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Mechanistic Insights on the Cycloisomerization of Polyunsaturated Precursors Catalyzed by Platinum and Gold Complexes

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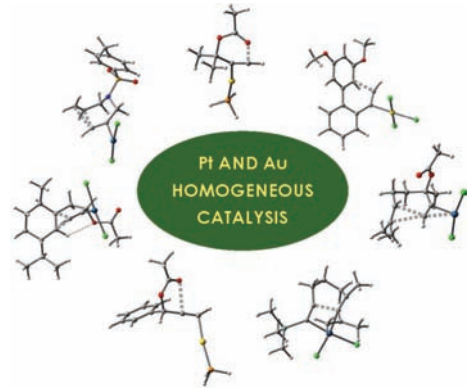
CONSPECTUS



Organometallic chemistry provides powerful tools for the stereocontrolled synthesis of heterocycles and carbocycles. The electrophilic transition metals Pt(II) and Au(I, III) are efficient catalysts in these transitions and promote a variety of organic transformations of unsaturated precursors. These reactions produce functionalized cyclic and acyclic scaffolds for the synthesis of natural and non-natural products efficiently, under mild conditions, and with excellent chemoselectivity.

Because these transformations are strongly substrate-dependent, they are versatile and may yield diverse molecular scaffolds. Therefore, synthetic chemists need a mechanistic interpretation to optimize this reaction process and design a new generation of catalysts. However, so far, no intermediate species has been isolated or characterized, so the formulated mechanistic hypotheses have been primarily based on labeling studies or trapping reactions. Recently, theoretical DFT studies have become a useful tool in our research, giving us insights into the key intermediates and into a variety of plausible reaction pathways.

In this Account, we present a comprehensive mechanistic overview of transformations promoted by Pt and Au in a non-nucleophilic medium based on quantum-mechanical studies. The calculations are consistent with the experimental observations and provide fundamental insights into the versatility of these reaction processes. The reactivity of these metals results from their peculiar Lewis acid properties: the alkynophilic character of these soft metals and the π-acid activation of unsaturated groups promotes the intra- or intermolecular attack of a nucleophile.

1,*n*-Enynes ($n = 3-8$) are particularly important precursors, and their transformation may yield a variety of cycloadducts depending on the molecular structure. However, the calculations suggest that these different cyclizations would have closely related reaction mechanisms, and we propose a unified mechanistic picture. The intramolecular nucleophilic attack of the double bond on the activated alkyne takes place by an endo-dig or exo-dig pathway to afford a cyclopropyl-metallocarbenoid. Through divergent routes, the cyclopropyl intermediate formed by *exo*-cyclopropanation could yield the metathesis adduct or bicyclic compounds. The *endo*-cyclization may be followed by a [1,2]-migration of the propargyl moiety to the internal acetylenic position to afford bicyclic [*n*.1.0] derivatives. This reaction mechanism is applicable for functional groups ranging from H to carboxylate propargyl substituents (Rautenstrauch reaction).

In intramolecular reactions in which a shorter enyne bears a propargyl ester or in intermolecular reactions of an ester with an alkene, the ester preferentially attacks the activated alkyne because of enthalpic (ring strain) and entropic effects. Our calculations can predict the correct stereochemical outcome, which may aid the rational design of further stereoselective syntheses.

The alkynes activated by electrophilic species can also react with other nucleophiles, such as aromatic rings. The calculations account for the high *endo*-selectivity observed and suggest that this transformation takes place through a Friedel–Crafts-type alkenylation mechanism, where the endo-dig cyclization promoted by $PtCl_2$ may involve a cyclopropylmetallacarbene as intermediate before the formation of the expected Wheland-type intermediate.

These comparisons of the computational approach with experiment demonstrate the value of theory in the development of a solid mechanistic understanding of these reaction processes.

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1. Introduction

One of the most active fields of research in modern organic chemistry is the development of efficient strategies for the stereocontrolled synthesis of complex functionalized hetero- and carbocycles. In this context, catalytic organometallic chemistry has emerged as a powerful tool.[1] Among the transition metals, those from groups 10−12 exhibit significant efficacy for catalyzing the formation of carbon−carbon and carbon−heteroatom bonds. In particular, complexes and salts derived from late transition metals Pt and Au (gold(III) and cationic gold(I)) have shown an exceptional ability to promote a variety of organic transformations of unsaturated precursors.[2] These processes result from the peculiar Lewis acid properties of these metals: the alkynophilic character of these soft metals and the π-acid activation of unsaturated groups promotes the intra- or intermolecular attack of a nucleophile.

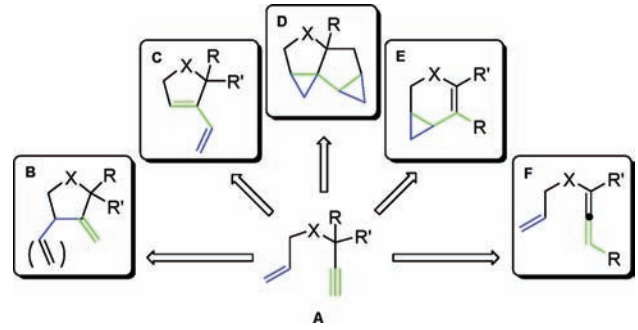
The pioneering efforts in this area in the early 1990s utilized simple metal salts, such as halides ($PtCl_2$ and $AuCl_3$) due to their apparent insensitivity under aqueous conditions and ability to successfully promote a diversity of synthetic transformations, but a decade later, Au(I) cationic species have proven to be superb catalysts for both carbon−carbon and carbon−heteroatom bond formations. Because the activation process invokes electrophilicity enhancement, a move toward cationic metal templates, which may be stabilized by a suitable spectator ligand, results in increased activity.

These catalysts allow us to overcome additional problems associated with other metal complexes that also promote the same transformations, such as Hg salts, since they are considered essentially nontoxic. Furthermore, they combine high affinity to the π system with the advantages of a kinetically labile carbon−metal bond that can be readily cleaved under the reaction conditions, thus ensuring efficient turnover.[3]

These reactions provide an atom-economical entry into functionalized cyclic and acyclic scaffolds useful for the synthesis of natural and non-natural products under mild conditions with excellent chemoselectivity and high synthetic efficiency. Consequently, during the last five years an explosive increase of interest in Au and Pt catalysis has taken place, thus becoming an extremely dynamic and innovative field of catalysis research.

In this context, an array of mechanistic hypotheses has been formulated to account for the results, leading many times to an astonishing diversity of proposals for the same reaction. Therefore, a mechanistic interpretation is needed to direct and improve a given process. The theoretical underpinnings have been considered later and, despite computational analyses being less abundant, they have become a useful tool for rationalizing the role of the molecular structure of precursor and catalyst and accounting for the versatility of these reactions.

SCHEME 1



In recent years, we have been actively working on the determination, by computational methodology, of reaction mechanisms of transformations catalyzed by Pt and Au. In this Account, we provide a perspective on the mechanisms and discuss the most significant features and results obtained in our group on this fascinating research area.

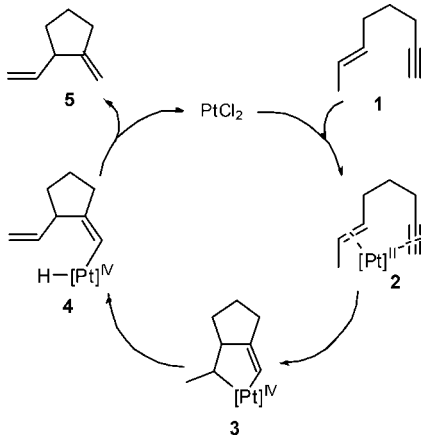
2. The Cycloisomerization of Enynes

The high synthetic potential of polyunsaturated systems has made possible the preparation of a wide variety of cyclic building blocks under homogeneous Pt and Au catalysis. In this context, enynes (mainly 1,5- and 1,6-enynes) are exceptionally valuable precursors that have shown a high versatility. For instance, 1,6-enynes (A) can be transformed into Alder-ene products (B), formal methatesis adducts (C), or cyclopropyl-derivatives (D, E) (Scheme 1).[4,5]

2.1. Preference for Alkyne Group. While these catalysts have been used with some success to activate allenes, alkenes, and dienes, the most important application concerns the activation of alkynes.

The coordinating behavior of these late transition metals can be accounted for by relativistic effects: relativity causes the contraction of the atomic s orbitals and expansion of the atomic d and f orbitals, because of an increased shielding effect by the contracted core. This leads to a net contraction and strengthenig of the M−L bonds, though it is dependent on the nature and electronegativity of the ligand. The decreased electron/electron repulsion in the diffuse 5d orbitals qualitatively explain the chemically soft character of these transition metals.[6] Thus, the complexes may be considered as "soft" Lewis acids, preferentially activating "soft" electrophiles such as π-systems.

SCHEME 2



A remarkable property of these catalyzed reactions is the preference of the metal complexes for activating alkyne over alkene moieties. Since a greater stabilization for the ethylene catalyst over the ethyne catalyst π-complex has been estimated,[7,8] the high selectivity is supposedly kinetic in origin. That is, the pronounced "alkynophilicity" of the late transition metal catalysts likely reflects the discrimination by the incoming nucleophile in selecting between activated electrophiles and the preference for attack at the coordinated triple bond.[3,6]

On the basis of the soft nature of these metals, one might expect orbital rather than charge interactions to dominate in binding to an unsaturated C−C fragment.[9] The lowest unoccupied molecular orbital (LUMO) contains the π^*−metal (backdonation) interaction. Hence, such selectivity can be understood by taking into account the LUMO energy for the catalyst coordinated to ethyne and ethylene. The former shows a LUMO energy lower than the latter (by 0.39 and 0.37 eV, for $PtCl_2$ and $AuPH_3^+$, respectively), a gap slightly lower than that for the uncoordinated organic fragments (by 0.62 eV). Consequently, the π-M−alkyne complexes are more electrophilic, so the orbital overlap with the nucleophile should be more efficient.

2.2. Simultaneous Activation of the Double and Triple Bonds. It is well-known that transition-metal complexes, such as $PtCl_2$, catalyze the Alder-ene cycloisomerization.[10] It proceeds by simultaneous coordination of the alkyne and the alkene to the metal followed by an oxidative cyclometalation to form metallacycle **3** (Scheme 2).[11] This intermediate evolves by regioselective β-hydrogen elimination (**4**) followed by reductive elimination to give the cycloisomerized product **5**. Theoretical calculations have suggested a rate-limiting oxidative cyclometalation and that a quaternary propargylic center may cause congestion in the course of the catalyst approach, in such a way that the cyclometalation may be inhibited and alternative cycloisomerizations might be observed.[12] In contrast, this process does not occur for gold(I) since oxidative addition processes are rare for this metal. Products of apparent Alder-ene cycloisomerization have occasionally been found, although they are formed by other mechanisms.[13]

2.3. Activation of the Triple Bond. Other transformations take place through a common electrophilic activation of the triple bond by the catalyst, which generates, as described above, highly electrophilic species and triggers the nucleophilic attack of other functionalities. An asymmetric alkyne implies two differently activated carbon positions, which accounts for the high versatility, although other structural factors come into play. Theoretical calculations have shown that the nucleophilic attack of an alkene can take place through exo-dig or endo-dig pathways (Figure 1) to afford the key cyclopropyl metallocarbenoid intermediates.[14] The involvement of these structures[15] was previously speculated on the basis of trapping reactions.[16]

As proposed by Fürstner,[3] these intermediates can be described in terms of either cationic or carbenoid resonance extremes (Scheme 3) depending on the metal template. Thus, while calculations show a short C−Pt(II) bond (1.88−1.90 Å), resembling a double bond, the C−Au(I) bond length

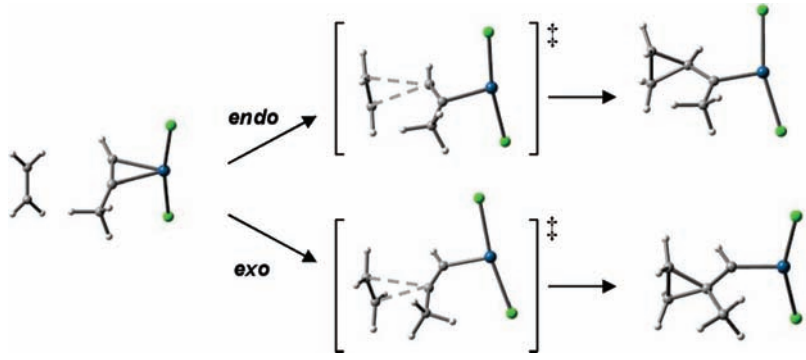


FIGURE 1. Formation of cyclopropyl Pt-carbenoid intermediates by nucleophilic attack of an alkene to the activated triple bond by an endo- or exo-dig pathway (B3LYP/6-31G(d)/LANL2DZ).

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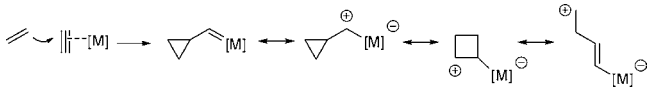

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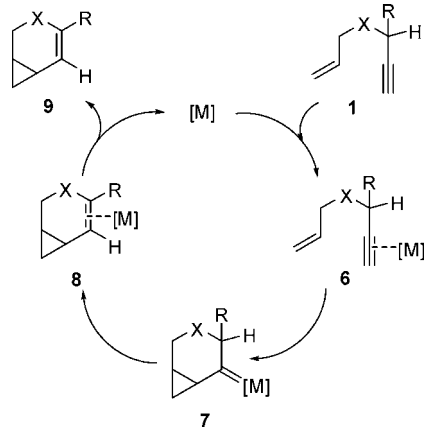

(2.02−2.04 Å) falls within the range for a single bond. The gold intermediates are, hence, more appropriately described as gold-stabilized carbocations rather than "gold-carbenes". This conclusion is supported by recent NMR spectroscopic data.[17]

In a non-nucleophilic medium, the nucleophile that attacks the activated alkyne may be an intramolecular group, such as an alkene in enynes. The catalyzed cycloisomerization of 1,5- and 1,6-enynes bearing a heteroatom as a tether between propargylic and allylic units furnishes heterobicyclo-[3.1.0]hexene and bicyclo[4.1.0]heptene derivatives, respectively. Mono-, di-, and trisubstituted alkenes efficiently participate in this process. This transformation has been explained by invoking several mechanisms;[10] however, a simple picture can be drawn from a theoretical approach. Calculations have revealed that the kinetically preferred pathway is a two-step mechanism through initial endo-dig cyclization from a triggered reactant complex **6** to afford a cyclopropyl metallacarbenoid **7**, followed by a [1,2]-hydrogen shift (Scheme 4).[18] The final 1,2-hydrogen shift and metal elimination are characteristic of metal-carbene chemistry, as proven by deuterium labeling experiments.[19] The presence of a heteroatom at the propargylic site favors this process due to the stabilization of the intermediate by the heteroatom lone pair.

A structurally related precursor can be envisioned by placing the heteroatom at the acetylenic position. The heteroatom controls the evolution of the cycloisomerization to yield a different skeleton.[20] A comparison between the activated complexes for the Pt(II)-mediated processes shows that steric and electronic effects due to the heterogroup induce the formation of an η^1-reactant complex for eneynamides, in contrast with the η^2-complex found for precursors with the tethered heteroatom at the propagylic site (Figure 2).

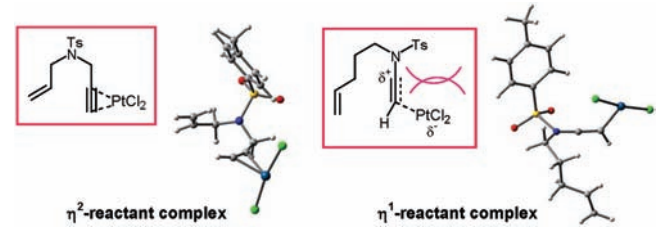

FIGURE 2. Effect of a tethered heterogroup on the π-reactant complexes (B3LYP/6-31G(d)/LANL2DZ).

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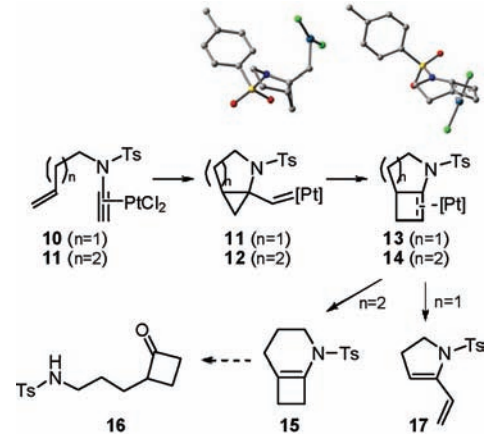

This slippage away from the symmetrical η^2-coordination has a critical impact in the course of the cycloisomerization of eneynamides because the exo-dig cyclization is now the favored route. Calculations[21] suggest that under $PtCl_2$ conditions[20a] the ensuing cyclopropyl intermediate undergoes smooth ring expansion to form the unstable cyclobutene, which evolves through alternative paths depending on the tether length. For 1,7-eneynamides, the reaction leads to the isomerized cyclobutene **15**, which is best hydrolyzed to the cyclobutanone (**16**), whereas for 1,6-eneynamides, the skeletal-rearrangement diene **17** (formal metathesis product) is obtained by conrotatory ring opening to alleviate the ring tension of the fused bicycle (Scheme 5).[20a] As reported by Cossy,[20b] the eneynamides show a similar reactivity in the presence of AuCl, albeit at a lower temperature, and the cyclobutene (**13**/**14**) experiences an easier hydrolysis than under Pt conditions.

The skeletal-rearrangement diene is the usual product for enynes in the absence of nucleophiles (**18**, Scheme 6). Trost[22a] reported the first platinum-catalyzed skeletal rearrangement of an enyne to a 1,3-diene in the presence of $[Pt(PPh_3)_2](OAc)_2$. Later on Murai[22b] and Oi[22c] introduced other Pt(II) complexes as catalysts ($PtCl_2$ at 80 °C and dicationic plat-

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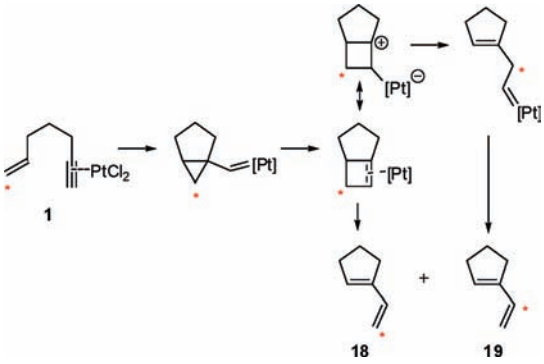


inum complexes at rt, respectively). Similar transformations have been performed with gold(I) at lower temperatures.[20b,c] It soon became clear from the number of structurally interesting products that the mechanism diverged from that accepted for metathesis (Grubbs metathesis) and Alder-ene-type reactions.

Some results described in literature involve anomalous C−C bond formation (**19**, Scheme 6) that cannot be justified on the basis of a single mechanism.[22b] A theoretical study aimed at justifying this divergence under Pt(II) conditions has suggested two operative competing pathways.[23] On one hand, the formation of the "metathesis product" **18** takes place by conrotatory ring opening of the cyclobutene intermediate. The involvement of the cyclobutene is supported by isolation of a less strained bicyclo[4.2.0]oct-1(8)-ene structure from 1,7-enynes[24] and an isomerized cyclobutene from 1,6-enyne.[25] Additionally, the formation of dienes in a stereospecific rearrangement in which the configuration of the starting alkene is retained in the final product supports a final conrotatory opening process.

On other hand, the divergent transformation (**19**) results from a concerted ring-opening/C−H insertion process of the cyclobutene intermediate, followed by a [1,2]-hydrogen shift (Figure 3).[23]

Theoretical analyses by Echavarren for the more active gold(I) cationic complexes have suggested that the catalyst induces the anomalous C−C bond formation on the cyclopropylcarbenoid intemediate by a 1,2-alkyl shift, before a cyclobutene species can be formed (Scheme 7).[26] These mechanistic differences relative to $PtCl_2$ are most likely due to the more-electrophilic character of gold cationic species, which moves the intermediate nature from a carbenoid-dictated outcome toward a more polarized character complex, as deduced by comparison between the computed structures for both catalytic conditions.[23,26]

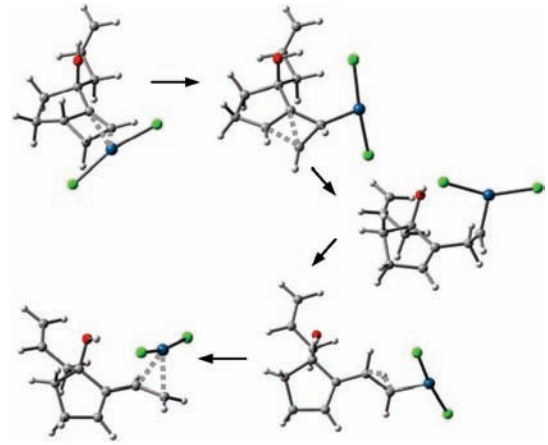
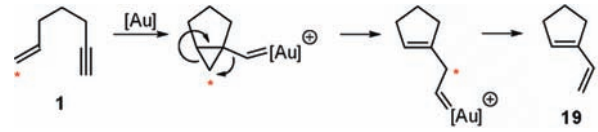
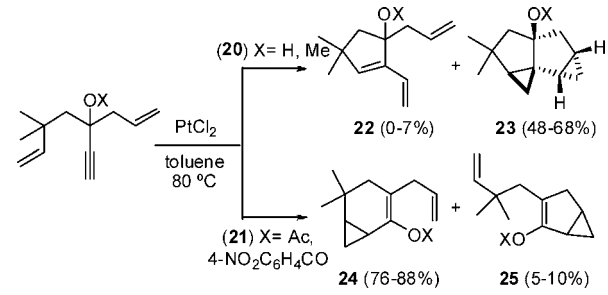


FIGURE 3. Optimized structures for the $PtCl_2$ cycloisomerization of 1,6-enynes to the anomalous skeletal-rearrangement product (B3LYP/6-31G(d)/LANL2DZ).

SCHEME 7



SCHEME 8



The cycloisomerization of dienynes has been revealed as one of the most helpful transformations to get mechanistic insights into these processes. A seminal report on the $PtCl_2$-catalyzed cycloisomerization of dienynes **20** and **21** bearing O-functionalization at the propargylic position (Scheme 8) showed that the nature of the O-protecting group induces different chemo-, regio-, and stereoselective outcomes.[27] A free hydroxy group provides tetracyclic systems **23** and the metathesis adduct **22** as a minor product, while precursors containing *O*-acyl groups afford bicyclic enol esters **24** and **25** with a fused cyclopropane ring at the α,β-positions.

The cycloisomerization of propargylic esters catalyzed by Au and Pt is an active research field studied extensively by several groups[28,29] that shows a highly valuable reactivity and strong synthetic potential and scope. Accordingly, it will be discussed separately.

Precursors **20** showing a 1,6-enyne core and a pendant alkene undergo stereoselective cyclizations to yield tetracy-

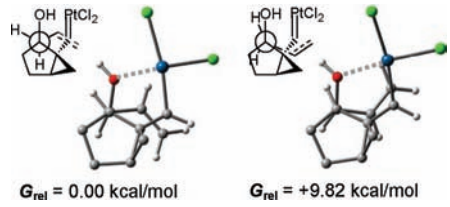


FIGURE 4. Transition structures for the steresoselective second cyclopropanation of dienynes (B3LYP/6-31G(d)/LANL2DZ).

clic compounds (**23**) highlighting the stereoselective increase in molecular complexity that can be achieved.[23,30] DFT calculations support the notion that the formation of the key intermediate cyclopropyl metallacarbenoid by exo-dig nucleophilic attack is a common step to the formation of the skeletal-rearrangement adducts (**22**). Then, the second alkene should be intramolecularly trapped by the carbenoid intermediate to afford steroselective tetracycles in a second formal cyclopropanation. A stepwise process through an oxidative coupling to form a metallacyclobutane intermediate, which decomposes in an eliminative reduction to the cyclopropane, has been ruled out by calculations, which instead support a concerted cyclopropanation by direct carbene insertion as the most favorable route.

Stereoelectronic factors due to the propargylic substituents have been shown to control the high diastereoselectivity. In the first step, the *syn* addition of the alkene relative to the heteroatom is favored over the *anti* periplanar counterpart due to resonance effects, as revealed by NBO analyses. The stereoselectivity of the second cyclopropanation results from the kinetically controlled trapping of the *syn* periplanar intermediate, driven by the propargylic heteroatom. It undergoes a cyclopropanation through a staggered transition structure to form the observed product rather than through an eclipsed transition structure to its diastereoisomer (Figure 4).[23]

Similar mechanisms might be operative in the intermolecular catalyzed cyclopropanation of alkenes. Therefore, the presence of a second alkene unit able to be trapped by the metallacarbene intermediate opens new synthetic opportunities to novel complex polycyclized scaffolds.

3. The Cycloisomerization of Propargylic Esters

A particularly relevant and versatile kind of alkyne precursors are the readily available propargylic esters, which have attracted much attention lately because they may lead to a diverse and rich reactivity (Scheme 9).[28,29]

One of the most important processes from a synthetic point of view concerns the Rautenstrauch cyclopropanation, namely, the formation of functionalized bicyclo[(n − 2).1.0]enol-esters (**I**, Scheme 9) from enynes, which are valuable building blocks for the preparation of a diversity of natural products. This process has been described for 1,n-enynes (n = 3−8), but it is most commonly applied to 1,5- and 1,6-enynes. It has also been reported that the cycloisomerization of trisubstituted alkenes is possible and proceeds stereospecifically translating the configuration of the reacting alkene into the stereochemistry of the forming cyclopropane.[31]

$PtCl_2$, $AuCl_3$, and cationic Au(I) complexes successfully catalyze this transformation, providing from good to excellent yields in general, although gold catalysis requires lower temperature.[19,31−33]

Regarding the molecular mechanism, calculations have shown that the intramolecular reaction follows different paths in the available manifold, depending on the nature of the enyne. The activated alkyne may undergo attack by two possible (tethered) nucleophiles, the carboxylic group and the alkene (Figure 5).

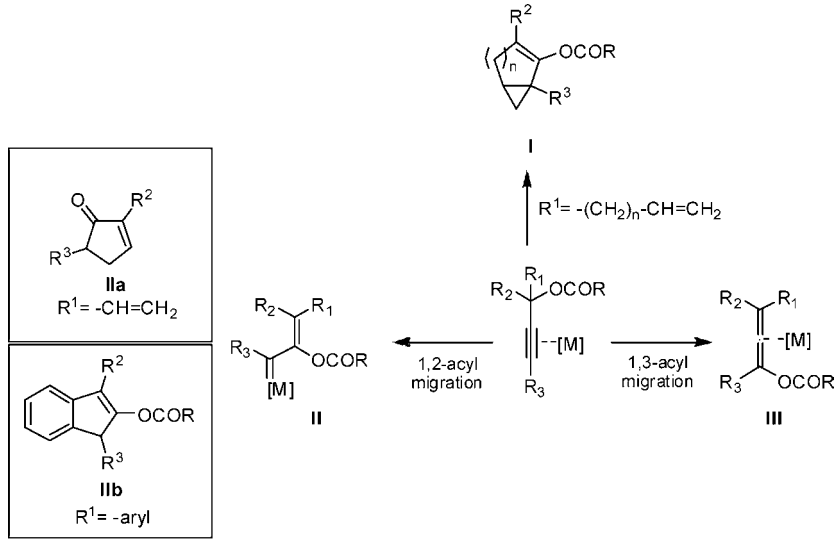
The initial nucleophilic addition of the alkene to furnish the cyclopropylcarbene intermediate E by an *endo*-cyclization is kinetically favored (by 2 kcal mol^{-1} for 1,6-enynes) over the initial 1,2-shift of the acyl function through an exo-dig cyclization to form a polarized oxacycle C. Futhermore, the formation of two σ-bonds from two π-bonds in the key intermediate E exerts a high thermodynamic driving force to the formation of the final enol ester, and hence the remainder energy profile (Figure 5) shows values up to 20 kcal mol^{-1} below those calculated for the alternative mechanism.

According to these findings, for racemic or enantiomerically pure precursors, if the cyclopropanation proceeds before the 1,2-acyloxy migration, the stereochemical outcome should be dependent on the absolute configuration of the stereocenter being destroyed. In this context, this mechanism has been later supported by experimental observations in the synthesis of (−)-cubebol, which provide strong evidence for a remarkable transfer of chirality from the propargylic carbon to the newly formed stereocenters.[32,33] The transfer of chiral information cannot be justified by a planarized, achiral, vinyl carbene intermediate (D) but results from a C−C bond formation event prior to the cleavage of the stereogenic C−O bond.

Interestingly, further calculations on this topic correctly predict that the degree of chirality transfer from the stereogenic center depends on the precursor structure.[34] Thus, subtle intramolecular steric interactions in the cyclopropanation step are responsible for the diastereoselectivity of the cyclopropanation.

For 1,5-enynes, a comparison with the mechanism deduced for enynes bearing a propargylic heteroatom

SCHEME 9



(Scheme 4) shows a notable similarity: a 1,2-hydrogen shift leaves the heteroatom at the same position, while in the carboxylate-containing precursors the migrating group is the acyloxy moiety affording the rearranged enol ester.[19,35] Hence, a subtle change of the type of propargylic group favors the migration of one of the possible groups on a common mechanistic scheme and, consequently, the preparation of different bicyclo[3.1.0]hexane ketones from readily available derivatives.

Shorter 1,4-enynes do not yield cyclopropyl derivatives because of ring strain but allow an efficient enantioselective synthesis of cyclopentenones (**IIa**, Scheme 9).[36] These transformations follow an inverse sequence of steps [1,2-acyl shift to **II** (Scheme 9), then cyclization] due to the conformationally restricted environment. This rearrangement reveals a high degree of chirality transfer, which has been computationally justified by Lera et al. through a mechanism via 1,2-acyl migration to a pentadienyl intermediate that displays helical

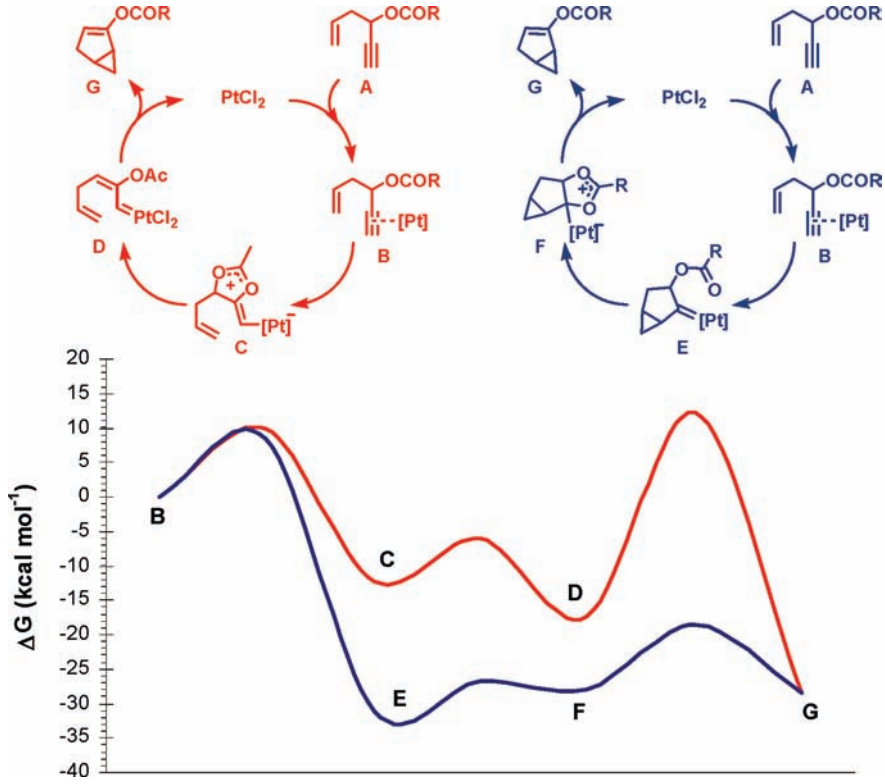


FIGURE 5. Free-energy profiles for the cycloisomerization of the propargylic ester A following two alternative paths (B3LYP/6-31G(d)/LANL2DZ).

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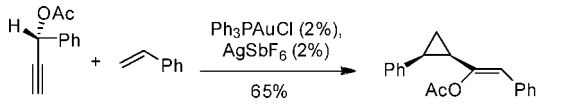


26 **27** **28**

>95:5 cis:trans; 95:5 Z:E; 0% ee

nature, which indeed preserves the chiral information.[37] A related transformation has been reported by Sarpong,[38] who has shown that indene derivatives are furnished in the presence of $[PtCl_2(PPh_3)_2]$ when the nucleophile is an aryl group (**IIb**, Scheme 9).

The intermolecular reaction of propargylic esters with alkenes, which can be promoted by a variety of catalysts such as $AuCl_3$, and $PtCl_2$, was first reported by Uemura.[39] More recently, Toste et al. have carried out the Au(I)-catalyzed intermolecular cyclopropanation with enantioenriched propargylic carboxylates (**26**) and found a different stereochemical outcome to the intramolecular reaction.[40] Their results revealed the formation of racemic allyl cyclopropanes **28** with complete loss of optical purity (Scheme 10). This observation is consistent with the intermediacy 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.

A DFT-based study has indicated the reasons behind the difference with the intramolecular version of this process.[41] A pathway through the cyclopropanation as first step expectedly involves a low enthalpy barrier but a very unfavorable entropy contribution. This yields a free energy of activation higher than any step of the alternative mechanism. Additionally, the computed data cannot account for the stereochemical outcome following this path. Therefore, the results strongly suggest that the entropic effects could modulate the operative mechanism and account for the mechanistic discrepancy. Thus, the entropy preferentially drives the intermolecular reaction through an initial intramolecular exo-dig cyclization of the ester oxygen, which is kinetically more favorable than an intermolecular cyclopropanation with the alkene. The calculations are consistent with the experimental stereoselectivity, due to intra- and intermolecular interactions, and the energy values yield product ratios in good agreement with the observed *cis*/*trans* diastereoselectivity.

A significant limitation for the Rautenstrauch cyclopropanation concerns the substitution at the terminal acetylene carbon.[31,32,41] Hept-6-en-1-yne derivatives bearing alkyl substituents are transformed into allenes or open-chain trienes when exposed to $PtCl_2$.[42] In addition, the striking formation of an open-chain diene in the course of the Pt(II)-mediated cycloisomerization of precursors bearing an acetylenic ester has been reported by Marco-Contelles, Fensterbank, and Malacria[43] and, independently, by Sarpong.[38] This electron-withdrawing substituent induces steric and electronic effects on the alkyne that inhibit the expected Rautenstrauch reaction and force the process to follow an alternative path involving catalyst-mediated diastereoselective hydride abstraction.[44] This diastereoselectivity is supported by the computed hyperconjugation interaction energies on the possible transition structures.

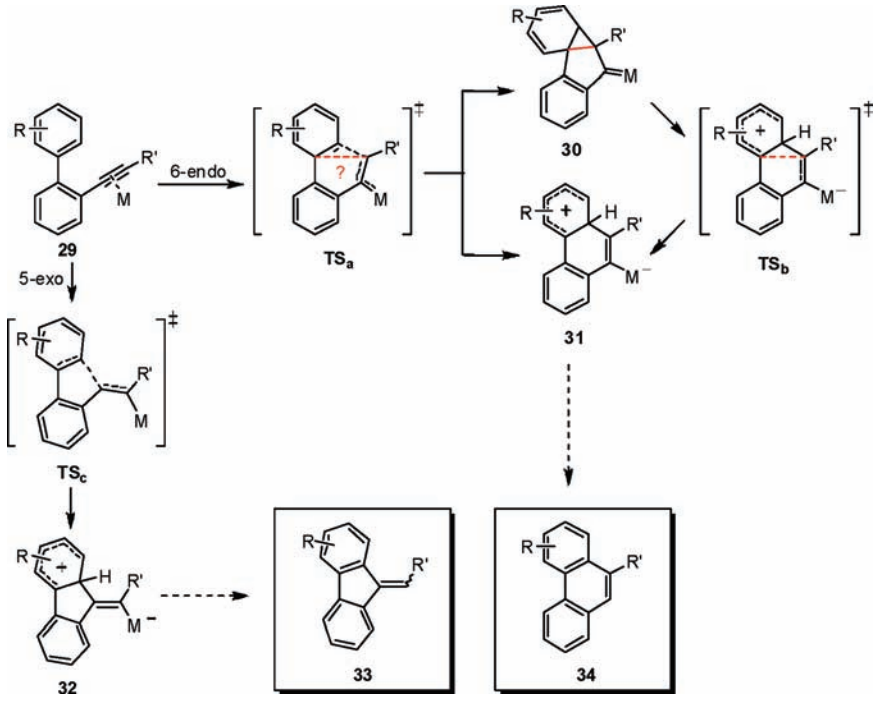
As has been described above, the electrophilic activation of the alkyne promotes the attack of a nucleophile to one of the aceteylenic positions. Consequently, besides the 1,2-ester rearrangement (**II**, Scheme 9), the corresponding 1,3-migration of the ester yields allenyl derivatives (**III**, Scheme 9), which interestingly provide access to a wide variety of useful functionalized adducts since these catalysts can further activate the allene formed for subsequent reactivity.[28,29] This transformation is a common reaction than can be mediated by late transition metals (Pt, Au, Ag, Cu).[42,45,46] In analogy with the 1,2-ester migration, the 1,3-shift is not concerted but proceeds through two steps involving low activation barriers according to recent DFT studies:[12,47,48] the rate-limiting 6-endo-dig attack of the carboxylic oxygen onto the alkynyl group to form a six-membered heterocycle is followed by the ring-opening step.

The dual behavior, 1,2-/1,3-shift, critically depends on the alkyne substitution (although other factors come into play) in such a way that alkyl/phenyl substituents enhance the 1,3-rearrangement that becomes a competing, or even leading, path. The effects of alkyl substituents have been recently assessed by computational methods[41] and the results suggest that the change in regioselectivity is due to electronic factors enhanced by steric effects. The catalyst is pushed out and the metal$-C^1$ distance increases with the alkyne substitution to reduce the steric hindrance, giving rise to a shorter metal$-C^2$ length. Overall, this effect reverses the polarization of the coordinated alkyne and induces a higher electrophilicity at C^1, as opposed to the unsubstituted model.

4. Reactions of Arenes with Alkynes

As a part of the broad scope, this flexible protocol allows that activated alkynes react with other nucleophiles, such as electron-rich aromatic rings. This methodology, a formal hydroarylation of alkynes,[49] has been successfully applied in the synthesis of carbo- and heteroarene derivatives, such as cou-

SCHEME 11



marins and quinolinones. Both inter- and intramolecular processes have been disclosed by various groups. Fürstner et al. have reported the intramolecular formation of phenanthrenes and polycyclic heteroarenes catalyzed by a variety of soft Lewis acids: $PtCl_2$, $AuCl_3$, $GaCl_3$, and $InCl_3$.[50] They found that the regioselectivity was dependent on the catalyst system and on the precursor structure.

Overall, these reactions resemble the Friedel–Crafts process. However, the high endo selectivity usually observed suggests that the mechanism might be more complex than a simple Friedel–Crafts reaction. Following a rationale based on the intermediacy of carbenoid intermediates, it has been proposed that the outcome of the reaction may be explained by analogous pathways. Thus, computational studies[51,52] have shown that the intramolecular hydroarylation of aryl alkynes proceeds via endo- or exo-dig cyclization routes, depending on the catalyst and precursor structure (Scheme 11).

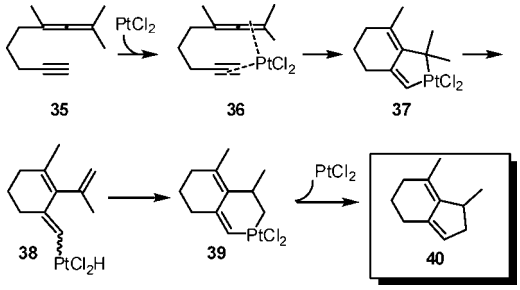
The endo/exo selectivity has been shown to deeply depend on the precursor substituents, where structural and electronic factors play a critical role. Although these reactions take place through a Friedel–Crafts-type alkenylation mechanism, the endo-dig cyclization promoted by $PtCl_2$ may involve a cyclopropylmetallacarbene as intermediate (**30**, Scheme 11) before the formation of the expected Wheland-type intermediate (vinylic metal intermediate **31**, Scheme 11). This unusual electrophilic aromatic substitution pathway has been observed for precursors with a strong nucleophilic arene or with a highly electrophilic C^1 alkyne carbon. Interestingly, this cyclopropyl–metal intermediate must be a more stable species than the vinylic intermediate to be characterized as a local minimum along the reaction coordinate.[52]

5. Reactions of Allenynes

The presence of an allene moiety as nucleophile dramatically changes the outcome of the catalyzed cycloisomerization and 1,6-allenynes are transformed into Alder-ene type products or bicycles depending on the molecular structure.[46] A DFT study suggests that a simultaneous coordination of $PtCl_2$ to the alkyne and allene promotes the formation of a six-membered ring intermediate (platina(IV)cyclopentene) through oxidative cyclometalation, which evolves to alternative routes depending on the steric or electronic effects of the alkyne and allene substituents.[53]

The computational analysis suggests that for a tetrasubstituted allene (**35**, Scheme 12) the most favorable path to hydrindiene (**40**), involves a regioselective β-hydride elimination of the platinacyclopentene key intermediate **37**, followed by a metal-induced H-shift leading to an octahedral Pt(IV) chelate **39**. It evolves to the product via intramolecular migratory insertion. The results show that the alternative Alder-ene process should be less favored from a kinetic point of view, which is supported by the experimental observations.[53]

SCHEME 12



Recent computational studies[54] on the same process catalyzed by Au(I) and Au(III) point out a different mechanism involving nucleophilic addition of an allene on the π-complexed alkyne rather than a metallacyclic route through oxidative addition. This is an expected result due to gold's low tendency for β-hydride elimination, fast protodemetalation, and reluctance to undergo the change of oxidation states. In this sense, a recent work by Houk et al.[55] should be noted evidencing that a mechanism via nucleophilic addition of an allene double bond to a gold-complexed gold acetylide is more likely than oxidative cyclization or simple nucleophilic addition to gold-complexed substrate.

6. Conclusions and Outlook

Transition metals exhibit significant efficacy for catalyzing the formation of carbon−carbon and carbon−heteroatom bonds, and in particular, Pt and Au (gold(III) and cationic gold(I)) show an exceptional capacity to promote a growing variety of organic transformations of unsaturated precursors. These processes result from their unique ability to activate carbon−carbon multiple bonds as soft, carbophilic Lewis acids, thus promoting the intra- or intermolecular attack of a nucleophile.

In this Account, we have provided an overview of the reaction mechanisms for a diversity of transformations promoted by Pt and Au in a non-nucleophilic medium, on the basis of computational studies performed in the last years. We have described the electronic factors that explain the reactivity of the catalyst systems and their behavior as "soft" Lewis acids, hence preferentially activating "soft" electrophiles such as π-systems. Furthermore, the pronounced "alkynophilicity" can be explained by orbital rather than charge interactions. The increase of electrophilicity resulting from the coordination of the π-acceptor ligand at the metal center triggers the intra- or intermolecular attack of nucleophiles such as alkene, heteroatoms, allene, or arene groups, which can occur by exo-dig or endo-dig pathways.

The notable chemo-, regio-, and stereoselectivity of these transformations can be accounted for by structural and electronic effects on the key steps, so the computational methodology currently represents a valuable tool for the development of a solid conceptual framework and a better understanding of these processes.

Although a diversity of reaction pathways have been clarified in the last years, the growing number of synthetic transformations and applications of this methodology strongly requires a deep mechanistic knowledge. It can be concluded that a close connection between theory and experimentation will undoubtedly help us to answer unresolved questions that still remain or emerge in this innovative area.

BIOGRAPHICAL INFORMATION

Elena Soriano obtained her Ph.D. degree in 2003 at UNED (Madrid). She was a postdoctoral fellow from Gobierno de La Rioja (2005−2006) and MEC (Juan de la Cierva contract, 2006−2008) working at the Instituto de Investigaciones Biomédicas. She currently holds a position as *Cientifico Titular del Consejo Superior de Investigaciones Cientificas* at the Instituto de Quimica Orgánica General (Madrid). Her research interests focus on the application of computational tools to the study of reaction mechanisms and drug design.

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REFERENCES

1 Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 2002.
2 Zhang, L.; Sun, J.; Kozmin, S. A. Gold and platinum catalysis of enyne cycloisomerization. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296.
3 Fürstner, A.; Davies, P. W. Catalytic carbophilic activation: Catalysis by platinum and gold π acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449.
4 Bruneau, C. Electrophilic activation and cycloisomerization of enynes: A new route to functional cyclopropanes. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328–2334.
5 Jiménez-Núñez, E.; Echavarren, A. M. Gold-catalyzed cycloisomerizations of enynes: A mechanistic perspective. *Chem. Rev.* **2008**, *108*, 3326–3350.
6 Gorin, D. J.; Toste, F. D. Relativistic effects in homogeneous gold catalysis. *Nature* **2007**, *446*, 395–403.
7 Nechaev, M. S.; Rayon, V. M.; Frenking, G. Energy partitioning analysis of the bonding in ethylene and acetylene complexes of group 6, 8, and 11 metals. *J. Phys. Chem. A* **2004**, *108*, 3134–3142.
8 Garcia-Mota, M.; Cabello, N.; Maseras, F.; Echavarren, A. M.; Pérez-Ramirez, J.; Lopez, N. Selective homogeneous and heterogeneous gold catalysis with alkynes and alkenes: Similar behavior, different origin. *ChemPhysChem* **2008**, *9*, 1624–1629.
9 Shapiro, N. D.; Toste, F. D. Synthesis and structural characterization of isolable phosphine coinage metal π-complexes. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2779–2782.
10 Lloyd-Jones, G. C. Mechanistic aspects of transition metal catalysed 1,6-diene and 1,6-enyne cycloisomerisation reactions. *Org. Biomol. Chem.* **2003**, *1*, 215–236.
11 Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. Cyclizations of enynes catalyzed by $PtCl_2$ or other transition metal chlorides: Divergent reaction pathways. *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520.
12 Soriano, E.; Ballesteros, P.; Marco-Contelles, J. Theoretical investigation on the mechanisms of the $PtCl_2$-mediated cycloisomerization of polyfunctionalized 1,6-enynes. 2. Propargylic carboxylates. *Organometallics* **2005**, *24*, 3182–3191.

13 Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M., Gold(I)-catalyzed cyclizations of 1,6-enynes: alkoxycyclizations and exo/endo skeletal rearrangements, *Chem.—Eur. J.* **2006** *12*, 1677−1693; erratum *Chem.—Eur. J.* **2008**, *14*, 5096.

14 Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. Reaction of enol ethers with alkynes catalyzed by transition metals. *Chem.—Eur. J.* **2003**, *9*, 2627–2635.

15 Very recently a gold-carbene complex has been isolated in the gas phase: Fedorov, A.; Moret, M. E.; Chen, P. Gas-phase synthesis and reactivity of a gold carbene complex. *J. Am. Chem. Soc.* **2008**, *130*, 8880–8881.

16 Trost, B. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1085–1087.

17 (a) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030–5033. (b) Seidel, S.; Mynott, R.; Fürstner, A. Elementary steps of gold catalysis: NMR spectroscopy reveals the highly cationic character of a "gold carbenoid". *Angew. Chem., Int. Ed.* **2009**, *48*, 2510–2513.

18 Soriano, E.; Ballesteros, P.; Marco-Contelles, J. A theoretical investigation on the mechanism of the $PtCl_2$-mediated cycloisomerization of heteroatom-tethered 1,6-enynes. *J. Org. Chem.* **2004**, *69*, 8018–8023.

19 Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. Platinum- and gold-catalyzed cycloisomerization reactions of hydroxylated enynes. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655.

20 (a) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. Platinum dichloride-catalyzed cycloisomerization of ene-ynamides. *Org. Lett.* **2004**, *6*, 1509–1511. (b) Couty, S.; Meyer, C.; Cossy, J. Diastereoselective gold-catalyzed cycloisomerizations of ene-ynamides. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726–6730. (c) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. Cationic gold(I) complexes: Highly alkynophilic catalysts for the exo- and endo-cyclization of enynes. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406.

21 Soriano, E.; Marco-Contelles, J. Theoretical analysis of the high versatility in $PtCl_2$-mediated cycloisomerization of enynes on a common mechanistic basis. *J. Org. Chem.* **2005**, *70*, 9345–9353.

22 (a) Trost, B. M.; Chang, V. K. An approach to botrydianes. On the steric demands of a metal catalyzed enyne metathesis. *Synthesis* **1993**, 824–832. (b) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. $PtCl_2$-catalyzed conversion of 1,6- and 1,7-enynes to 1-vinylcycloalkenes. Anomalous bond connection in skeletal reorganization of enynes. *Organometallics* **1996**, *15*, 901–903. (c) Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. Cationic platinum-complex-catalyzed skeletal reorganization of enynes. *Organometallics* **2001**, *20*, 3704–3709.

23 Soriano, E.; Ballesteros, P.; Marco-Contelles, J. Theoretical investigation on the mechanisms of the $PtCl_2$-mediated cycloisomerization of polyfunctionalized 1,6-enynes. 1. Role of the propargylic substituents. *Organometallics* **2005**, *24*, 3172–3181.

24 Trost, B. M.; Yanai, M.; Hoogsteen, K. A palladium-catalyzed [2 + 2] cycloaddition. Mechanism of a Pd-catalyzed enyne metathesis. *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295.

25 Fürstner, A.; Davies, P. W.; Gress, T. Cyclobutenes by platinum-catalyzed cycloisomerization reactions of enynes. *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245.

26 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. Divergent mechanisms for the skeletal rearrangement and [2 + 2] cycloaddition of enynes catalyzed by gold. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146–6148. (b) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. The mechanistic puzzle of transition-metal-catalyzed skeletal rearrangements of enynes. *Chem.—Eur. J.* **2006**, *11*, 5916–5923.

27 Mainetti, E.; Mouries, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. The effect of a hydroxy protecting group on the $PtCl_2$-catalyzed cyclization of dienynes-A novel, efficient, and selective synthesis of carbocycles. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132–2135.

28 Marco-Contelles, J.; Soriano, E. Recent developments in the metal-catalyzed reactions of metallocarbenoids from propargylic esters. *Chem.—Eur. J.* **2007**, *13*, 1350–1357.

29 Marion, N.; Nolan, S. P. Propargylic esters in gold catalysis: Access to diversity. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750–2752.

30 For related transformations and calculations under $Au(I)^+$-catalysis: Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. Gold(I)-catalyzed intramolecular cyclopropanation of dienynes. *Chem.—Eur. J.* **2006**, *12*, 1694–1702.

31 Anjum, S.; Marco-Contelles, J. $PtCl_2$-mediated cycloisomerization of unsaturated propargylic carboxylates. *Tetrahedron* **2005**, *61*, 4793–4803.

32 Fürstner, A.; Hannen, P. Platinum- and gold-catalyzed rearrangement reactions of propargyl acetates: Total syntheses of (−)-α-cubebene, (−)-cubebol, sesquicarene and related terpenes. *Chem.—Eur. J.* **2006**, *12*, 3006–3019.

33 Fehr, C.; Galindo, J. Synthesis of (−)-cubebol by face-selective platinum-, gold-, or copper-catalyzed cycloisomerization: Evidence for chirality transfer. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901–2904.

34 Soriano, E.; Marco-Contelles, J. On accounting for the stereoselective control of the metal-catalyzed Rautenstrauch cyclopropanation by computational methods. *J. Org. Chem.* **2007**, *72*, 2651–2654.

35 Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. $PtCl_2$-catalyzed cycloisomerizations of 5-en-1-yn-3-ol systems. *J. Am. Chem. Soc.* **2004**, *126*, 8656–8657.

36 Shi, X.; Gorin, D. J.; Toste, F. D. Synthesis of 2-cyclopentenones by gold(I)-catalyzed Rautenstrauch rearrangement. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803.

37 Faza, O. N.; López, C. S.; Álvarez, R.; de Lera, A. R. Mechanism of the gold(I)-catalyzed Rautenstrauch rearrangement: A center-to-helix-to-center chirality transfer. *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437.

38 Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. Pt-catalyzed pentannulations from in situ generated metallo-carbenoids utilizing propargylic esters. *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469.

39 Miki, K.; Ohe, K.; Uemura, S. Ruthenium-catalyzed cyclopropanation of alkenes using propargylic carboxylates as precursors of vinylcarbenoids. *J. Org. Chem.* **2003**, *68*, 8505–8513.

40 Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. Gold(I)-catalyzed stereoselective olefin cyclopropanation. *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003.

41 Soriano, E.; Marco-Contelles, J. New insights on the mechanism of the transition-metal stereoselective olefin cyclopropanation. *Chem.—Eur. J.* **2008**, *14*, 6771–6779.

42 Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. Tandem $PtCl_2$ catalyzed-thermal [3,3] rearrangements of enyne acetates. *Tetrahedron* **2004**, *60*, 9745–9755.

43 Marco-Contelles, J.; Arroyo, N.; Anjum, S.; Mainetti, E.; Marion, N.; Cariou, K.; Lemière, G.; Mouries, V.; Fensterbank, L.; Malacria, M. $PtCl_2$- and $PtCl_4$-catalyzed cycloisomerization of polyunsaturated precursors. *Eur. J. Org. Chem.* **2006**, *461*, 8–4633.

44 Soriano, E.; Marco-Contelles, J. DFT-based mechanism for the unexpected formation of dienes in the $PtCl_2$ isomerization of propargylic acetates: Examples of inhibition of the Rautenstrauch process. *J. Org. Chem.* **2007**, *72*, 1443–1448.

45 (a) For AgI salts: Sromek, A. W.; Kel'in, V.; Gevorgyan, A. V. *Angew* **2004**, *43*, 2280–2282. (b) For Au^I and $AuCl_3$: Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemière, G.; López-Romero, J. M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43–48.

46 Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M; Marco-Contelles, J. $PtCl_2$-catalyzed cycloisomerizations of allenynes. *J. Am. Chem. Soc.* **2004**, *126*, 3408–3409.

47 Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. Golden carousel in catalysis: The cationic gold/propargylic ester cycle. *Angew. Chem., Int. Ed.* **2008**, *47*, 718–721.

48 Mauleón, P.; Krinsky, J. L.; Toste, F. D. Mechanistic studies on Au(I)-catalyzed [3,3]-sigmatropic rearrangements using cyclopropane probes. *J. Am. Chem. Soc.* **2009**, *131*, 4513–4520.

49 For a review, see: Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182.

50 Mamane, V.; Hannen, P.; Fürstner, A. Synthesis of phenanthrenes and polycyclic heteroarenes by transition-metal catalyzed cycloisomerization reactions. *Chem.—Eur. J.* **2004**, *10*, 4556–4575.

51 Nevado, C.; Echavarren, A. M. Intramolecular hydroarylation of alkynes catalyzed by platinum or gold. *Chem.—Eur. J.* **2005**, *11*, 3155–3164.

52 Soriano, E.; Marco-Contelles, J. Mechanisms of the transition metal-mediated hydroarylation of alkynes and allenes. *Organometallics* **2006**, *25*, 4542–4553.

53 Soriano, E.; Marco-Contelles, J. A DFT-based theoretical investigation of the mechanism of the $PtCl_2$-mediated cycloisomerization of allenynes. *Chem.—Eur. J.* **2005**, *11*, 521–533.

54 Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. Gold(I)- and gold(III)-catalyzed cycloisomerization of allenynes. *Angew. Chem., Int. Ed.* **2006**, *45*, 7596–7599.

55 Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. Gold-catalyzed cycloisomerization of 1,5-allenynes via dual activation of an ene reaction. *J. Am. Chem. Soc.* **2008**, *130*, 4517–4526.