Theoretical Investigation on the Mechanisms of the $PtCl_2$-Mediated Cycloisomerization of Polyfunctionalized 1,6-Enynes. 1. Role of the Propargylic Substituents

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Received February 23, 2005

The $PtCl_2$-mediated intramolecular cycloisomerization of 1,6-enynes functionalized at propargylic positions shows a high versatility and can give rise to a variety of products with potential synthetic applications. A broad computational study at the DFT level is reported to provide a better mechanistic understanding of these reactions and of the factors that control the course of these processes. For every type of cycloisomerization, several reasonable pathways have been proposed and evaluated. The results suggest that these reactions probably share common steps and could proceed through the formation of cyclopropyl platinum carbenes by endo- or by exo-cyclization routes. The role of the propargylic substituent and the additional alkene chain for dienyne precursors is also discussed. The metathesis process involves an initial 5-exo cyclopropanation path, in common with the formation of polycyclic adducts, but it is retarded or inhibited by the presence of an additional alkene chain.

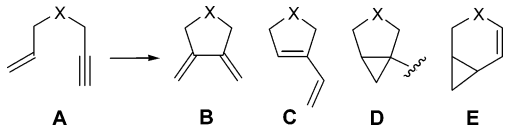
Introduction

One of the most important endeavors in synthetic organic chemistry is the design and development of efficient strategies for the stereocontrolled synthesis of functionalized polycycles. In this context, catalytic organometallic chemistry has emerged as a powerful tool during the past decade.[1] Transition-metal-catalyzed intramolecular cycloisomerizations with unsaturated precursors, such as enynes, dienes, diynes, allenynes, and dienynes, have been widely studied.[2] Thus, in the case of hept-1,6-enyne precursors (**A**) (Scheme 1) the formation of different kinds of products has been reported: cycloisomerization (**B**), skeletal reorganization products (**C**), and/or polycyclic systems (**D**, **E**). Interestingly, these processes have been revealed as strongly substrate dependent, and it has been observed that the regio-, chemo-, or enantioselectivity depends not only on the transition-metal catalyst[3] and reaction conditions but also on the functional groups on unsaturated precursors.[4]

The transformation of enynes leading to products of type **B** was first described in 1985,[5] and since then it has been used in the synthesis of useful functionalized carbocyclic[6] and heterocyclic compounds.[7]

The application of enyne metathesis[8] to organic synthesis has developed rapidly.[9] This reaction yields

Scheme 1



1-alkenylcycloalkenes (product **C**) from simple building blocks. Enyne metathesis is mediated by a range of transition-metal complexes involving two mechanisms. The first mechanism proceeds through a [2 + 2] cy-

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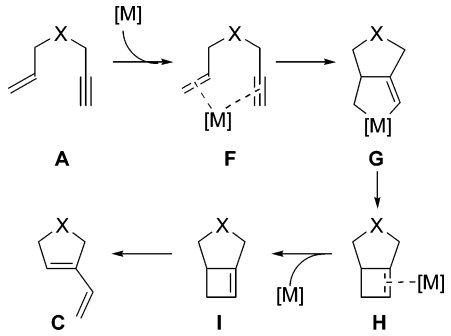
Publication on Web 05/24/2005

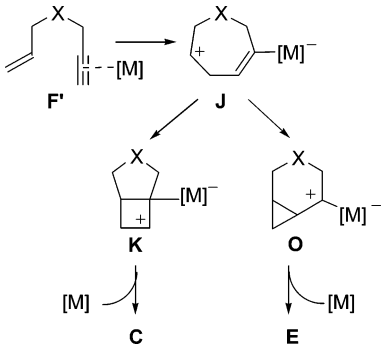
Scheme 2



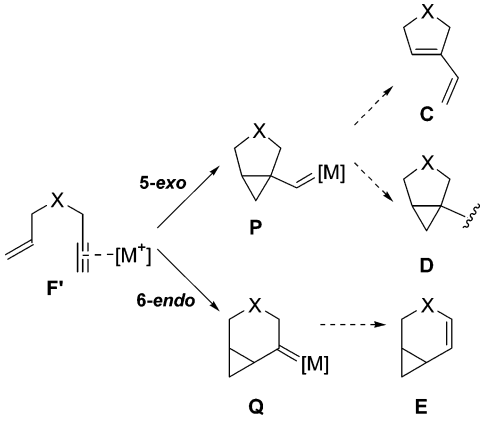
cloaddition of a multiple bond to a transition-metal carbene, as for Grubbs' catalyst.[10] The other mechanism is an oxidative cyclization catalyzed by low-valent transition-metal complexes, such as Pd(II),[11] Pt(II),[12] Ru(II),[13] Ir(I),[14] and Au(I) salts.[15] As formulated by Trost,[16,17] the enyne could coordinate to the catalyst to form a complex that undergoes oxidative cyclization to afford a metallacyclopentene intermediate (**G**). Then, reductive elimination of the catalyst generates cyclobutene (**I**), which provides the enyne metathesis product by electrocyclic ring opening (Scheme 2).

Alternatively, Murai et al.[18] suggested slipped η^1-alkyne complexes as potential intermediates. Later, Fürstner et al. observed that Pt(II)-catalyzed cycloisomerization of heteroatom-tethered 1,6-enynes are substrate dependent, giving rise to metathesis product **C** and/or vinylcyclopropane **E** (Scheme 3). They suggested that η^2 coordination of the catalyst to the alkyne favors

Scheme 3



Scheme 4



nucleophilic attack by the alkene, and the resulting delocalized cation **J** rearranges to the metathesis product **C** or to **E**. Thus, although both catalytic processes yield different structural motifs, they could share a common mechanism comprising a cationic manifold.[19]

The formation of cyclopentane- (**D**) and cyclohexane-type (**E**) structures has also been observed in some intramolecular cycloisomerizations of enynes promoted by electrophilic transition-metal complexes.[19–22] It suggests the involvement of cyclopropylmetallacarbenes as key intermediates (**P** and **Q**, Scheme 4), formed by exo and endo cyclization steps, respectively.[23] In fact, a recent theoretical study performed by us has revealed that the preferred reaction pathway for the Pt(II)-promoted formation of 3-azabicyclo[4.1.0]hept-4-enes from heteroatom-tethered enynes proceeds through a cyclopropyl Pt−carbene intermediate, rather than through any other conceivable route.[24]

Further support for this proposal[25] is found from the cyclization of dienynes catalyzed by Pt(II),[4] Au(I),[15] or

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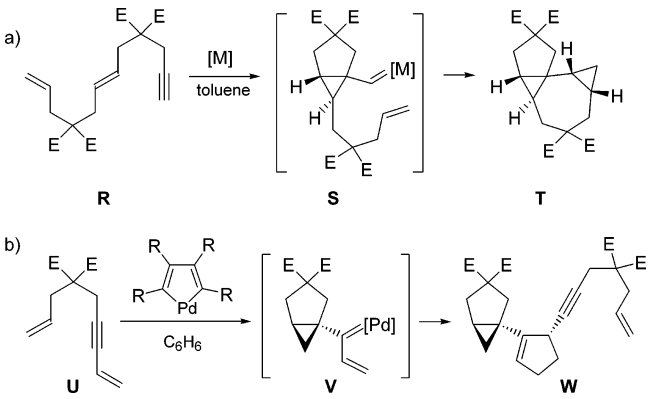
Scheme 5



Scheme 6

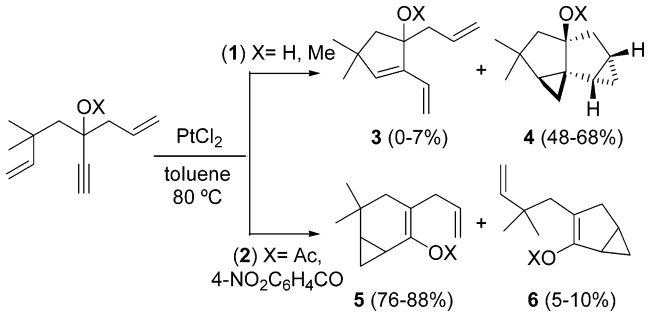
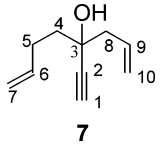
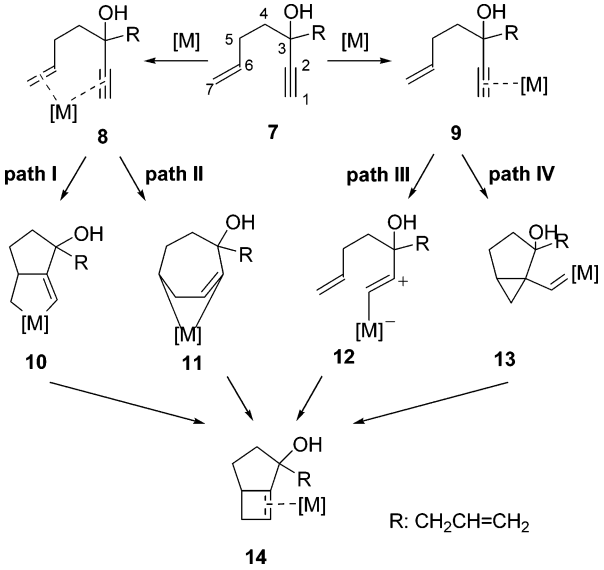


Chart 1



7

Scheme 7



Ru(II)[26] complexes (Scheme 5a), in which the presumed metallacarbene (**S**) should be intramolecularly trapped by the pendant alkene, to afford steroselective tetracycles. In this sense, a pioneering work[27a] by Trost also suggested the intermediacy of cyclopropylalkylidene complexes[27] **V** (Pd(II) carbenes), which would be intermolecularly trapped by a second reactant molecule (Scheme 5b).

These metallacarbene intermediates could also be viewed as analogues of cyclopropyl carbinyl cations[28] stabilized by a metal complex, in line with the cationic manifold pointed out by Fürstner.[19] It could be argued that the degree of metal-carbenic vs metal-stabilized carbocation character depends on the catalyst system and reaction conditions.

Intriguingly, the formation of a cyclopentane skeleton in the metathesis rearrangement suggests a common initial 5-exo-cyclization path (Scheme 4).[29]

Very interestingly, Marco-Contelles, Malacria, Fensterbank, et al. have reported the Pt-catalyzed cyclizations of dienyne precursors with O-protecting groups at the propargylic position (Scheme 6).[4] These results clearly reveal that the nature of the protecting group induces different chemo-, regio-, and stereoselective outcomes. A free hydroxy or silyl ether group provides tetracyclic systems and the metathesis adduct as a minor product, while precursors containing O-acyl protecting groups afford bicyclic enol esters with a fused cyclopropane ring at the α,β-positions.[30]

In view of the versatility of these highly substrate dependent processes, it seems crucial to shed light on the role of the substituents at propargylic positions on the course of these $PtCl_2$-mediated cycloisomerizations. This could be helpful information for the future development of more efficient and specific synthetic strategies.

As a part of a broad study of $PtCl_2$-mediated cycloisomerizations of polyunsaturated systems,[24,31] we present herein a DFT analysis to elucidate the mechanisms and identify the factors that selectively lead to the cycloisomerizations shown in Scheme 6. In the next section, we will discuss in detail the mechanism for (1) metathesis reactions and (2) formation of polycycles from 1,6-enynes. The formation of bicyclic enol esters has been thoroughly analyzed elsewhere.[32] We have chosen **7** (Chart 1) lacking a *gem*-dimethyl group as the model precursor to simplify the study of the potential energy surfaces (PES).

Results and Discussion

1. Enyne Metathesis. As noted above, different mechanistic hypotheses have been developed to clarify the metathesis process. First, we have analyzed the mechanism suggested by Trost[16,17,29] (Scheme 7, path I), involving an initial oxidative cycloisomerization to generate the metallacyclopentene **10**, which would evolve to the cyclobutene **14** via reductive elimination. Due to the high steric strain, **14** is unstable and

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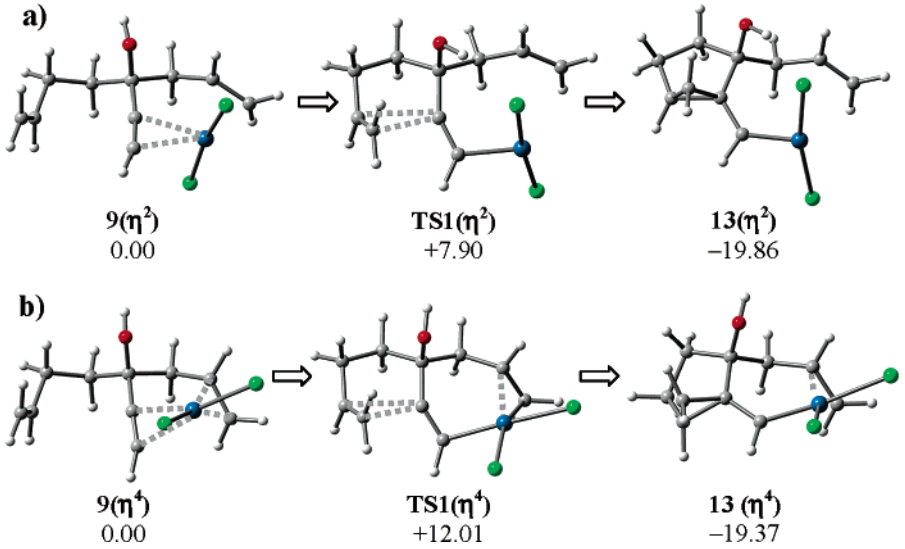
Scheme 8. Optimized Structures for the $PtCl_2$-Mediated Cyclopropanation of 7 According to Path IV (Scheme 7) from (a) a η^2 Reactant Complex and (b) a η^4 Reactant Complex[a]



[a] Relative free energies are given in kcal mol^{-1}.

undergoes electrocyclic ring opening to afford the skeletal rearrangement product. The involvement of the cyclobutene intermediate has been clearly supported by isolation of a less strained bicyclo[4.2.0]oct-1(8)-ene structure from 1,7-enynes[11] and of an isomerized cyclobutene from 1,6-enyne.[17]

The π complexation of enyne **7**, as bidentate ligand, onto Pt(II) leads to the square-planar η^4 structure **8** (path I in Scheme 7 and Scheme S1 (see the Supporting Information). The oxidative cyclization to form the platinacyclopentene **10** is exothermic and proceeds with an activation energy of 33.08 kcal mol^{-1}. Then, this intermediate should rearrange to **14**, but all the efforts to locate a valid transition structure connecting both intermediates were unfruitful.

A second plausible route implicates an equivalent oxidative cyclization step but is related to the formation of the external C_1-C_7 bond (path II in Scheme 7 and Scheme S2 (see the Supporting Information). Nevertheless, the computed results revealed that the formation of the intermediate **11** takes place[33] with a very high activation energy (52.86 kcal mol^{-1}), which prompted us to explore other possibilities.

As there is clear evidence for the intermediacy of cyclobutene (**14**) in metathesis processes,[11,17] we have considered other plausible precursor complexes. Accordingly, we have analyzed the reaction path involving a slipped polarized η^1-alkyne−Pt(II) complex of type **12** (path III of Scheme 7), which might undergo a [2 + 2] cycloaddition to form the cyclobutene structure. However, we did not locate either the η^1 complex as a stable structure or the expected [2 + 2] transition structure.

Given that transition-metal-mediated metathesis rearrangement has been reported as closely related to the formation of cyclopropane derivatives,[4,12,15,18,19] a reaction pathway through the cyclopropylmetallacarbene intermediate **13** can also be envisaged (path IV of Scheme 7). Some studies have provided support for the involvement of this structure in the metathesis process through trapping with alkenes.[27]

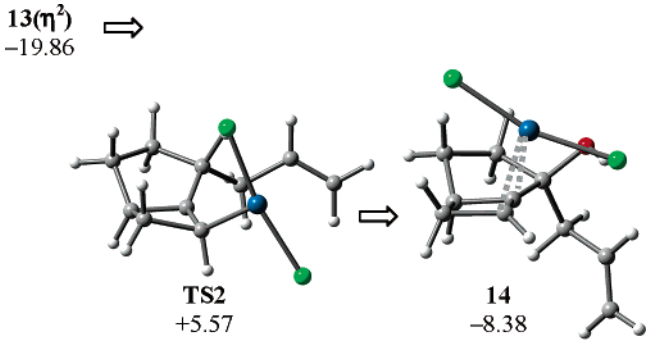
This transition-metal-mediated transformation of 1,6-enyne into a cyclopropylmetallacarbene, **13**, can be easily explained by theoretical calculations.[22a] The initial π complexation of the alkyne moiety onto the metal center triggers the nucleophilic attack of the alkene (path IV of Scheme 7), through a 5-exo cyclization (although a 6-endo process is also likely). Initially, we located the T-shaped tricoordinated complex **9(η^2)**, formed by π coordination of the alkyne (Scheme 8a). The internal carbon of the activated alkyne reacts with the nucleophilic $C_6{=}C_7$ bond through the nearly synchronous transition structure **TS1(η^2)** (C_2-C_6 = 2.463 Å; C_2-C_7 = 2.412 Å) to afford the Pt−cyclopropylcarbene[34] **13(η^2)**, the new C_2-C_6 bond being syn-periplanar to the $HO-C_3$ bond. This step is exothermic (−19.86 kcal mol^{-1}) and proceeds with a low activation energy, 7.90 kcal mol^{-1}.

Since the dienyne precursor bears an additional alkene as a side chain, it is interesting to test the effect of this moiety acting as a second π ligand. Coordination of alkyne and alkene onto the catalyst gives rise to the η^4 reactant complex **9(η^4)** ($Pt-C_1$ = 2.206 Å; $Pt-C_2$ = 2.246 Å; $Pt-C_9$ = 2.254 Å; $Pt-C_{10}$ = 2.215 Å), which shows square-planar coordination around the metal (Scheme 8b). The alkene is nearly perpendicular to the plane Cl−Pt−Cl (91.3°), while the alkyne ligand is twisted (52.1°). As expected, the 16-electron species **9(η^4)** is more stable (14.66 kcal mol^{-1}) than the deficient 14-electron species **9(η^2)**. Starting from the η^4 complex, we located the asynchronous 5-exo cyclization transition structure **TS1(η^4)** by having the electrophilic carbon C_2 approach the alkene unit (C_2-C_6 = 2.478 Å; C_2-C_7 = 2.255 Å). IRC analysis reveals that **TS1(η^4)** evolves to the cyclopropyl platinacarbene **13(η^4)** ($Pt-C_1$ = 1.919 Å), a bicyclic structure showing C_2-C_6 (1.577 Å) and C_2-C_7 (1.569 Å) bonds fully formed. Remarkably,

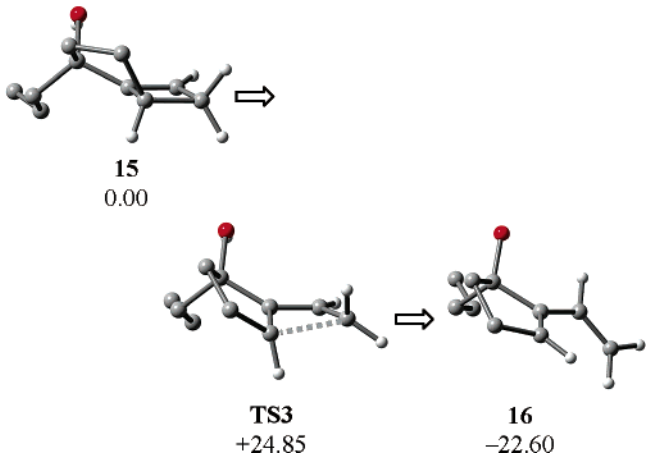
(33) This metallabicyclo[3.2.1]octene might be envisaged as the intermediate delocalized carbocation proposed by Fürstner.[12,19] However, on the basis of our computational results, the true nature of this structure should be considered as an organometallic species rather than a nonclassical carbocation (NPA charge: −0.433 for C_6 in **11**).

(34) (a) Cave, G. W. V.; Hallett, A. J.; Errington, W.; Rourke, J. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3270−3272. (b) Cucciolito, M. E.; Panunzi, A.; Ruffo, F.; Albano, V. G.; Monari, M. *Organometallics* **1999**, *18*, 3482−3489. (c) Jones, N. D.; Lin, G.; Gossage, R. A.; McDonald, R.; Cavell, R. G. *Organometallics* **2003**, *22*, 2832−2841.

Scheme 9. Optimized Structures for the Second Step of the $PtCl_2$-Mediated Skeletal Rearrangement of 7 According to Path IV (Scheme 7)



Scheme 10. Optimized Structures for the Conrotatory Ring-Opening Process



formation of **13(η^4)** proceeds with a higher activation energy than **13(η^2)** (12.01[35] vs 7.90 kcal/mol). These results are due to a more effective back-donation from the metal into the π^* of the alkyne. The square-planar η^4 reactant complex has a chloride ligand trans to the alkyne moiety; thus, the back-bonding interaction is stronger and C_2 becomes less electrophilic than in the η^2 complex, as can be easily confirmed from the computed NPA charges (−0.021 vs +0.038 for C_2 in η^4 and η^2 complexes, respectively).

A solvent molecule may act as additional ligand to complete the Pt(II) coordination sphere. Thus, the possibility of solvent coordination has also been evaluated by including H_2O and toluene (experimental conditions). In the former case (i.e., H_2O), we observed an activation barrier of 11.86 kcal mol^{-1} and an exothermic formation of the subsequent Pt−carbene (−19.51 kcal mol^{-1}). These values are similar to those computed for the η^4-reactant complex **9(η^4)** shown in Scheme 8 and are parallel to the ones reported by other authors for an analogous complex.[22a] On the other hand, the participation of toluene is somewhat less evident. The coordination to the metal center is weak, due to electrostatic repulsion between the π cloud and the halide atoms (see Figure S1 in the Supporting Information). This effect induces a behavior halfway between the coordinatively saturated and unsaturated complexes (activation barrier of 9.21 kcal mol^{-1}). Interestingly, our calculations also revealed that the pendant alkene in the precursor can displace the toluene molecule from the coordination sphere.[36]

The reaction of **13** to give **14** should take place by opening of the cyclopropane ring through the attack of the carbene carbon. However, the transition structure for the π-coordinated system **13(η^4)** could not be located even after an extensive search. In contrast, we were able to find it for the uncoordinated system, probably as a consequence of the enhanced electrophilic character of C_1 (NPA: −0.041 in **13(η^2)** vs −0.141 in **13(η^4)** for C_1). Cleavage of the cyclopropane bond C_2−C_7 and formation of the cyclobutene framework takes place through the late transition state **TS2** (Scheme 9), which shows a long C_2−C_7 length (2.066 Å) and a short C_1−C_7 length (1.594 Å). This structure evolves to form the cyclobutene **14** (C_1−C_7 = 1.548, C_2−C_7 = 2.150 Å).

It can be easily deduced from the optimized structures depicted in Scheme 9 that this step should be more difficult for precursors bearing bulky substituents at the propargylic position due to steric restrictions.[37] Formation of the η^2 complex **14** is an endothermic process (11.48 kcal mol^{-1}, **14** being −8.38 kcal mol^{-1} below the reactant complex) and proceeds with a rather high activation energy (25.43 kcal mol^{-1}).

The highly strained cycloalkene **14** is unstable and undergoes electrocyclic ring opening to yield the metathesis product. As Figure S2 illustrates (see the Supporting Information), the molecular orbital analysis carried out over the product **16** indicates that the final step should be a (thermal) conrotatory ring opening.[38] Thus, we have located the transition structure **TS3** (C_6−C_7 = 2.107 Å) connecting the cyclobutene intermediate **15** and the diene product **16** (Scheme 10) and found that this elementary step implies a moderately high energy barrier (24.85 kcal mol^{-1}) but, as expected, is largely favored from a thermodynamic viewpoint (−22.60 kcal mol^{-1}).

However, this mechanistic scheme cannot completely justify the formation of other types of skeletal rearrangement products that involve anomalous carbon−carbon bond formation (**Y**, Scheme 11).[18,29] Oi proposed that external bond of the cyclopropane in the metallacarbene intermediate **P** can cleave to give **X** (Scheme 11).[13a] It may suffer two new bond cleavages (path **a** or **b**), leading to the expected metathesis product **C** or to the anomalous product **Y**, respectively. Nevertheless, our calculations suggest a simpler mechanistic picture.

Starting from the π-coordinated complex **14′** (Pt−C_1 = 2.081, Pt−C_2 = 2.243 Å), a conformer 1.83 kcal mol^{-1} less stable than **14**, we found the transition structure **TS4** (Scheme 12) by cleavage of the C_6–C_7 bond (1.976 Å). The short C_2−C_7 distance (1.717 Å) suggests that the C−H insertion is a concerted rather than stepwise process from the cyclobutene complex (formation of **X**, Scheme 11), as is confirmed by IRC analysis. **TS4** evolves to **17**, which shows the rearranged chain. This

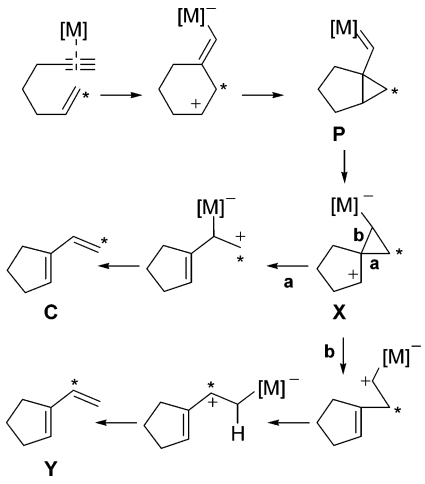
(35) This value is similar to that reported by other authors (11.5 kcal mol^{-1}) for the Pt(II)-catalyzed hydroxycyclization of (*E*)-oct-6-en-1-yne, where they assumed that a water molecule might act as an additional ligand around the metal.[22a]

(36) Further details are provided in the Suppoting Information.

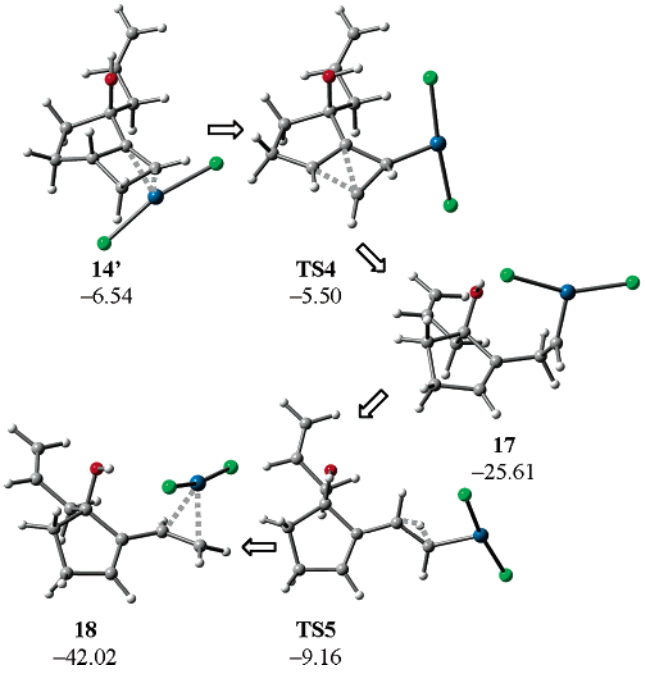
(37) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824−832.

(38) A conrotatory ring opening process is supported by stereoselective reactions which gave *Z*-diene from *E*-enyne and *E*-diene from *Z*-enyne.[29]

Scheme 11



Scheme 12. Optimized Structures for the Anomalous Skeletal Rearrangement Process



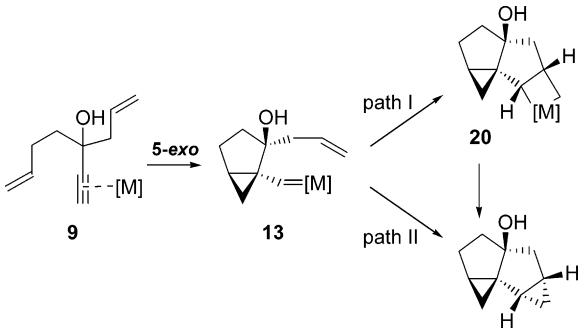
catalyst-assisted C−H insertion is exothermic (−20.11 kcal mol^{-1}), and the energy barrier to achieve **TS4** is very low (1.04 kcal mol^{-1}).

At this point, the transformation of the Pt−carbene **17** into the "anomalous" product **18** (**Y**, Scheme 11) involves a formal [1,2]-hydrogen shift,[24] which takes place via **TS5** ($H-C_1$ = 1.416, $H-C_7$ = 1.263 Å). This step is thermodynamically favored (−16.41 kcal mol^{-1}) and shows an activation energy of 16.45 kcal mol^{-1}.

To sum up, this alternative route involves a simultaneous catalyst-assisted ring opening/C−H insertion process of the cyclobutene intermediate, followed by a [1,2]-hydrogen shift that could account for the formation of anomalous rearrangement products. As can be presumed from **TS4**, the substitution on alkene should retard or inhibit this alternative route due to steric hindrance, while this feature appears less influential in the conrotatory ring opening pathway (Scheme 10).[39]

2. Formation of Polycycles. Experimental results have shown that treatment of dienyne **1** with $PtCl_2$ affords mainly (X = H) or exclusively (X = Me) the tetracyclic system **4** in a diastereoselective mode (Scheme 6).

Scheme 13



Formation of a bicyclo[3.1.0]hexane framework in the transition-metal-catalyzed cycloisomerization of enynes has been observed with different catalyst systems and suggests the involvement of cyclopropyl platinum−carbenes as intermediate species.[4,15,26,27] Since the reactant complex **9**(η^4) is more stable than **9**(η^2), we can assume a 5-exo cyclization from that structure as the first step of the cycloisomerization of **7** (Scheme 8b). As we have seen above, the formation of the cyclopropyl Pt−carbene **13** is exothermic and takes place with a low activation energy.

The evolution to the tetracyclic product implies a formal cylopropanation. Two possible mechanisms can be envisaged: (i) the stepwise process through an oxidative coupling to form a metallacyclobutane intermediate, which decomposes in an eliminative reduction to yield the cyclopropane derivative (path I of Scheme 13)[40,41] and (ii) the concerted cyclopropanation by direct carbene insertion (path II of Scheme 13).[42,43]

(i) First, the stepwise pathway requires the proper disposition between the alkene and the Pt−carbene to allow an intramolecular [2 + 2] cycloaddition; therefore, the decoordination of the alkene is needed. We have found that evolution of **13** to the uncoordinated intermediate **19** proceeds via **TS6** (Scheme 14) and involves a relatively high activation barrier (24.13 kcal mol^{-1}; **TS6** lies 4.76 kcal mol^{-1} above **9**(η^4)). The oxidative

(39) This proposal is supported by experimental evidence which concludes that a methyl-substituted alkene affords a normal skeletal rearrangement, while an anomalous reorganization is observed for unsubstituted alkene.[13a,29]

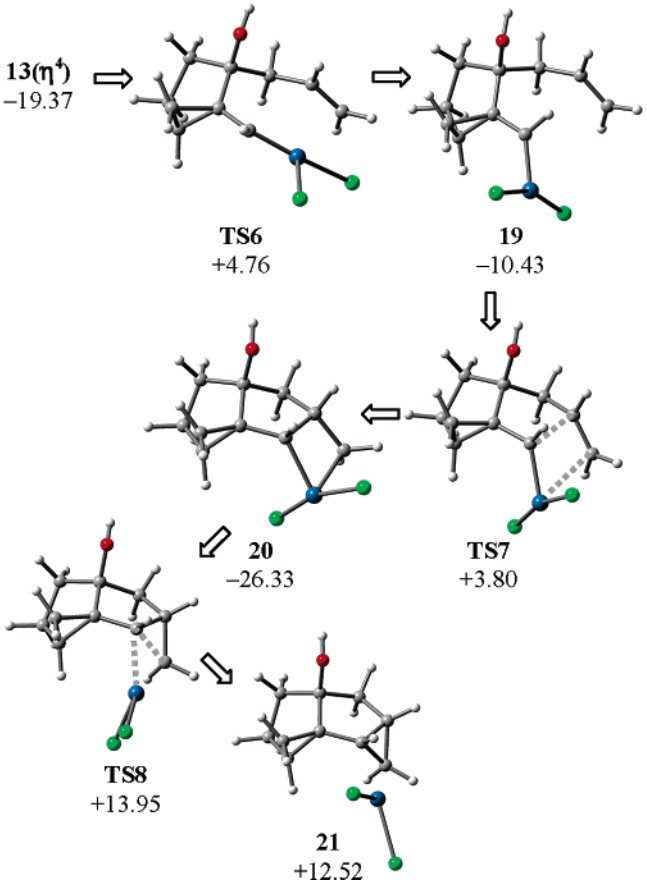
(40) (a) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839−1844. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* **1997**, *53*, 9599−9610. (d) Cho, D.-J.; Jeon, S.-J.; Kim, H.-S.; Cho, C.-S.; Shim, S.-C.; Kim, T.-J. *Tetrahedron: Asymmetry* **1999**, *10*, 3833−3848. (e) Li, Z.; Liu, G.; Zheng, Z.; Chen, H. *Tetrahedron* **2000**, *56*, 7187−7191.

(41) (a) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241−2290. (b) Williams, B.; Jennings, P. W. *Inorg. Chim. Acta* **1997**, *265*, 23−33. (c) Cámpora, J.; Palma, P.; Carmona, E. *Coord. Chem. Rev.* **1999**, *193−195*, 207−281.

(42) (a) Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183−190. (b) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553−1565. (c) Gupta, A. D.; Bhuniya, D.; Singh, V. K. *Tetrahedron* **1994**, *50*, 13725−13730. (d) Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745−8748. (e) Kwong, H.-L.; Lee, W.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 2299−2308.

(43) The related Simmons−Smith cyclopropanation of zinc carbenoid species also takes place through a direct carbene insertion: (a) Dargel, T. K.; Koch, W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 877−881. (b) Bernardi, F.; Bottoni, A.; Miscione, G. P. *J. Am. Chem. Soc.* **1997**, *119*, 12300−12305. (c) Hiri, A.; Nakamura, M.; Nakamura, E. *Chem. Lett.* **1998**, 927−928.

Scheme 14. Optimized Structures for the Stepwise Cyclopropanation of the Pt−Carbene 13(η^4)

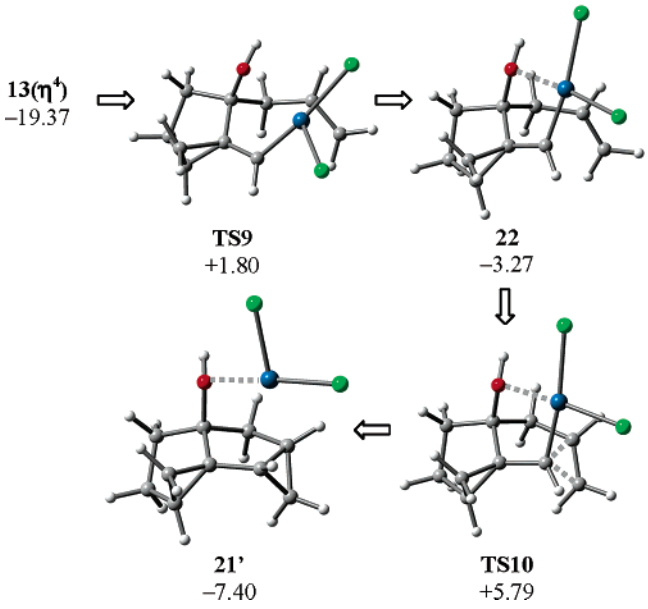


coupling to form the platina(IV)cyclobutane intermediate **20** takes place through the concerted but highly asymmetric **TS7** (C_{10}−Pt = 2.699 and C_1−C_9 = 2.052 Å) and implies an activation energy of 14.22 kcal mol^{-1}. Then, the eliminative reduction of **20** leads to the cyclopropane[44] product **21** through the transition structure **TS8**. Calculations indicate a surprisingly high activation barrier for this elementary step (40.28 kcal mol^{-1}), in stark contrast with our previous calculations,[24] probably due to the lack of additional stabilizing donor ligands for the deficient 12-electron complex.

To verify this hypothesis, we performed further studies by taking into account the participation, as coordinating solvent, of H_2O and toluene. While the ligand H_2O only induces a slight reduction of the activation barrier for the transformation of **19** to the metallacyclobutane **20** (13.26 kcal mol^{-1}), the conversion of **20** into **21** proceeds with a significantly decreased energy barrier (28.32 kcal mol^{-1}).[36] In contrast, toluene has only weak stabilizing effects with respect to the unsaturated complex for the final step (energy barrier of 37.64 kcal mol^{-1}).

(ii) The proper disposition between the carbene Pt−C_1 and the alkene is also required in order for the direct cyclopropanation to take place (path II of Scheme 13). As the molecular structure bears the donor group OX, able to act as an additional ligand in the coordinatively unsaturated system, **13** can evolve, by metal fragment rearrangement, to the metallaoxycyclopentane intermediate **22** (Scheme 15). It must be remarked that

Scheme 15. Optimized Structures for the Proposed Stereoselective Formation of the Tetracyclic Adduct



this possibility is not viable for the stepwise path, since it would drive to an unsuitable structure for the intramolecular [2 + 2] cycloaddition.

Pt−halide bonds become less equal in length (2.382/2.418 Å in **13** vs 2.404/2.313 Å in **22**) because of the increased degree of pπ bonding interactions between C_1 and the trans chloride ligand and the improved backdonation. It is noteworthy that **22** depicts a more evident carbene character[34] than **13**, since there is a higher coplanarity between the plane of the carbene substituents and the metal coordination plane,[45] due to steric factors. The interchange displacement step is endothermic (+16.10 kcal mol^{-1}) and takes place with an energy barrier of 21.18 kcal mol^{-1} (+1.80 kcal mol^{-1} above **9**(η^4)).

Finally, **22** leads to the tetracyclic system **21′** via transition structure **TS10**, which shows the concerted formation of C_1−C_9 (2.129 Å) and C_1−C_{10} (2.019 Å) bonds.[46] The activation energy to reach the transition state **TS10** is 9.06 kcal/mol (+5.79 kcal mol^{-1} relative to **9**(η^4)). Therefore, the concerted cyclopropanation pathway should be kinetically favored over the stepwise route.[47]

In summary, the proposed reaction mechanism consists of three steps, two of them being intramolecular concerted cyclopropanation and involving low energy barriers (Table 1). Free energy results indicate that the overall process is exothermic (−7.40 kcal mol^{-1}).

(44) (a) Casey, C. P.; Hornung, N. L.; Kosar, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4908−4916. (b) Van Koppen, P. A. M.; Jacobson, D. B.; Illies, A.; Bowers, M. T.; Hanratty, M.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 1991−2001.

(45) The dihedral angle H−C_1−Pt−Cl is 38.9 and 94.4° in **13** vs 8.2 and 11.6° in **22**.

(46) (a) These bond lengths contrast with other results that indicate an early transition structure for concerted cyclopropanation from metal−carbene, such that found for intermolecular cyclopropanation of the Cu(I) carbene complex: Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, J. M.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616−7625. (b) For the related Simmons−Smith cyclopropanation of Zn(II) carbenoid species, see ref 43.

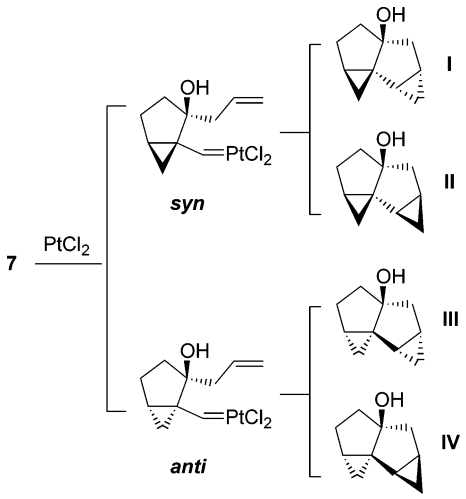
(47) For previous theoretical works about formation of cyclopropanes from transition-metal carbene complexes and alkenes, see: (a) Jaeger, M.; Prosenc, M. H.; Sontag, C.; Fischer, H. *New J. Chem.* **1995**, *19*, 911−919. (b) Straub, B. F. *J. Am. Chem. Soc.* **2002**, *124*, 14195−14201.

Table 1. Total[a] and Free[b] Energy Differences Computed for $PtCl_2$-Mediated Cycloisomerization of 7: Comparison between the Metathesis Reaction and the Formation of Tetracyclic Product

	metathesis process[c]			formation of polycyclic adduct	
	ΔE (kcal mol^{-1})	ΔG_{298} (kcal mol^{-1})		ΔE (kcal mol^{-1})	ΔG_{298} (kcal mol^{-1})
9(η^2)	0.00 (+14.92)	0.00 (+14.66)	**9**(η^4)	0.00	0.00
TS1(η^2)	+7.54 (+22.46)	+7.90 (+22.56)	**TS1**(η^4)	+10.46	+12.01
13(η^2)	−20.48 (−5.56)	−19.86 (−5.20)	**13**(η^4)	−21.65	−19.37
TS2	+5.57 (+20.49)	+5.57 (+20.23)	**TS9**	+0.78	+1.80
14	−8.38 (+6.54)	−8.38 (+6.28)	**22**	−4.95	−3.27
			TS10	+4.23	+5.79
			21′	−9.89	−7.40

[a] Zero-point corrected values. [b] Includes thermal corrections at 298 K. [c] Total and free energy differences (in kcal mol^{-1}) relative to **9**(η^4) are given in parentheses.

Scheme 16

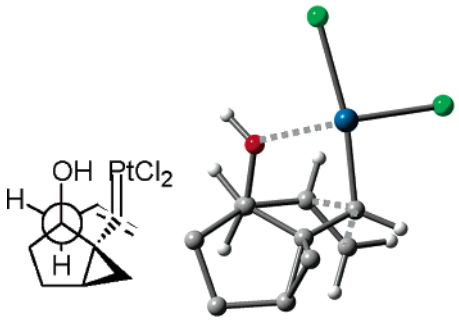


The metathesis reaction and the formation of the tetracyclic product from a dienyne share a common key step (5-exo cyclization). The presence of the propargylic hydroxy (donor group) and alkene moieties promotes the formation of tetracyclic adducts, while retards the metathesis process (Table 1), because it should proceed through the less stable unsaturated system (**TS1**(η^2) is 10.55 kcal mol^{-1} above **TS1**(η^4)). Therefore, precursors of type **7** should yield predominantly the tetracyclic adduct, in agreement with the experimental evidence.

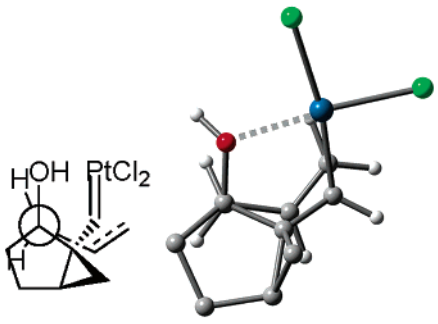
2.1. Regio- and Stereoselectivity Implications of the Proposed Mechanism. Now that a probable reaction pathway has been suggested, next we will analyze the formation of the isomers **II**−**IV** (Scheme 16), not observed experimentally, to understand the factors that lead to the high stereoselectivity.

The calculations reveal that formation of **II** can proceed through a nearly eclipsed transition structure (**TS11**), 9.82 kcal mol^{-1} higher in energy than the staggered **TS10** (see Figure 1). Hence, the formation of **I** is clearly favored over **II**,[48] in qualitative agreement with the observed stereochemistry.

On the other hand, the formation of isomers **III** and **IV** could arise from the anti-periplanar cyclopropyl Pt-carbene (Scheme 16). The computed data indicate that formation of the antiperiplanar intermediate **13**(η^4)$_{\mathbf{ANTI}}$ involves an activation energy higher (13.49 kcal mol^{-1})



TS10
G_{rel} = 0.00 kcal/mol



TS11
G_{rel} = +9.82 kcal/mol

Figure 1. Transition structures for the direct cyclopropanation path to afford isomers of types **I** (**TS10**) and **II** (**TS11**) (see Scheme 16). Some H atoms have been omitted for clarity.

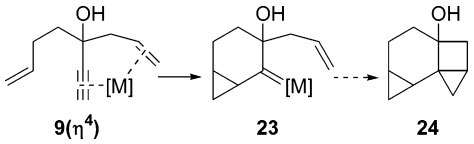
than that of the syn counterpart **13**(η^4), and **TS1**(η^4)$_{\mathbf{ANTI}}$ lies 1.8 kcal mol^{-1} above **TS1**(η^4). These results can be attributed to resonance effects.[49] NBO analysis performed on syn- and anti-periplanar transition structures indicates a strong overlap between the filled π orbital of the C_6-C_7 bond and the π^* orbital of the highly polarized C_1-C_2 bond (70% on C_2). However, **TS1**(η^4) shows a delocalization energy due to a $\pi_{C6-C7} \rightarrow \pi^*_{(C1)-C2}$ interaction 3 kcal mol^{-1} higher than **TS1**(η^4)$_{\mathbf{ANTI}}$ (39.86 vs 36.74 kcal mol^{-1}). This energy difference, probably due to the field induced by the OR group, could account for the higher stabilization of the syn-periplanar structure. Further support for this hypothesis arises from the study of the unhydroxylated precursor, which shows no energy difference between both cyclization transition structures ("syn" and "anti" only differ by 0.4 kcal mol^{-1}; in fact, the latter is favored).

In addition to the 5-exo cyclization mode, a 6-endo process to afford the cyclopropyl Pt(II)−carbene **Q**

(48) Munslow, I. J.; Gillespie, K. M.; Deeth, R. J.; Scott, P. *Chem. Commun.* **2001**, 1638−1639.

(49) A variety of explanations based on hyperconjugative interactions at the transition state and various orbital mixing/tilting effects have been provided to explain the control of diastereoselectivity during additions to unsaturated groups. (a) Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437−1468. (b) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552. (c) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447−8462. (d) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690−6695. (e) Paddow-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638-10639. (f) Ohwada, T. *J. Am. Chem. Soc.* **1992**, *114*, 8818. (g) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678−11688. (h) Fraser, R. R.; Faibish, N. C.; Kong, F.; Bednarski, F. *J. Org. Chem.* **1997**, *62*, 6164−6176. (i) Jeyaraj, D.; Yadav, A. A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 4483−4486.

Scheme 17



(Scheme 4) is also possible, and it has been found as a key step in the cycloisomerization of heteroatom-tethered 1,6-enynes.[24] The terminal cyclization mode could proceed to the intermediate **23** (Scheme 17), which could evolve to the conceivable, although highly strained, tetracyclic adduct **24** through a further (stepwise or concerted) cyclopropanation. Our results show that formation of **23** is more exothermic (−21.04 kcal mol^{-1}) than formation of **13** for the exo-cyclization mode, but the transition structure involved, **TS12** (Scheme S5; see the Supporting Information) is 1.4 kcal/mol higher in energy than **TS1(η^4)**, which makes the 5-exo attack faster than the alternative endo cyclization. This kinetic preference is due to the enhanced electrophilic character at the internal alkyne center[23] induced by the catalyst (NPA charges: −0.021 for C_2 and −0.231 for C_1 in the reactant complex **9(η^4)**).

Moreover, **24** is a less stable product than the cyclopentane adduct **21′** (17.4−25.2 kcal mol^{-1}, depending on the possible diastereomers), because of the high tension of the bicyclo[2.1.0]pentane framework. Thus, on the basis of our calculations the 5-exo-cyclization mode is favored from both kinetic and thermodynamic viewpoints, in perfect agreement with experimental observations.

Conclusions

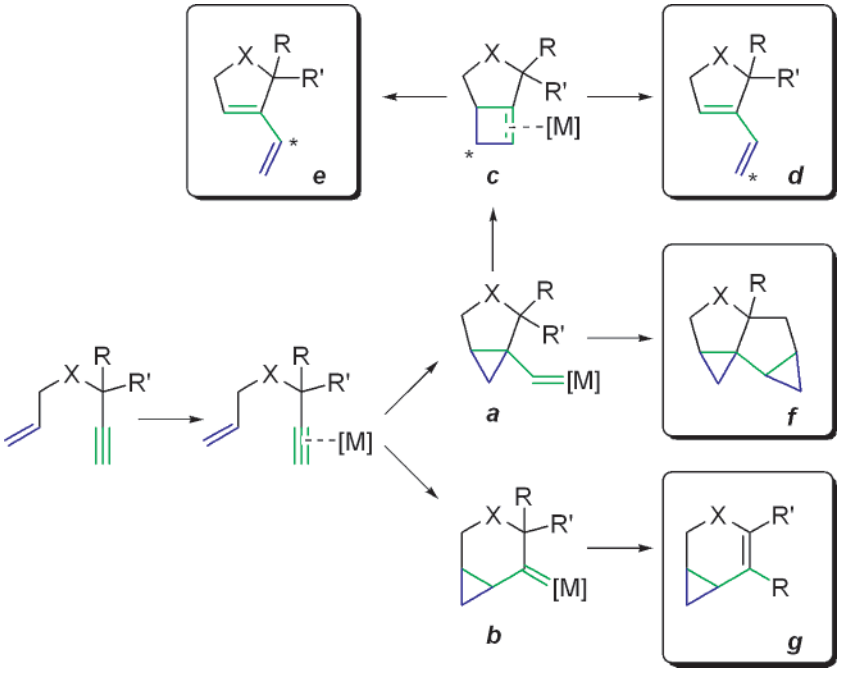
As a part of a broad study, we report a DFT mechanistic analysis of the $PtCl_2$-mediated cycloisomerizations of 1,6-enyne precursors bearing different propargylic substituents.[32] On the basis of our theoretical calculations, the reaction pathway for each of the possible, strikingly mechanism-related, kinds of cycloisomerization has been proposed. In addition, the intriguing effects of the substituents on the course of the reactions have been clarified.

The electrophilic activation of the alkyne, upon coordination to $PtCl_2$, to the intramolecular nucleophilic attack by the tethered alkene leads to the key Pt−carbene intermediates ***a*** and ***b*** (Scheme 18) through exo or endo cyclopropanation, respectively. The selection of the initial cyclization mode is governed by the substitution pattern, although a 5-exo cyclization is the kinetically favored route.

Formation of the intermediate ***a*** should be the common path for the formation of the metathesis adduct and functionalized polycyclic structures. The metathesis process would involve the transformation of the carbene ***a*** into the strained cyclobutene intermediate ***c***, which may afford the normal skeletal rearrangement product ***d*** by electrocyclic ring opening. According to our calculations, the generation of the anomalous rearrangement product ***e*** is envisaged as proceeding via simultaneous catalyst-assisted ring opening/C−H insertion processes, leading to a Pt−carbene, which yields the anomalous product by a [1,2]-H-shift elimination sequence. The presence of an additional alkene group and the propargylic hydroxy group allows the formation of tetracyclic adducts, while retarding the metathesis process. Thus, the fused bicyclic intermediate ***a*** evolves, by coordination of the propargylic OR group to the catalyst, to a reactive carbene, which easily may suffer a further concerted cyclopropanation by trapping of the lateral alkene, to yield steroselectively the polycyclic adduct ***f***. Electronic and steric factors from propargylic substituents have been shown to control the high stereoselectivity.

By comparing the energetic requirements for the formation of ***d/e*** and ***f*** products, we can conclude that formation of polycyclic adducts is the clearly favored pathway for polyenyne precursors bearing a hydroxylic

Scheme 18. $PtCl_2$-Mediated Cycloisomerization of 1,6-Enynes



(or ether) group at the propargylic position, due to the stabilizing role of the additional alkene chain in the course of the reaction, in agreement with experimental evidence.

In summary, these results provide new insights into the $PtCl_2$-mediated cycloisomerization mechanisms and the origin of the chemo-, regio-, and stereoselectivities observed.

Computational Methods

Calculations have been carried out using the Gaussian03 program.[50] The geometries have been fully optimized at the DFT level by means of the B3LYP hybrid functional.[51] Pt has been described by the LANL2DZ basis set,[52] where the innermost electrons are replaced by a relativistic ECP and the 18 valence electrons are explicitly treated by a double-ζ basis set. For all other atoms, the 6-31G(d) basis set has been employed.

Harmonic frequencies were calculated at the optimization level, and the nature of the stationary points was determined in each case according to the right number of negative eigenvalues of the Hessian matrix. The intrinsic reaction coordinate (IRC) pathways[53a] from the transition structures have been followed using a second-order integration method,[53b] to verify the expected connections of the first-order saddle points with the correct local minima found on the potential energy surface. Zero-point vibration energy (ZPVE) and thermal corrections (at 298 K) to the energy have been estimated on the basis of the frequency calculations at the optimization level and scaled by the recommended factor.

In the case of **TS2**, the normal strategy used to converge to a transition structure met with failure, probably as a result of the extremely flat energy surface around this stationary point, with very small force constants. To solve this problem, we used the Tight option to tighten the cutoffs on forces and step size that are used to determine convergence, to ensure adequate convergence and reliability of frequencies.

To obtain more reliable energy values, some single-point energy calculations at the B3LYP/6-311+G(2d,p)/LANL2DZ level were carried out on the B3LYP/6-31G(d)/LANL2DZ geometries. The results revealed a negligible basis set effect.

Natural bond orbital (NBO) analysis[54] have been performed at the DFT level by the module NBO v.3.1 implemented in Gaussian03 in order to evaluate the NPA atomic charges and delocalization interactions.

Supporting Information Available: Figures and tables giving alternative mechanistic proposals evaluated throughout this study for the cycloisomerization reactions and atomic coordinates for the computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

OM050131E

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