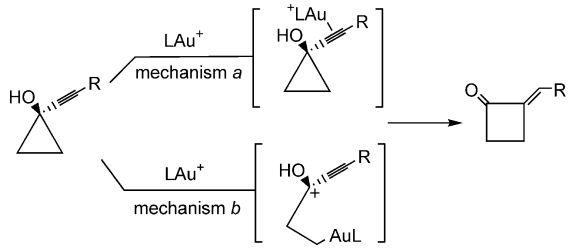
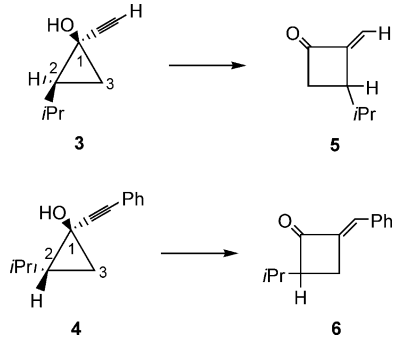


Scheme 2.

given that the ring expansion of compound **3** affords exclusively **5**, which is in agreement with the expected migratory aptitude of the substituted carbon atom of the cyclopropanol ring.



Scheme 3.

The rearrangement of **4**, however, selectively yields **6** because of the larger strain in the transition structure for cyclization expected in mechanism *a* owing to the interaction between the phenyl group and the isopropyl substituent.

Theoretical studies have been shown to be useful for elucidating the mechanism of different nucleophilic attacks on Au^I activated C–C triple bonds.[21–23] The aim of the present work is to learn about the two mechanistic proposals for the $[AuP(Ph)_3]^+$-catalyzed one carbon ring-expansion reaction of 1-(1-alkynyl)cyclopropanols through nucleophilic attack of a σ bond to the C–C triple bond activated by Au^I and to understand the role played by substituents in these processes. To this end, we present a theoretical analysis of mechanisms *a* and *b* for the $[AuP(Ph)_3]^+$-catalyzed ring-expansion reaction of 1-(1-propynyl)cyclopropanol to yield (*E*)-2-ethylylidenecyclobutanone, and a theoretical study of the different possible rearrangements of **3** and **4** along mechanism *a*.

Computational Methodology

Quantum chemical computations were carried out with the Gaussian 03 series of programs[24] by employing the hybrid density functional B3LYP.[25–27] Full geometry optimizations of stable species and transition states (TS) were performed in the gas phase by using Schlegel's algorithm[28] with the LANL2DZ relativistic effective core potential (ECP) for Au[29] and the 6-31G(d) basis set[30] for the remaining atoms. Harmonic vibrational frequencies were also calculated at the same theory level to characterize the critical points and to evaluate the zero-point vibrational energy (ZPVE). Intrinsic reaction coordinate (IRC) calculations by using the Gonzalez and Schlegel methods were employed to check the two minimum energy structures connected by every TS.[31–32]

ΔG values were computed in the gas phase within the ideal gas, rigid rotor, and harmonic oscillator approximations. A pressure of 1 atm and a temperature of 300 K were assumed in the calculations to simulate experimental conditions. To take into account condensed-phase effects, we performed single-point calculations of the Gibbs energy in solution on all the gas-phase optimized structures by using the polarizable continuum model (PCM) of Tomasi et al.[33,34] with the united atom Hartree–Fock (UAHF) parametrization.[35] Relative permittivities of 8.93, 32.63, 17.8, and 78.39 were used to simulate, respectively, dichloromethane, methanol, 1,1,1,3,3,3-hexafluoropropanol (HFIP), and H_2O as solvents. A natural bond orbital (NBO) analysis was performed on the most important critical structures located along the reaction coordinates.[36,37]

In the text we will discuss the variation of Gibbs energy in solution along the different reaction coordinates.

Results and Discussion

First, we will present the results obtained for the two mechanistic proposals for the $[AuP(Ph)_3]^+$-catalyzed ring expansion of 1-(1-propynyl)cyclopropanol into (*E*)-2-ethylidene cyclobutanone, and second, we will analyze the rearrangements of **3** and **4** in Scheme 3 through the migration of both substituted and nonsubstituted carbon atoms of the cyclopropanol ring along mechanism *a*.

$[AuP(Ph)_3]^+$-Catalyzed Ring Expansion of 1-(1-Propynyl)-cyclopropanol into (*E*)-2-Ethylidenecyclobutanone along Mechanisms *a* and *b*

Figure 1 displays the Gibbs energy profile for the rearrangement of 1-(1-propynyl)cyclopropanol along mechanism *b* (see Scheme 2) in CH_2Cl_2. Table S1 (Supporting Information) collects the relative electronic energy, ZPVE, and Gibbs energy in both the gas phase and in solution for all the critical structures located along the reaction coordinate. The $[AuP(Ph)_3]^+$ activation of 1-(1-propynyl)cyclopropanol yields an initial open-chain complex, RC-me-b, which is 7.8 kcal/mol more stable than the separate reactants. The subsequent insertion into the propyne moiety takes place through the TSRC1-me-b TS with a Gibbs energy barrier of 42.1 kcal/mol to render the intermediate M1-me-b, which is 31.1 kcal/mol less stable than the separate reactants. In the final stage, a 1,4-H shift takes place from the oxygen atom to the ethylidene carbon atom to form the $[AuP(Ph)_3]^+$-cyclobutanone complex, PC-me-b, which is 36.1 kcal/mol more stable than the reactants through the TS1PC-me-b TS (32.0 kcal/mol). Finally, PC-me-b

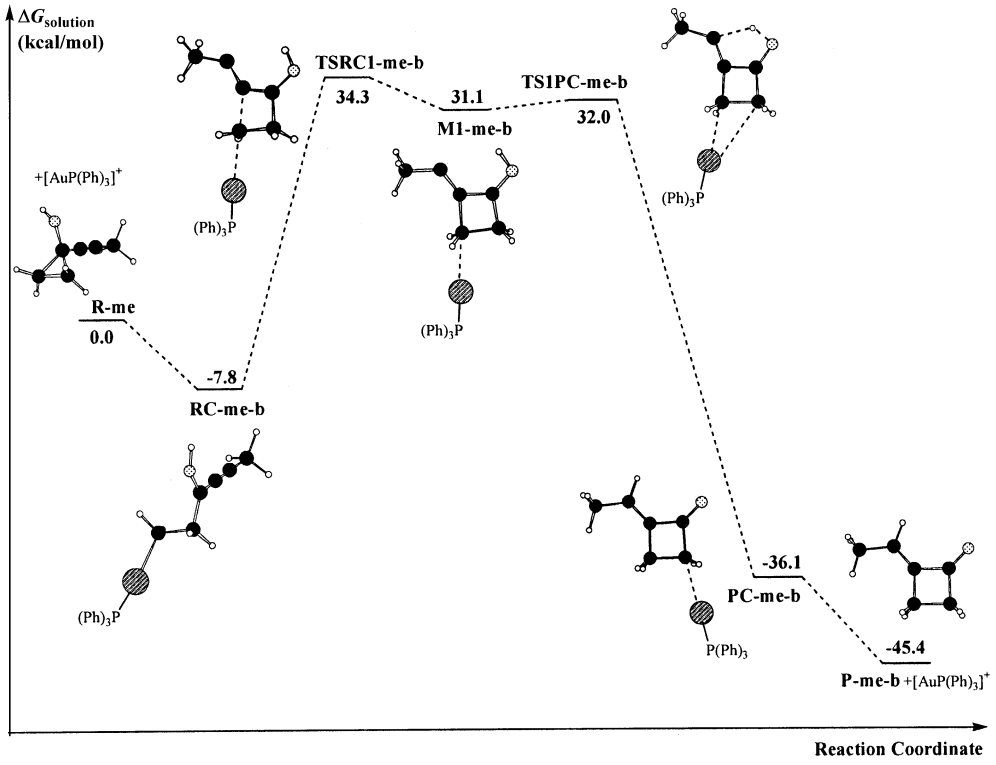
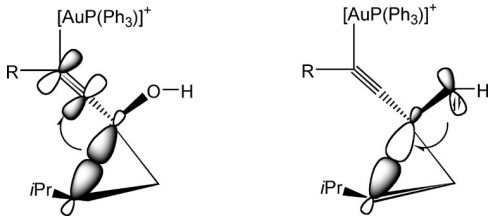


Figure 1. Gibbs energy profile in CH_2Cl_2 solution for $[AuP(Ph)_3]^+$-catalyzed rearrangement of 1-(1-propynyl)cyclopropanol into (*E*)-2-ethylidenecyclobutanone along mechanism *b*.

dissociates into the final product P-me-b + $[AuP(Ph)_3]^+$ (–45.4 kcal/mol).

According to our theoretical results, the $[AuP(Ph)_3]^+$-catalyzed rearrangement of 1-(1-propynyl)cyclopropanol along mechanism *a* is a two-step process. The first step consists of a 1,2-alkyl shift induced by coordination of $[AuP(Ph)_3]^+$ to the triple bond. NBO analysis shows that in mechanism *a* the activation of the reactive C–C σ bonds is due to the stabilizing hyperconjugation interactions of their antibonding MOs with one of the lone pairs of electrons on the oxygen atom and of their bonding MOs with the π antibonding MOs of the alkyne moiety (see Scheme 4). This second interaction is strongly favored by the stabilization of the MOs of the alkyne moiety by the presence of the cationic gold(I) complex.[38]



Scheme 4.

In the second step, a 1,4-H shift takes place from the oxygen atom to the ethylidene carbon atom. This 1,4-H shift implies a TS with a Gibbs energy barrier of 32.2 kcal/mol, which makes this an unfavorable route. However, we found that this mechanism, which rationalizes the experimental observations, becomes easily accessible through assistance by a second molecule of cyclopropanol, which in turn plays a crucial catalytic role in the 1,4-H shift. Theoretical calculations have already made it possible to suggest that solvent-assisted hydrogen migration might be crucial for the addition of an alcohol to an Au^I activated C–C triple bond[22] and very recently have revealed the important role played by water in the catalysis of a 1,2-H shift in the Nazarov reaction.[23]

Figure 2 and Table S2 (Supporting Information) present the results corresponding to the assisted mechanism *a*. The second reactant molecule coordinates to the gold(I) activated one through an OH(assisting cyclopropanol)···O(activated cyclopropanol) interaction to form initial complex RC-me-a, which becomes a transient structure (0.8 kcal/mol) when taking into account solvent effects. RC-me-a evolves through TSRC1-me-a, with a Gibbs energy barrier of 12.3 kcal/mol to give intermediate M1-me-a (–16.7 kcal/mol). It must be remarked here that although the energy barrier for the first step is not practically sensitive to the presence of the second assisting reactant molecule, it is necessary to include this assisting molecule from the very beginning of the process to avoid a high energy barrier for the second step because of the formation of a very stable intermediate. M1-me-a evolves into the $[AuP(Ph)_3]^+$–(*E*)-2-ethylidenecyclobutanone complex PC-me-a (–30.1 kcal/mol) through TS1PC-me-a for the assisted 1,4-H shift with a Gibbs energy barrier of 18.2 kcal/mol,

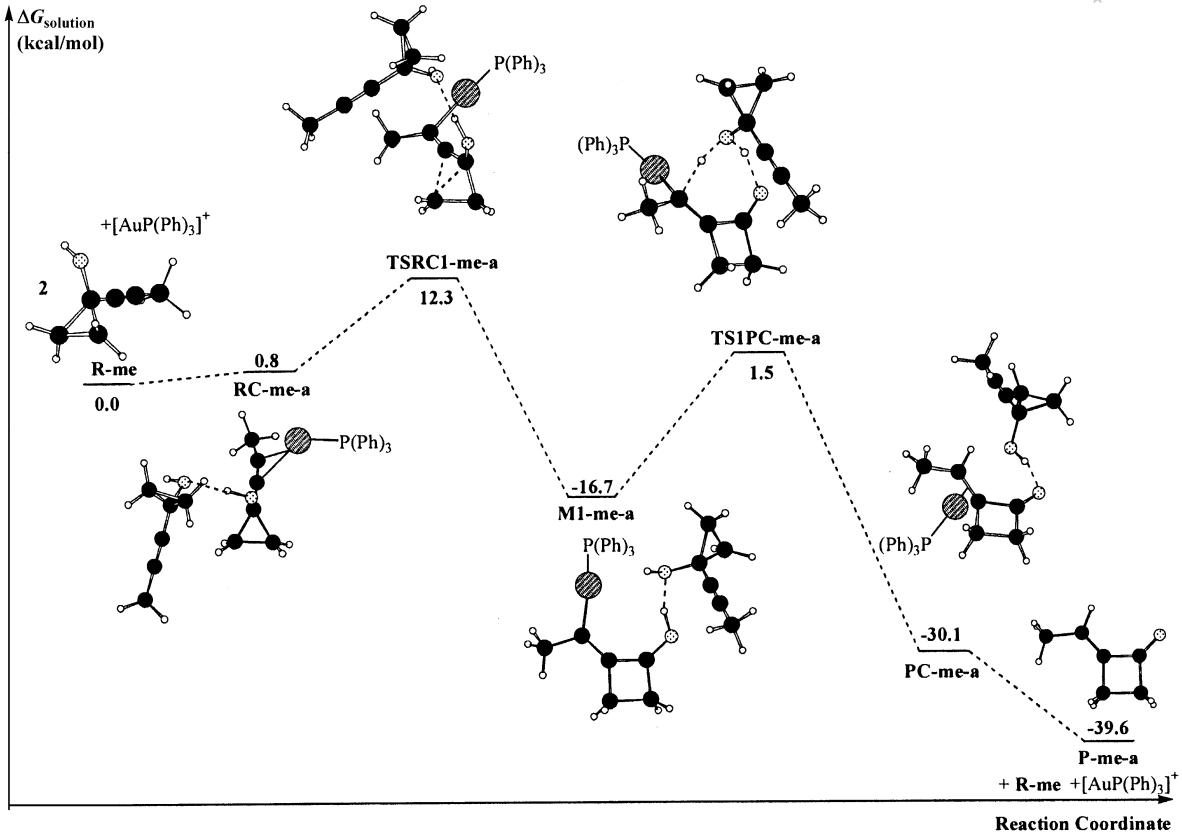


Figure 2. Gibbs energy profile in CH_2Cl_2 solution for $[AuP(Ph)_3]^+$-catalyzed rearrangement of 1-(1-propynyl)cyclopropanol into (*E*)-2-ethylidenecyclobutanone along mechanism *a* assisted by a second molecule of 1-(1-propynyl)cyclopropanol.

which is much lower than that for the process without assistance. The assisting cyclopropanol molecule then plays a very efficient bifunctional catalytic role by accepting the H atom from the oxygen atom of the cyclobutanone formed and simultaneously transferring its hydroxy hydrogen atom to the ethylidene carbon atom. No analogous catalytic role was shown by a dichloromethane molecule when including it explicitly in the calculations. Anyway, the second step of the reaction remains the rate-determining one. Finally, PC-me-a dissociates into P-me-a + R-me + $[AuP(Ph)_3]^+$ (–39.6 kcal/mol).

Efficiency of Different Assisting Molecules to the 1,4-H Shift

Our theoretical calculations showed that assistance to the 1,4-H shift is necessary to make this process readily viable, and that this assistance can only come from a second reactant molecule when the reaction is run in CH_2Cl_2.solution. Now the question could be raised of whether an adequate solvent or additive could play the necessary bifunctional catalytic role more effectively than a second reactant molecule.

To investigate this point, we studied the $[AuP(Ph)_3]^+$-catalyzed rearrangement of 1-(1-propynyl)cyclopropanol along mechanism *a* by using as assisting molecules alternatively CH_3OH, H_2O, and HFIP, which present with quite different acidities. As a solvent (polarizable continuum), we tested in each case both the assisting substance and CH_2Cl_2.

In Figure 3 and Table S3 (Supporting Information) we present the results corresponding to the process assisted by a CH_3OH molecule. We will comment first on the results obtained by using CH_2Cl_2 as a solvent (figures without parentheses in Figure 3). The reaction is a two-step process with initial formation of complex RC-me-MeOH (–5.0 kcal/mol), which evolves through TSRC1-me-MeOH with a Gibbs energy barrier of 11.9 kcal/mol to yield intermediate M1-me-MeOH (–24.3 kcal/mol).

This intermediate transforms into complex PC-me-MeOH (–34.2 kcal/mol) through TS1PC-me-MeOH for the CH_3OH-assisted 1,4-H shift with an energy barrier of 15.9 kcal/mol. Finally, PC-me-MeOH directly dissociates into P-me-H_2O + H_2O + $[AuP(Ph)_3]^+$ (–37.5 kcal/mol). Then, by using CH_3OH as the assisting molecule instead of a second reactant molecule in CH_2Cl_2 solvent, the Gibbs energy barrier for the two steps of the mechanism diminishes, particularly that for the second step, which continues to be the rate-determining one. In Figure 3 the figures in round and square parentheses correspond, respectively, to the use of CH_3OH and H_2O as continuum solvents. We see that, except for the final products, the higher the permittivity of the continuum the lower the relative stability of all the species along the reaction coordinate. The Gibbs energy

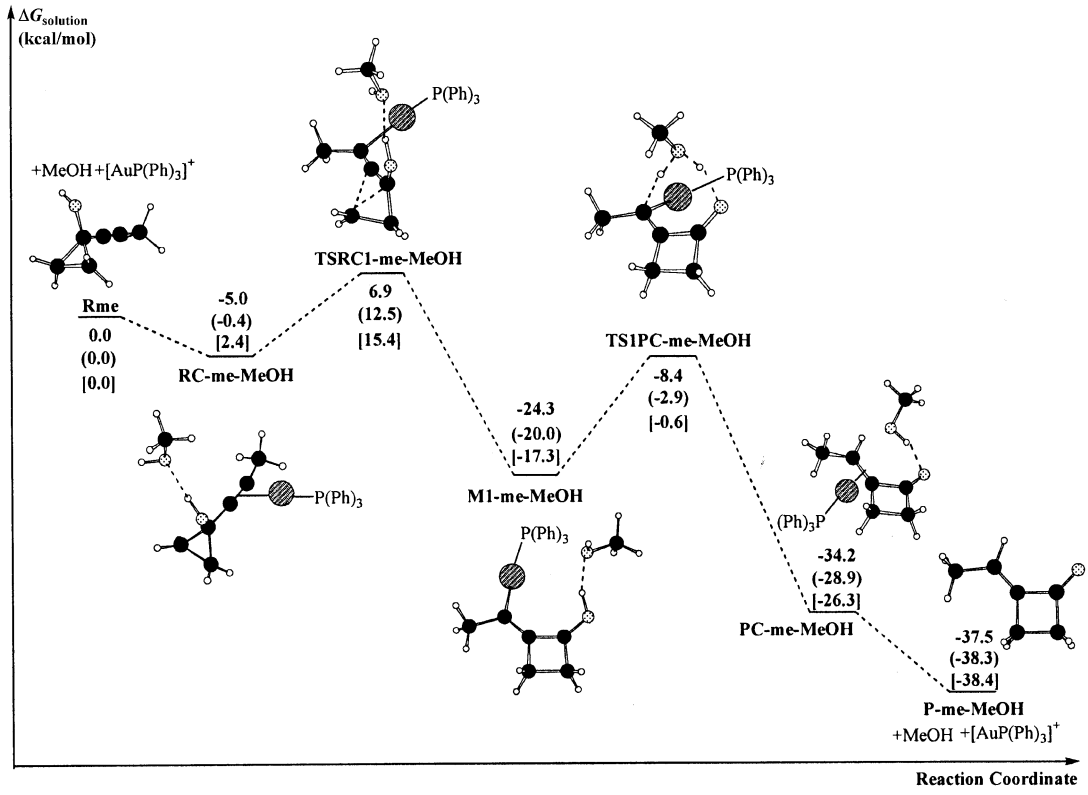


Figure 3. Gibbs energy profile in solution for $[AuP(Ph)_3]^+$-catalyzed rearrangement of 1-(1-propynyl)cyclopropanol into (*E*)-2-ethylidenecyclobutanone along mechanism *a* assisted by a molecule of methanol. Both CH_2Cl_2 (figures without parentheses), CH_3OH (figures in round parentheses), and H_2O (figures in square parentheses) were used as continuum solvents.

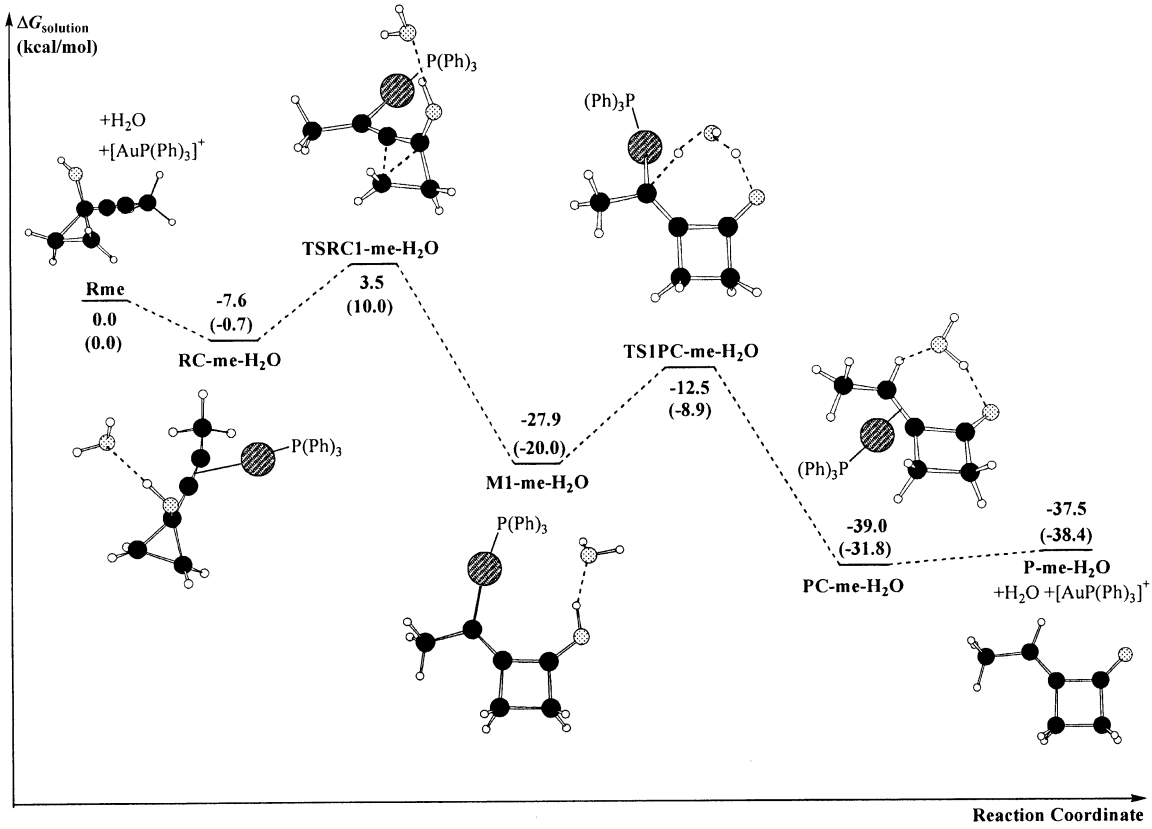


Figure 4. Gibbs energy profile in solution for $[AuP(Ph)_3]^+$-catalyzed rearrangement of 1-(1-propynyl)cyclopropanol into (*E*)-2-ethylidenecyclobutanone along mechanism *a* assisted by a molecule of water. Both CH_2Cl_2 (figures without parentheses) and H_2O (figures in parentheses) were used as continuum solvents.

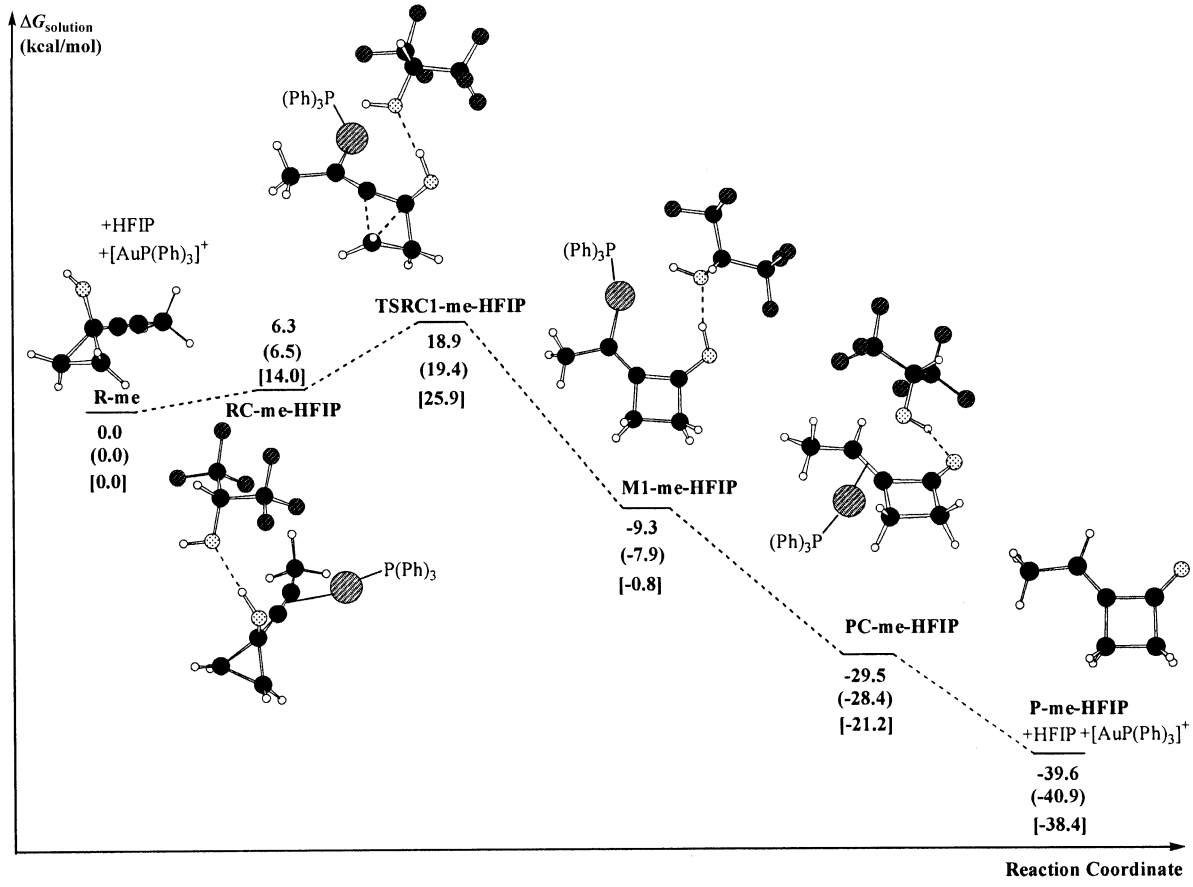


Figure 5. Gibbs energy profile in solution for $[AuP(Ph)_3]^+$-catalyzed rearrangement of 1-(1-propynyl)cyclopropanol into (*E*)-2-ethylidenecyclobutanone along mechanism *a* assisted by a molecule of HFIP. CH_2Cl_2 (figures without parentheses), HFIP (figures in round parentheses), and H_2O (figures in square parentheses) were used as continuum solvents.

barriers for the first TS increase with the permittivity of the continuum; the rate-determining barrier for the 1,4-H shift presents its maximum value (17.1 kcal/mol) with CH_3OH as a continuum and is larger (16.7 kcal/mol) with H_2O than with CH_2Cl_2 as a continuum.

Figure 4 and Table S4 (Supporting Information) display the results obtained when H_2O is used as the assisting molecule both with the use of CH_2Cl_2 and H_2O as continuum solvents. The energy profile obtained by using CH_2Cl_2 as a continuum is more stable relative to separate reactants than when the process is assisted by CH_3OH. However, when H_2O is taken as a continuum, all the intermediates and TSs appreciably destabilize relative to the separate reactants. H_2O is a slightly better assisting molecule than CH_3OH and reduces the rate-determining Gibbs energy barrier for the 1,4-H shift to 15.4 kcal/mol when using CH_2Cl_2 as a solvent; it is also by far the best assisting molecule when it is also used as a continuum, as it renders a Gibbs energy barrier of only 11.1 kcal/mol for the H shift, which remains the rate-determining step by only 0.4 kcal/mol.

Figure 5 and Table S5 (Supporting Information) display the results obtained when HFIP is used as the assisting molecule with CH_2Cl_2, HFIP, and H_2O as continuum solvents. We see that HFIP is an excellent assisting molecule that allows the 1,4-H shift to proceed without any Gibbs energy barrier by transforming the reaction into a concerted process. However, the coordination of HFIP to the activated cyclopropanol molecule considerably hinders the 1,2-alkyl shift that presents Gibbs energy barriers of 18.9, 19.4, and 25.9 kcal/mol when using CH_2Cl_2, HFIP, and H_2O as solvents, respectively.

Therefore, the best reaction conditions for the $[AuP(Ph)_3]^+$-catalyzed ring expansion of 1-(1-propynyl)cyclopropanol into (*E*)-2-ethylidenecyclobutanone would be using H_2O both as the assisting molecule and as the continuum (i.e., running the reaction in water). The frequent practice of using a low acidity alcohol (CH_3OH) as an additive and a low permittivity solvent (CH_2Cl_2) is more favorable than using CH_2Cl_2 alone but gives rise to a rate-determining barrier larger than that in water by over 4 kcal/mol.

Selectivity and Migratory Aptitude in Substituted Cyclopropanols

To investigate the migratory competition between substituted and nonsubstituted carbon atoms in the Au^I-assisted

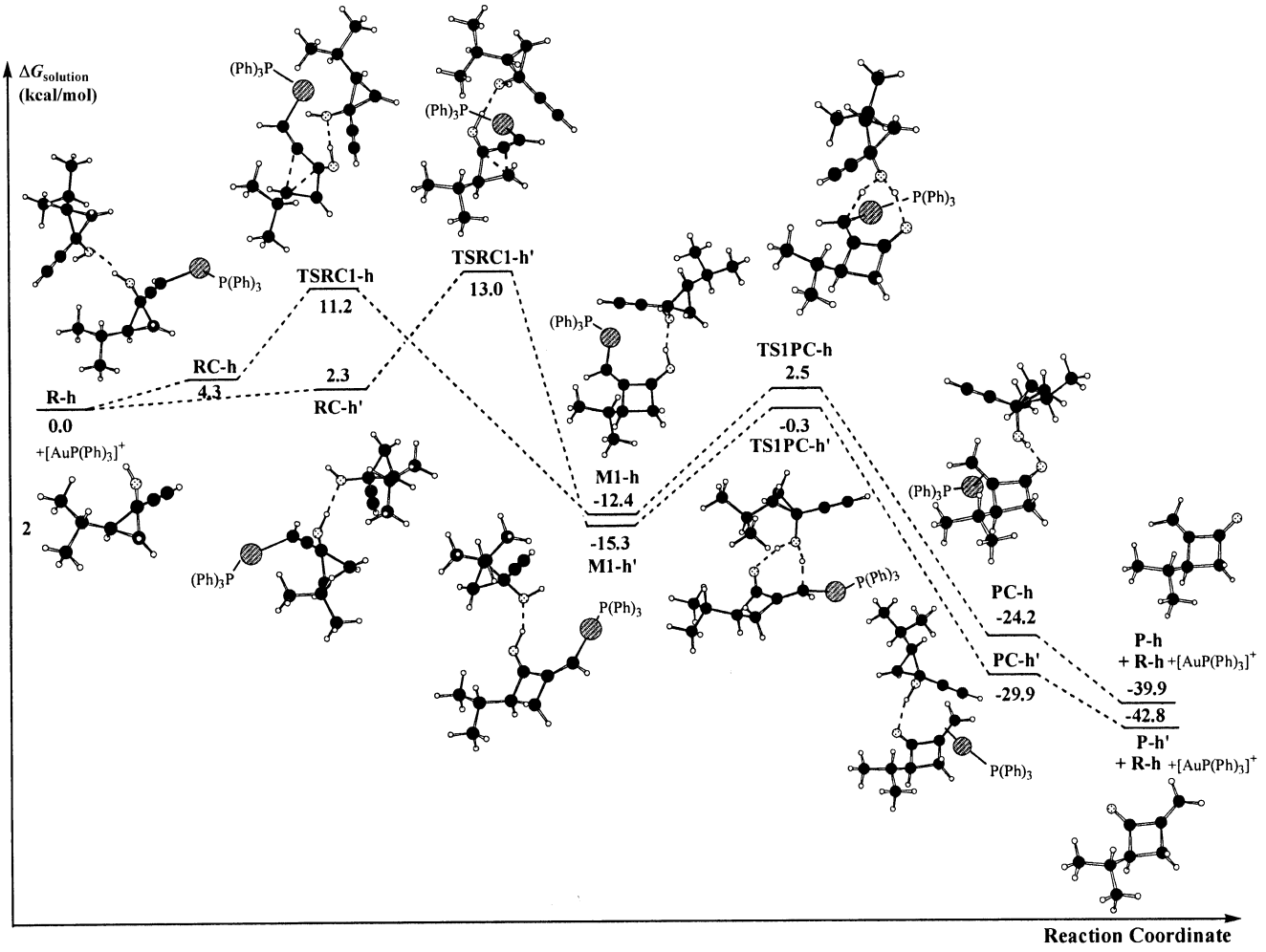


Figure 6. Gibbs energy profiles in CH_2Cl_2 solution for the $[AuP(Ph)_3]^+$-catalyzed rearrangements of **3** along mechanism *a* assisted by a second molecule of **3**. Primed structures correspond to the migration of the nonsubstituted carbon atom.

ring expansion of substituted cyclopropanols, we studied the evolution of **3** and **4** (see Scheme 3) along mechanism *a* to yield the corresponding 2-methylene-3-isobutylcyclobutanones and 2-methylene-4-isobutylcyclobutanones. Figures 6 and 7 and Tables S6 and S7 (Supporting Information) display the data corresponding to these processes. Let us analyze first the evolution of **3** and then that of **4**.

In the first step for the rearrangement of **3** in CH_2Cl_2 solution the migration of the substituted carbon atom takes place through the initial complex RC-h, which becomes a transient species (4.3 kcal/mol) after taking into account the effect of solvent, and TSRC1-h with a Gibbs energy barrier of 11.2 kcal/mol to yield intermediate M1-h (–12.4 kcal/mol; see Figure 6). The migration of the nonsubstituted carbon atom proceeds through RC-h′ (2.3 kcal/mol) and TSRC1-h′ with an energy barrier of 13.0 kcal/mol to form intermediate M1-h′ (–15.3 kcal/mol). The second step presents quite similar Gibbs energy barriers (about 15 kcal/mol) for the evolution of the two intermediates M1-h (through TS1PC-h) and M1-h′ (through TS1PC-h′) into the product complexes PC-h (–24.2 kcal/mol) and PC-h′ (–29.9 kcal/mol), respectively. In both cases, the above-mentioned bifunctional catalysis by a second cyclopropanol molecule is again necessary for making readily viable the 1,4-H shift. Finally, PC-h and PC-h′ dissociate into products P-h + R-h + $[AuP(Ph)_3]^+$ (–39.9 kcal/mol) and P-h′ + R-h′ + $[AuP(Ph)_3]^+$ (–42.8 kcal/mol), respectively.

Therefore, according to our theoretical results the two ring expansions of **3**, through migration of the substituted or the nonsubstituted carbon atom, are two-step processes. The regiochemistry of the process results from the first step of the reaction, whereas the second step is the rate-determining one. Theoretical calculations render a Gibbs energy barrier for the migration of the substituted carbon atom, which is 1.8 kcal/mol lower than that for the nonsubstituted carbon atom, which thus predicts that the product expected from this rearrangement is **5** (see Scheme 3) in agreement with experiment.[8] NBO analysis shows that this preference is the result of an electronic effect. The two stabilizing hyperconjugation interactions above mentioned are more important for the C1–C2 bond (for atom numbering see Scheme 3) because the presence of the substituent di-

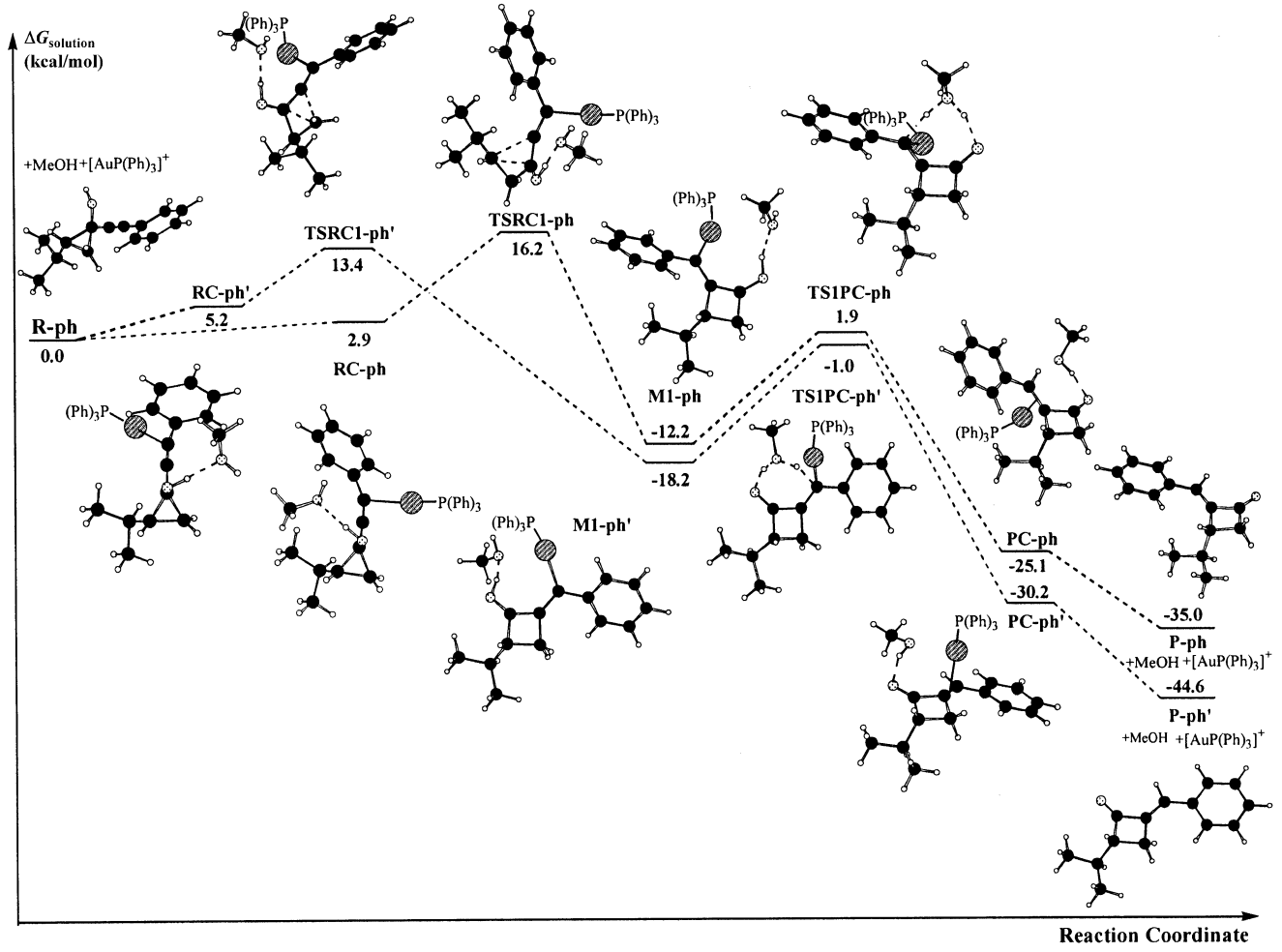


Figure 7. Gibbs energy profiles in CH_2Cl_2 solution for $[AuP(Ph)_3]^+$-catalyzed rearrangements of **4** along mechanism *a* assisted by a CH_3OH molecule. Primed structures correspond to the migration of the nonsubstituted carbon atom.

minishes the energy gap between the C1–C2 bonding MO and the alkyne π antibonding MOs and between the C1–C2 antibonding MO and the oxygen lone pair. As a consequence, C1–C2 is more reactive than C1–C3.

Given the size of the system, we studied the rearrangements of **4** by using CH_3OH as the assisting molecule (see Figure 7). The initial complexes RC-ph (2.9 kcal/mol) and RC-ph′ (5.2 kcal/mol), in which the cyclopropanol molecule is activated by $[AuP(Ph)_3]^+$ and a CH_3OH molecule is coordinated to it become transient species after including the effect of solvent. The migrations of the substituted and nonsubstituted carbon atoms take place through TSs TSRC1-ph and TSRC1-ph′ with Gibbs energy barriers in CH_2Cl_2 solution of 16.2 kcal/mol and 13.4 kcal/mol, respectively, to yield intermediates M1-ph (–12.2 kcal/mol) and M1-ph′ (–18.2 kcal/mol). The assisted 1,4-H shifts through TSs TS1PC-ph and TS1PC-ph′ present, respectively, Gibbs energy barriers of 14.1 and 17.2 kcal/mol to yield final complexes PC-ph (–25.1 kcal/mol) and PC-ph′ (–30.2 kcal/mol). Finally, PC-ph and PC-ph′ dissociate, respectively, into P-ph + MeOH + $[AuP(Ph)_3]^+$ (–35.0 kcal/mol) and P-ph′ + MeOH + $[AuP(Ph)_3]^+$ (–44.6 kcal/mol).

Thus, in agreement with experimental findings,[8] calculations render the Gibbs energy barrier for the migration of the nonsubstituted carbon atom 2.8 kcal/mol lower than that for the substituted one, which thus predicts that the only product obtained from the rearrangement of **4** will be **6**. As predicted by Toste and collaborators,[8] the reason for this reverse preference with respect to **3** is the repulsion between the isopropyl and the phenyl substituents in the TSs corresponding to the first step of the rearrangement. In effect, the same stabilizing hyperconjugative interactions of C1–C2 and C1–C3 bonds with one of the lone pairs of O and the alkyne π antibonding MOs exist now and for the same reason as above the interactions involving the C1–C2 bond are more important. However, in TSRC1-ph the relative position of the isopropyl and the phenyl substituents determines H–H distances as short as 2.2 Å, whereas in TSRC1-ph′ the average H–H distance is about 2.8 Å. By using these geometrical parameters we evaluated the coulombic interaction between the implied hydrogen atoms and checked that this interaction accounts for the reversion of the relative stability of the two TSs dictated by hyperconjugative interactions.

Conclusions

Theoretical calculations show that the most favorable mechanistic route for the $[AuP(Ph)_3]^+$-catalyzed rearrangement of 1-(1-propynyl)cyclopropanol into (*E*)-2-ethylidenecyclobutanone in CH_2Cl_2 solution is a two-step one. In the first step, the cationic gold(I) complex coordinates to the alkyne moiety with subsequent evolution into a four-membered ring cycloalkanone through 1,2-alkyl shift. Activation of the reactive C–C bonds takes place through their stabilizing hyperconjugation interactions with one of the lone pairs on the oxygen atom and with the π antibonding MOs of the alkyne moiety. This second interaction is favored by the presence of the cationic gold(I) complex. The second step consists of a 1,4-H shift, which requires the assistance of a second molecule of cyclopropanol to be easily accessible. The assisting cyclopropanol molecule plays a very efficient bifunctional catalytic role by accepting the H atom from the oxygen atom of the cyclobutanone formed and simultaneously transferring its hydroxy hydrogen atom to the ethylidene carbon atom. This catalytic role cannot be played by a CH_2Cl_2 molecule. We also investigated the efficiency of CH_3OH, H_2O, and HFIP both as assisting molecules and as continuum solvents. According to our calculations, the best assisting molecule would be H_2O in a high permittivity solvent (water).

In agreement with experiment, we found that the most favorable ring expansion of **3** takes place along a two-step mechanism to yield **5** through migration of the substituted carbon atom and an assisted 1,4-H shift. The second step is the rate-determining one. This preference is due to the reinforcement of the hyperconjugative interactions of C1–C2 with the oxygen atom and the alkyne moiety by the isopropyl substituent. Theoretical calculations also confirm that the reason why experiments yield **6** as the only product from the rearrangement of **4** is the lower steric repulsion between the isopropyl and the phenyl substituents in the TS for the migration of the nonsubstituted carbon atom, which thus reverses the relative stability of the TSs for migration of the substituted and nonsubstituted carbon atoms determined by the hyperconjugative interactions.

Supporting Information (see footnote on the first page of this article): Absolute electronic energies, ZPVEs, relative electronic energies, relative Gibbs free energies in the gas phase and in solution for all the critical structures located; imaginary vibrational frequencies corresponding to all the TSs; cartesian coordinates of all the critical structures.

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