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New Insights on the Mechanism of the Transition-Metal Stereoselective Olefin Cyclopropanation

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Abstract: We have carried out a theoretical analysis of the intermolecular cyclopropanation of propargylic esters with alkenes. DFT calculations allow us to propose a reaction mechanism, and provide explanations for the reasons behind the difference between the inter- and intramolecular versions of this process. The results strongly suggest that the entropic effects could modulate the operative mechanism and account for the mechanistic discrepancy. The calculated model also justifies the experimental stereoselectivity on the basis of intra- and intermolecular interactions. In addition, we have taken into account other transformations of propargylic carboxylates catalyzed by late transition metals, and the results rationalize the accumulated experimental observations.

Keywords: cyclopropanation · metallocarbenoids · reaction mechanisms · stereoselectivity · transition metals

Introduction

In the last decade Pt^{II} and $Au^{I,III}$ complexes and salts have increasingly found use as efficient catalysts in a wide variety of organic reactions involving C–C bond formation.[1] The soft and alkynophilic character of these noble metals enables mild and chemoselective transformations of readily available acyclic alkynes into useful, functionalized cyclic skeletons.[2] Experimental and theoretical studies have suggested that these catalysts activate alkyne moieties upon coordination toward nucleophilic addition, to yield carbenoid intermediates, which generate different cyclic adducts depending on the molecular structure.[3,4] In this context, one of the most important reactions from a synthetic point of view concerns propargylic carboxylates,[5] which afford functionalized bicyclo[*n*.1.0]enol esters from 1,5- and 1,6-enynes, which are valuable building blocks for the preparation of a diversity of natural products.[6,7] Thus, this methodology has emerged as a more convenient, less hazardous alternative to the use of α-diazocarbonyl compounds.[8]

Regarding the molecular mechanism of the cycloisomerization of propargylic esters with alkene groups, the intramolecular reaction follows different paths in the available manifold, depending on the nature of the enyne. Thus, our previous computational results,[9] which were later confirmed by experimental evidence,[7] have suggested that for 1,5- and 1,6-enynes the mechanism proceeds through a cyclopropanation step to generate a metallocyclopropyl carbenoid intermediate, which undergoes a 1,2-acyl shift to yield the cyclopropane-fused bicyclic compounds **I** (Scheme 1). This pathway can account for the experimentally observed transfer of chiral information from the propargylic position to the product, on the basis of subtle intramolecular interactions in the cyclopropanation transition structure.

However, 1,4-enynes do not yield cyclopropyl derivatives because of ring strain, but allow an efficient synthesis of cyclopentenones **II** (Scheme 1),[10] as an alternative to classical reactions such as the Pauson–Khand cyclocarbonylation[11] and the Nazarov cyclization;[12] alternatively, indene derivatives **III** are produced when the nucleophile is an aryl group (Scheme 1).[13] These transformations follow an inverse sequence of steps (i.e., 1,2-acyl shift, then cyclization) due to the conformationally restricted environment. This rearrangement reveals a high degree of chirality transfer, which has been computationally justified through a mechanism via carboxylate migration to yield a pentadienyl intermediate

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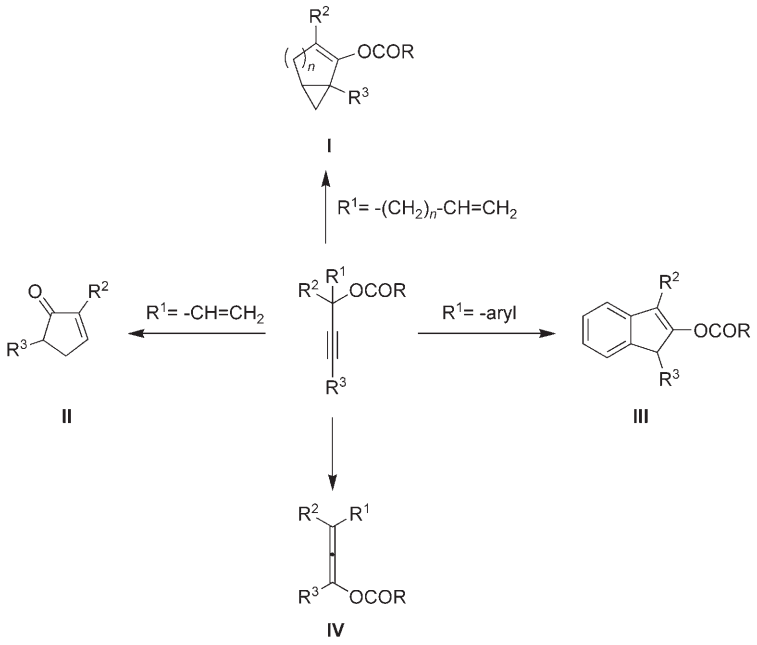


Scheme 1. Transformations of propargylic esters promoted by late-transition-metal complexes.

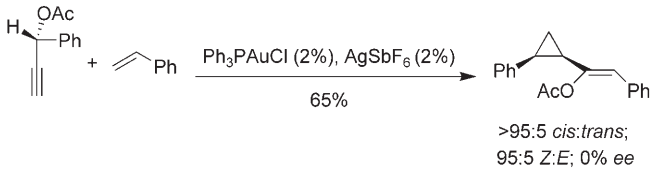
On other hand, besides the 1,2-ester rearrangement, the corresponding 1,3-migration of the ester is also possible to yield allenyl derivatives **IV** (Scheme 1), which interestingly provide access to a wide variety of useful functionalized adducts. This divergent behavior critically depends on the alkyne substitution in such a way that alkyl substituents enhance the 1,3-rearrangement.[6,7a,15b,17,18]

As can be deduced, this complex scenario requires a deep analysis to understand the factors that control the regio- and stereoselectivity of the reaction. This will allow the improvement and development of more selective and efficient reactions, of significant synthetic potential. Herein, we present a thorough study of the plausible mechanisms of the intermolecular process by means of a theoretical approach based on density functional theory (DFT) calculations. Particular attention has been paid to the stereoselectivity of the catalytic cycle. In addition, to gain insights into the chemo- and regioselectivity issues, we have evaluated the possible competing reactions in an effort to describe the factors that control the evolution of the activated alkyne.

that displays a helical nature, which indeed preserves the chiral information.[14]

The intermolecular reaction of propargylic esters with alkenes, which is promoted by a variety of catalysts was first reported by Uemura et al.,[15] who observed the formation of two diastereomers on the cyclopropanated product in addition to the competing formation of an allenyl ester.

Based on the ability of phosphine–Au^I complexes to promote the intramolecular cycloisomerization of enynes, Toste et al. carried out the corresponding intermolecular reaction with alkenes.[16] Their results revealed, in sharp contrast with the intramolecular version, that the reaction of enantioenriched propargylic carboxylates with olefins leads to racemic allyl cyclopropanes with complete loss of optical purity (Scheme 2). This observation is consistent with the interme-



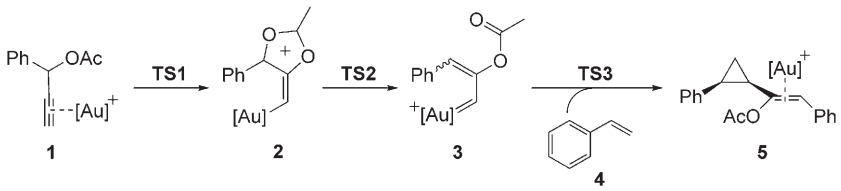
Scheme 2. Intermolecular cyclopropanation of enantioenriched propargylic esters catalyzed by gold(I) (ref. [16]).

diacy of a planar, achiral, alkylidene intermediate, which is formed by an initial 1,2-carboxylate migration. Experimental results also indicated a high *cis* selectivity in the formation of the C=C bond and the cyclopropane ring. However, the fact that the intermolecular version might follow a different mechanistic route that 1,5- and 1,6-enynes, which also exhibit a high conformational freedom, is intriguing and not justified so far.

Results and Discussion

The intermolecular Au^I-catalyzed cyclopropanation tolerates a wide range of olefin substitution patterns, including mono-, 1,2-di-, 1,1-di-, tri-, and tetrasubstituted alkenes. This reaction provides vinyl cyclopropanes with moderate to high *cis* selectivity,[16] and therefore complements the *trans* selectivity that is often observed in olefin cyclopropanations by using α-diazoacetates.[19] Uemura et al. also reported the same *cis* stereoselectivity in the presence of other catalysts, such as $[\{RuCl_2(CO)_3\}_2]$, $IrCl_3$, $AuCl_3$, and $PtCl_2$.[15b] Experimental results reported by Toste et al.[16] showed that the Au^I-catalyzed reaction of enantioenriched propargylic acetate with styrene yields racemic vinyl cyclopropane, but with high diastereoselectivity (Scheme 2).

On the basis of these observations, we first conducted a DFT analysis on the mechanism in which a 1,2-acyl shift was followed by the cyclopropanation step (Scheme 3). The metal complex is asymmetrically coordinated by the alkyne carbon atoms, with one shorter Au–C_1 distance (Au–C_1 = 2.285, Au–C_2 = 2.465 Å). The formation of the presumed vinyl carbenoid intermediate **3** (Scheme 3) takes place through two consecutive steps. The 5-*exo-dig anti* nucleo-



Scheme 3. Reaction mechanism for the intermolecular cyclopropanation of propargylic esters.

philic attack[20] of the ester onto the activated internal acetylenic carbon of **1** (Scheme 3) proceeds via transition structure **TS1** (O-C_2 = 2.473 Å), which evolves to the five-membered cyclic intermediate **2**. The subsequent ring opening may proceed through two paths, via transition structure **TS2a** or **TS2b**, to yield a (*Z*)-**3a** or *E*-vinyl carbene (**3b**), respectively (Figure 1). Whereas the ester group experiences a

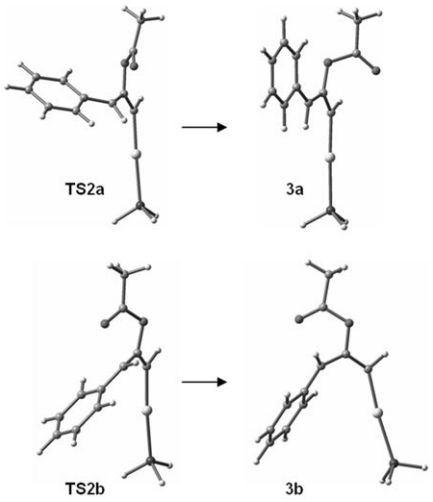


Figure 1. Optimized structures for the ring opening of **2** to the vinyl-carbenoids **3a** and **3b**.

barrierless torsion upon optimization to a planarized *Z* intermediate, to alleviate the steric congestion, the *E*-vinyl carbenoid exhibits steric hindrance between the phenyl moiety and the catalyst to yield a nonplanar π system. These structural effects have a deep impact on the electronic character of the carbene atom, as we will describe later.

At this point, we calculated the possible transition structures for the addition of the carbene to the double bond of a styrene molecule (**4**). From a stereochemical point of view, the cyclopropanation of the achiral *Z*- and *E*-vinyl intermediates can each affords two pair of enantiomers, given that the reaction generates two new stereocenters. A monosubstituted alkene, such as styrene, can attack a given carbene face in four different approaching trajectories, through four possible transition states. One might envision that the alkene could rotate around the approach vector to minimize unfavorable interactions.

We have herein focused only on the cyclopropanation via the *Z* intermediate because according to energy calculations (see below), it should be favored over the *E* intermediate (**TS3$_V$**, see Table 1), which in fact, agrees with the experimental stereochemical outcome (for transition structures that involve an *E* intermediate, see the Supporting Information).

The four isomeric transtion states of the approaching of the alkene to the *Z*-carbene are two pairs of *cis*-(**TS3$_I$**, **TS3$_{II}$**) and *trans*-(**TS3$_{III}$**, **TS3$_{IV}$**) adducts (Figure 2), each being, in

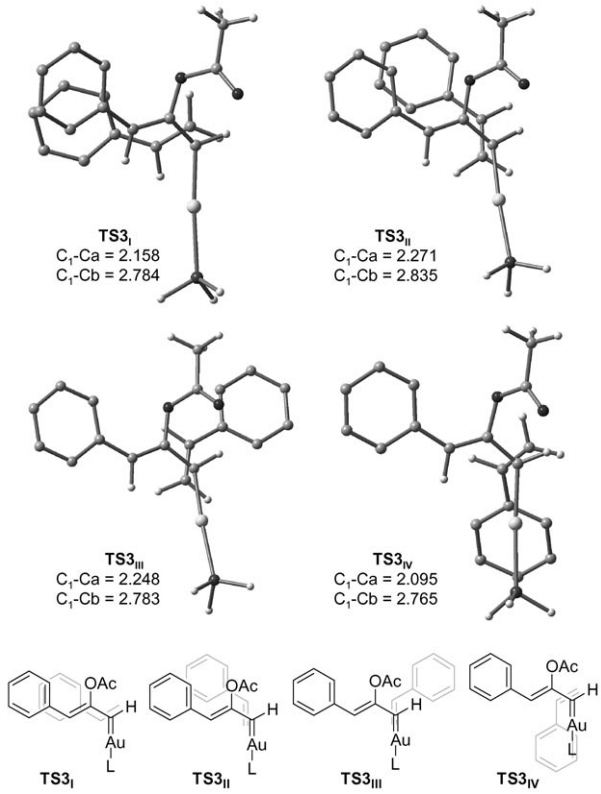


Figure 2. Transition structures of the cyclopropanation step for the styrene attack to the catalyst–carbenoid complex (distances with the unsubstituted Ca, and substituted, Cb, alkene atom are shown in Å). Most of the H's have been omitted for clarity.

turn, a pair of enantiomers. Noteworthy, conformers **TS3$_{II}$** and **TS3$_{III}$** present the C=C bond of the incoming alkene antiperiplanar to the Au–C_1 bond (torsion angle 175.4 and 166.3°, respectively), whereas **TS3$_I$** and **TS3$_{IV}$** show a *gauche* disposition (52.4 and 49.4°, respectively), which involves a high energy.[21] All our efforts to locate antiperiplanar transition structures for **TS3$_I$** and **TS3$_{IV}$** were unsuccessful; instead, the alkene rotated upon optimization around the approach vector to yield a *gauche* orientation. This effect minimizes the steric repulsion with the catalyst for **TS3$_{IV}$**. Regarding **TS3$_I$**, the alkene rotation is promoted by the formation by stabilizing π–π stacking interactions.

These TSs correspond to a concerted yet highly asynchronous reaction pathway; this is consistent with the reaction of an electrophilic carbene with an electron-rich olefin,[22] with different C–C bond forming distances ($\Delta d = 0.535$–0.670 Å) due to steric reasons, as can be deduced from comparison with the cyclopropanation with ethylene ($\Delta d = 0.190$ Å; not shown).

Table 1 summarizes the enthalpy and free energy differences computed in the gas phase and in nitromethane for this mechanism along the reaction coordinate (Figure 3). The first step proceeds with a very low activation barrier and is moderately exothermic, which points to a favorable 5-*exo-dig* cyclization of the ester group onto the activated alkyne. The heterocycle opening involves a somewhat higher activation barrier and is slightly endothermic. The calculated results reveal that the formation of the *E* intermediate **3b** is kinetically favored over the *Z* isomer **3a**, but thermodynamically disfavored due to steric repulsions between the phenyl moiety and the catalyst. In fact, the strong steric congestion exhibited by **3b** inhibits an efficient cyclopropanation, as revealed by the computed energy values (**TS3$_V$**). The loss of conjugation in the *E* isomer results in a change in the energy of the transition states.[23] The computed NPA charge on C_1 (-0.377 and -0.467 for the **3a** and **3b**, respectively) indicates a higher electron density on C_1 for **3b** which, in turn, makes the carbene less electrophilic and suggests a less favorable interaction with the nucleophile.

Table 1. Relative enthalpies and free-energies (in kcal mol^{-1}) for the cyclopropanation of propargylic ester **1** according to the mechanism depicted in Scheme 3.

	ΔH_{gas}	ΔG_{gas}	ΔH_{MeNO_2}	ΔG_{MeNO_2}
1	0.0	0.0	0.0	0.0
TS1	3.1	4.1	0.2	1.2
2	−16.4	−14.3	−13.6	−11.5
TS2a	−8.7	−5.9	−4.7	−2.0
3a	−15.5	−12.6	−13.0	−10.1
TS2b	−11.1	−7.8	−8.1	−4.8
3b	−11.4	−8.5	−9.4	−6.5
cyclopropane diastereoselectivity				
TS3$_I$	−13.2	1.0	−5.5	8.8
TS3$_{II}$	−13.2	0.6	**−5.8**	**7.9**
TS3$_{III}$	−11.7	1.7	**−4.3**	**9.2**
TS3$_{IV}$	−10.8	3.4	−3.8	10.4
TS3$_V$[a] (**3b**)	−5.7	8.1	1.6	15.5
cis-**5**	−35.1	−19.0	−30.4	−14.3
trans-**5**	−34.2	−20.8	−27.4	−14.0

[a] Only the most favorable result for the cyclopropanation of **3b** is shown.

The model suggests a mechanism based on three reaction steps, with the cyclopropanation being the rate-limiting step. The overall process is favored from a thermodynamic point of view (-19.0 kcal mol^{-1}). When solvent effects are taken into account, similar conclusions can be drawn. The most striking differences concern the lowered activation barrier for the first step, which is due to a better electrostatic solvation of the transition structure in comparison to the reactant, and the higher barrier for the cyclopropanation event, which can be explained by a poor stabilization of the styrene upon solvation by the polar environment.

The strong entropic contribution ($\Delta S^{\neq}$ in the range -46 to -48 cal mol^{-1} K^{-1} for the cyclopropanation step) could explain the difference in the presumed reaction pathway between the intra- and intermolecular cycloisomerization of propargylic esters, because an initial intermolecular cyclopropanation would involve a high free energy barrier. To test this hypothesis, we have performed geometry optimizations according to the proposed intramolecular mechanism, through initial cyclopropanation followed by acyl migration, by taking into account the stereochemical implications. To this end, we have analyzed precursors (*R*)- and (*S*)-**1**, and also enyne **6** for comparison with the intramolecular process (Scheme 4).

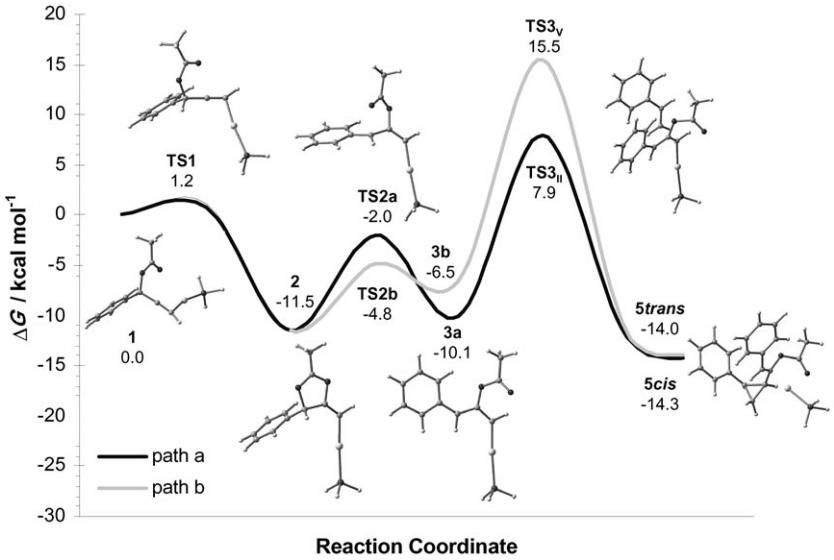
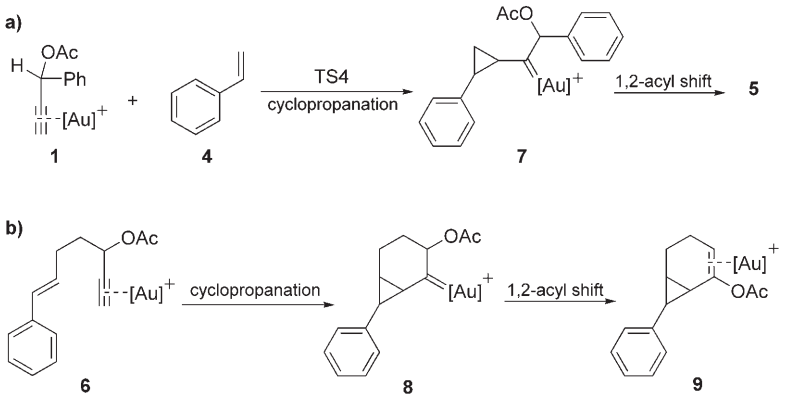


Figure 3. Free energy profile for the catalytic cycle. Formation and cyclopropanation of both the vinyl intermediates **3a** and **3b** are included. Only optimized structures for path **3a** are shown for the sake of clarity.

The eight conceivable transition structures for both enantiomers, *R* and *S* are depicted in Figure 4. The most stable structures are those arising from an *exo* approach of the alkene onto the least hindered side of the ester, *R*-**TS4$_I$** and *S*-**TS4$_I$**. They lack the destabilizing interactions found for other conformers because the alkene substituent remains far away from the propargylic substitu-



Scheme 4. Reaction mechanism through the initial cyclopropanation step.

ents. The most stable transition structures present a rather low enthalpy barrier, which is close to that computed for the intramolecular cyclopropanation of enyne **6** (4.0 for *R*-**TS4$_I$** vs. 5.7 kcal mol^{-1} for **6** in the gas phase); however, the entropy contribution (−40 for *R*-**TS4$_I$** vs. −2 cal mol^{-1} K^{-1} for **6**) yields a free energy of activation of 15.8 for the intermolecular process, which is higher than any step of the alternative mechanism. Remarkably, solvent effects clearly increase the free energy barrier to 22.4 kcal mol^{-1} for *R*-**TS4$_I$**, whereas they induce a faster intramolecular cyclopropanation of **6** (free energy of activation of 3.2 kcal mol^{-1}).

These results suggest a different mechanistic model for both processes. Furthermore, the data cannot account for the stereochemical outcome of **1**, because they point to a more favorable formation of the *trans* adducts, which is in disagreement with the experimental evidence. Hence, although the sequence depicted in Scheme 4a is plausible,[23] the high free energy barrier for the first step supports a different mechanistic picture for the inter- and intramolecular processes. Thus, it could be said that the entropy modulates the operative mechanism in the cyclopropanation of propargylic esters.

Insights into the stereochemistry

The results shown above give valuable information about the general mechanism of the intermolecular cyclopropanation, including important insights into the origin of the stereoselectivity. First of all, structural and energetic data rightly reproduces the marked *Z* diastereoselectivity of the olefin that is observed experimentally. As advanced above, the *E*-vinyl-carbenoid intermediate **3b** gives rise to a kinetically less favored cyclopropanation than the *Z* isomer due to its less electrophilic character (Table 1). Therefore, it seems a nonproductive route to afford cyclopropanated products, albeit this intermediate might evolve through a competing cyclization path in the case of a propargylic phenyl substituent, as we will discuss later.

Regarding the origin of the cyclopropane *cis*/*trans* diastereoselectivity, the transition structure **TS3$_{II}$** (Figure 2), which arises form the *cis* approach of the olefin to the carbene with respect to the ester fragment, shows a lower energy than the diastereomeric structure **TS3$_{III}$**. This is due to π-stacking interactions between the *syn* aromatic rings, which stabilize **TS3$_{II}$** and also **TS3$_I$**. In contrast, the steric repulsion between the olefin substituent and the metal center might account for the high energy in **TS3$_{IV}$**. The structure **TS3$_{III}$** shows neither stabilizing nor destabilizing interactions, and yields a more stable TS from the *trans* approach than **TS3$_{IV}$**. Additionally, the *gauche* orientation between the reactant moieties (**TS3$_I$**, **TS3$_{IV}$**) have been shown to be disfavored for styrenes on related cyclopropanations.[21] These results allow an estimation of the *cis*/*trans* selectivity (based on the Boltzmann distribution that was obtained from Gibbs free energies) of 91:9; this is consistent with the experimental value (>95:5).

To further test the mechanistic model, we have performed calculations of the cyclopropanation with a trisubstituted alkene, 1-methyl cyclopentene, which gives rise to a low *cis*/*trans* stereoselectivity. The Boltzmann distribution analysis computed from the free energy values for the transition structures, predicted a *cis*/*trans* ratio of 1.8:1, which is in good agreement with the reported experimental data (1.2:1).[16] The transition state structures are shown in Figure 5.

In summary, the calculations agree with the experimental observations and suggest a *cis* selectivity in the rate- and selectivity-determining cyclopropanation step.

Competitive processes

Intramolecular pentannulation: Sarpong et al. reported pentannulations of aryl propargylic esters for the synthesis of indenes **III** in the presence of [$PtCl_2(PPh_3)_2$] (Scheme 1).[13a] This process involves a formal C−H insertion of the vinyl carbene intermediate.[24] A related transformation has been recently performed by Wang and co-workers, who developed the Au-catalyzed synthesis of indene derivatives from propargylic sulfides and related dithioacetals.[25]

Given the aforementioned highly unfavorable entropic effect that accompanies the cyclopropanation from the vinyl carbenoid intermediate, the competing intramolecular formation of indene might be envisaged. In this context, very recently Ohe et al. have reported that the pentannulation reaction competes with the intermolecular cyclopropanation for *sec*- and *tert*-propargylic esters under catalytic conditions (Ru complexes or $PtCl_2$).[26] They have noted that the distribution of products is influenced by the substituents at the propargylic position (Figure 6).

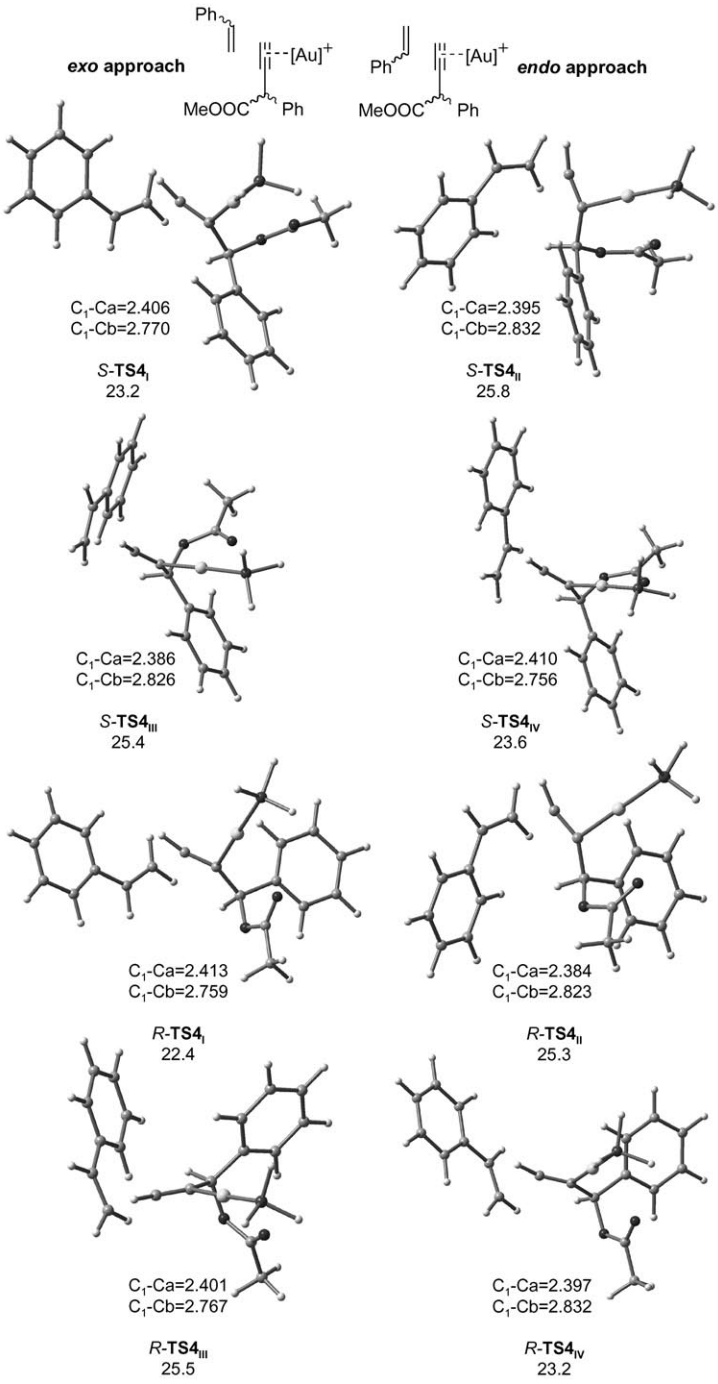


Figure 4. Transition structures of the cyclopropanation as first step of the cycloisomerization of *R*- and *S*-**1** and styrene (distances with the unsubstituted Ca, and substituted, Cb, alkene atom are shown in Å). Free energy barriers from the reactant complex are given in kcal mol^{-1}.

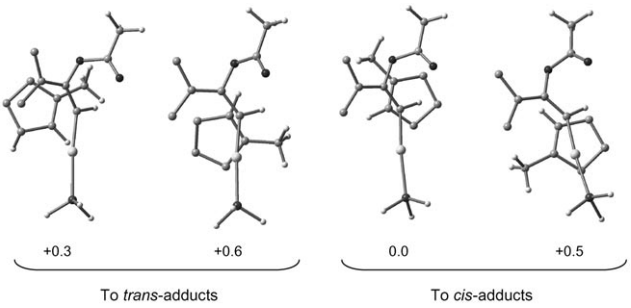


Figure 5. Transition structures of the cyclopropanation step of 1-methyl cyclopentene with the carbenoid complex. Most of the hydrogen atoms have been omitted for clarity. Free energy differences from the most stable TSs are given in kcal mol^{-1}.

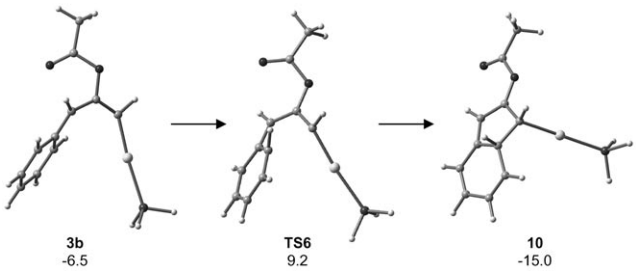


Figure 6. Optimized structures for the pentannulation process from the *E*-vinyl intermediate **3b**. Free energy differences from the reactant complex are given in kcal mol^{-1}.

The pentannulation step for precursor **1** (Figure 6) takes place through the sterically less-favored *E*-vinyl carbene intermediate,[24] which is thermodynamically less stable and less apt to undergo a cyclopropanation process than the *Z* intermediate, as noted above. The calculations indicate that the pentannulation proceeds with a free energy barrier of 15.7 kcal mol^{-1} (9.2 kcal mol^{-1} from the reactant complex), and is exothermic by -8.5 kcal mol^{-1} (-15.0 kcal mol^{-1} from the reactant). These results suggest that this path is certainly viable under the reaction conditions, albeit less favored than cyclopropanation in the presence of an olefin from kinetic and thermodynamic perspectives; this is consistent with the experimental observations for the Au^{I}-mediated cycloisomerization of precursor **1**.[16]

Formation of allene: The transformation of propargylic esters into allenyl esters is a common reaction than can be mediated by late transition metals.[18,27–29] Moreover, these catalysts can further activate the allene formed for subsequent reactivity; this gives rise to a wide diversity of products.[13b,30] Hence, this [3,3]-sigmatropic rearrangement competes with the formation of the vinyl carbenoid intermediate through another intramolecular mechanism that involves similar entropic effects. Moreover, a critical dependence of the acetylenic substitution on the nature of the ester shift has been found:[31] terminal alkynes preferentially undergo a 1,2-migration of the acetate fragment, although allene has been occasionally detected as a minor product during the inter- or intracyclopropanation of propargylic esters promoted by $PtCl_2$,[17] $AuCl_3$,[15b] and Au^{I};[28b] in contrast, internal alkynes bearing alkyl or phenyl substituents mainly exhibit the formation of allene through a 1,3-ester shift.

Theoretical calculations have revealed that the formation of allene is a stepwise process through two steps involving

low activation barriers:[4c,32] first, the rate-limiting 6-*endo-dig* attack of the carboxylic oxygen onto the alkynyl group, to form a six-membered heterocycle, followed by the ring-opening step.

To get insights into this competitive reaction, we have chosen as theoretical models the precursor **11**, because both Au^{I} and Pt^{II}-catalyzed processes have been reported, and the analogous methylated **12**, to cover the influence of the acetylenic substitution. Figure 7 and Figure 8 display the free energy profile for the 1,2- and 1,3-acyl shift for **11** and **12** catalyzed by Au^{I} and $PtCl_2$, respectively. These results are consistent with the reported data and indicate that: i) unsubstituted precursor **11** undergoes a most favorable 1,2-acyl shift, under both catalytic and solvent conditions, in contrast to precursor **12**; ii) the 1,3-acyl migration for **11** under $PtCl_2$ catalysis becomes less disfavored in comparison to the 1,2-shift in the polar solvent; iii) the apolar solvent enhances the regioselectivity for the ester migration that is mediated by $PtCl_2$ for **12**.

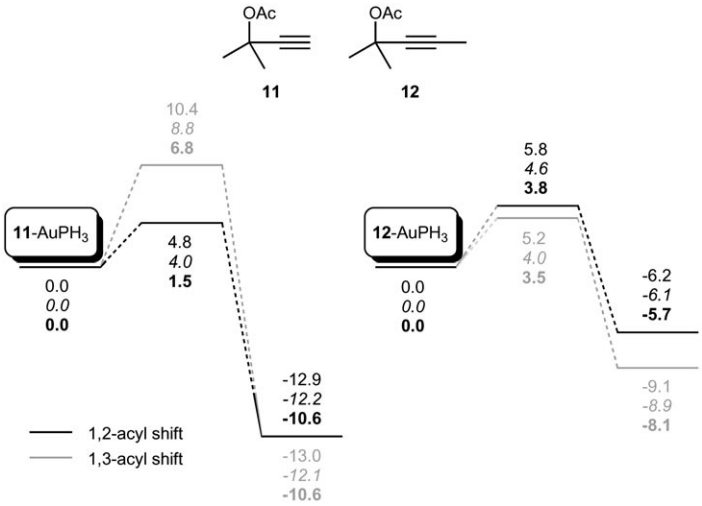


Figure 7. Free-energy profile for the 1,2- and 1,3-acyl shift for **11** and **12**, promoted by Au^{I}, in the gas-phase (normal), toluene (italic) and nitromethane (bold).

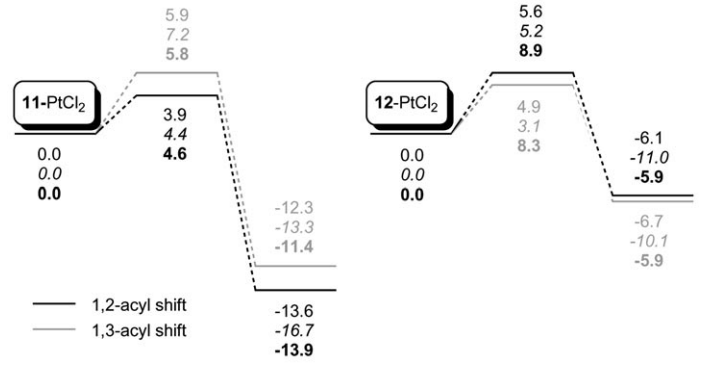


Figure 8. Free-energy profile for the 1,2- and 1,3-acyl shift for **11** and **12**, promoted by $PtCl_2$, in the gas-phase (normal), toluene (italic) and nitromethane (bold).

As far as a 1,3-migration for **12** would be disfavored due to the presence of the substituent, the change in regioselectivity must be due to electronic factors, which are probably enhanced by steric effects. According to the computed NPA charges, the acetylenic substituent enhances the electrophilic character of the methyl-substituted alkyne carbon. In a comparison with the unsubstituted model **11**, the substituent clearly induces a higher charge density in C_2 in **12** and an opposite effect in C_1 (Table 2), hence the 5-*exo-dig* cyclization of the ester oxygen (or other nucleophile) is inhibited, thus being the 6-*endo-dig* reaction mode a more favorable from a kinetic point of view.

Table 2. NPA charges on the alkyne carbon atoms activated by $AuPH_3$ and $PtCl_2$, and the relevant metal–C distances (Å).

	$AuPH_3$				$PtCl_2$			
	charge C_1	charge C_2	Au–C_1 distance	Au–C_2 distance	charge C_1	charge C_2	Pt–C_1 distance	Pt–C_2 distance
11	−0.356	**+0.063**	2.239	2.514	−0.171	**+0.006**	2.052	2.219
12	**+0.031**	−0.131	2.377	2.285	**+0.083**	−0.019	2.102	2.089

The catalyst is pushed out and the metal–C_1 distance increases with the alkyne substitution to reduce the steric hindrance. It gives rise to a shorter metal–C_2 length, which ultimately should depend on the substitution at the propargylic center. Overall, this effect reverses the polarization of the alkyne and induces a higher electrophilic center at C_1, as opposed to the unsubstituted model **11**.

Conclusion

The easily accessible propargylic esters are versatile substrates, and simple modifications of molecular structure result in diverse product patterns. Given that this methodology is very recent, many mechanistic details remain unknown and results are often difficult to explain. In this regard, a intriguingly issue concerns the notorious discrepancy between the reaction pathway followed in the intra- and intermolecular cyclopropanation processes. To this end, we have undertaken the analysis of the intermolecular cyclopropanation of propargylic esters with alkenes. DFT calculations allow us to propose a reaction mechanism and explanation for the reasons behind the difference with the intramolecular version of this process. The results strongly suggest that the entropic effects could modulate the operative mechanism and account for the aforementioned mechanistic discrepancy. Thus, the entropy preferentially drives the intermolecular reaction through an intramolecular *endo-dig* cyclization of the ester oxygen, which is kinetically more favorable than an intermolecular cyclopropanation with the alkene.

The data calculated according to this mechanistic model accounts for the experimental stereoselectivity on the basis of intra- and intermolecular interactions, and the energy

values yield product ratios in good agreement with the observed *cis*/*trans* diastereoselectivity.

Besides the cyclopropanation process, other transformations can take place and compete for such versatile precursors. Our results are supported by the experimental observations and suggest that a possible pentannulation with a propargylic aromatic ring is a feasible reaction, but it is kinetically and thermodynamically less favored than cyclopropanation in the presence of an alkene.

On other hand, a 1,3-acyl shift would also show a similar entropy barrier than that computed for the 1,2-acyl shift step implied in the intermolecular cyclopropanation. Although other factors may come into play, DFT results reveal that the former is a considerably kinetically less-favored process than the later for terminal alkynes, either in apolar or polar solvents, whereas the 1,3-migration becomes the preferred path for internal alkynes; this is in agreement with the experimental evidence. The alkyl substituent in the acetylenic position markedly modifies the electronic properties of the activated alkyne and enhances the electrophilicity of that acetylenic atom, and hence, allows a faster 1,3-acyl shift to take place.

In summary, these findings provide new mechanistic details about this complex scenario and the factors that control the versatility and mechanistic diversity found in the metal-catalyzed transformations of propargylic esters.

Computational Methods

Calculations were carried out using the Gaussian 03 program.[33] All the structures were optimized at the DFT level by means of the B3LYP functional.[34] The 6–31G(d) basis set was applied for all the atoms except Au and Pt, which have been described by the LANL2DZ basis set,[35] in which the innermost electrons are replaced by a relativistic ECP and the valence electrons are explicitly treated by a double-ζ basis set. To keep the computational cost practical, the original Au ligand, PPh_3 was substituted by PH_3. The optimized geometries were characterized by harmonic analysis, and the nature of the stationary points was determined according to the number of negative eigenvalues of the Hessian matrix. The intrinsic reaction coordinate (IRC) pathways[36a] from the transition structures have been followed by using a second-order integration method,[36b] to verify the proper connections. Zero-point vibration energy (ZPVE) and thermal corrections (at 298 K, 1 atm) to the energy have been estimated based on the frequency calculations.

Solvent effects were obtained through single-point calculations on the gas-phase-optimized geometries with the Polarizable Continuum Model PCM,[37] as implemented in Gaussian 03. Relative permittivities of 38.200 and 2.379 were assumed in the calculations to simulate nitromethane and toluene as solvent, respectively.

Natural bond orbital (NBO) analysis[38] was performed by the module NBO v.3.1 implemented in Gaussian 03 to evaluate the NPA atomic charges.

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