Selective Ruthenium-Catalyzed Transformations of Enynes with Diazoalkanes into Alkenylbicyclo[3.1.0]hexanes

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Abstract: Reaction of a variety of C≡CH bond-containing 1,6-enynes with $N_2CHSiMe_3$ in the presence of RuCl(COD)Cp* as catalyst precursor leads, at room temperature, to the general formation of alkenylbicyclo-[3.1.0]hexanes with high *Z*-stereoselectivity of the alkenyl group and *cis* arrangement of the alkenyl group and an initial double-bond substituent, for an *E*-configuration of this double bond. The stereochemistry is established by determining the X-ray structures of three bicyclic products. The same reaction with 1,6-enynes bearing an R substituent on the C_1 carbon of the triple bond results in either cyclopropanation of the double bond with bulky R groups ($SiMe_3$, Ph) or formation of alkylidene−alkenyl five-membered heterocycles, resulting from a β elimination process, with less bulky R groups (R = Me, $CH_2CH=CH_2$). The reaction can be applied to *in situ* desilylation in methanol and direct formation of vinylbicyclo[3.1.0]-hexanes and to the formation of some alkenylbicyclo[4.1.0]heptanes from 1,7-enynes. The catalytic formation of alkenylbicyclo[3.1.0]hexanes also takes place with enynes and N_2CHCO_2Et or N_2CHPh. The reaction can be understood to proceed by an initial [2+2] addition of the Ru=$CHSiMe_3$ bond with the enyne C≡CH bond, successively leading to an alkenylruthenium−carbene and a key alkenyl bicyclic ruthenacyclobutane, which promotes the cyclopropanation, rather than metathesis, into bicyclo[3.1.0]hexanes. Density functional theory calculations performed starting from the model system Ru(HC≡CH)($CH_2=CH_2$)Cl(C_5H_5) show that the transformation into a ruthenacyclobutane intermediate occurs with a temporary η^3-coordination of the cyclopentadienyl ligand. This step is followed by coordination of the alkenyl group, which leads to a mixed alkyl−allyl ligand. Because of the non-equivalence of the terminal allylic carbon atoms, their coupling favors cyclopropanation rather than the expected metathesis process. A direct comparison of the energy profiles with respect to those involving the Grubbs catalyst is presented, showing that cyclopropanation is favored with respect to enyne metathesis.

Introduction

Enynes have become crucial keys giving access to a variety of complex architectures, promoted by metal catalysts with atom economy.[1,2] Enyne metathesis[2,3] and cycloisomerization[4] are among the most general and useful transformations of enynes, and the catalytic Pauson−Kand reaction has now been applied to enynes.[5] Enynes constitute key building blocks for a variety of functionalized cycles via cycloadditions.[6,7] Recently, electrophilic activations of enynes with ruthenium(II),[8] platinum(II),[9] gold,[10] and gallium(III)[11] catalysts have opened new and efficient routes for the selective formation of bicyclic compounds, and the use of suitable dienynes leads to catalytic tricyclization with a vinylcyclopropane unit.[12]

The search for alkene metathesis catalysts arising from RuCl-(L)₂Cp* precursors (Cp* = C_5Me_5) and diazoalkane as a carbene

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source has actually led to the discovery of a new catalytic bicyclization of enynes, forming alkenylbicyclo[3.1.0]hexanes[13] (eq 1). This reaction, which tolerates functional groups, has been
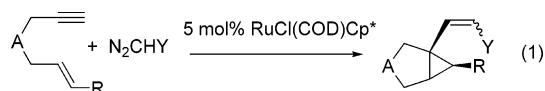
used for the controlled synthesis of bicyclic amino acid derivatives,[14] whereas a similar reaction in the additional presence of ethylene was successfully orientated toward the formation of a cycloalkenylcyclopropane derivative.[15] It was shown recently that this reaction of a functional enyne with diazoalkanes, but with the Ni(COD)$_2$ catalyst (COD = 1,5-cyclooctadiene), also led to alkenylbicyclo[3.1.0]hexane derivatives.[16]

Alkenylbicyclo[3.1.0]hexane intermediates have recently been shown to be powerful for building cyclopentenes with NHC–Ni(0) catalyst,[17] and especially larger cycles via catalyzed [4+2+1] cycloadditions with Ni(COD)$_2$ and [5+2] cycloadditions with rhodium(I) catalyst.[7]

As the vinylcyclopropane syntheses are not straightforward,[18] the interest in alkenylcyclopropanes and bicyclic[3.1.0]hexane derivatives for controlled building of larger cycles has led us

to develop their ruthenium-catalyzed formation and to explore the generality of the reaction.

We report here that the catalytic transformation of 1,6-enynes and diazoalkanes into alkenylbicyclo[3.1.0]hexane derivatives, with RuCl(COD)Cp* as catalyst precursor, constitutes a general reaction, including C=C bond substituted enynes, and shows high stereoselectivity. By contrast, triple-bond disubstituted enynes offer competitive reactions with a simple cyclopropanation of the enyne C=C bond or a new monocyclization reaction leading to alkenyl−alkylidene cyclopentane derivatives. Actually, we show that the RuCl(=CHY)Cp* catalytic intermediate behaves as an enyne metathesis catalyst inhibitor but favors cyclopropanation. Density functional theory (DFT) calculations on a RuCl(HC≡CH)(CH$_2$CH$_2$)C$_5$H$_5$ model show that the formation of an alkenylruthenacyclobutane intermediate is favored by an η^5-to-η^3 shift of the cyclopentadienyl ring and that the large stabilization of the metallacyclobutane intermediate is due to coordination of the alkenyl bond, leading to an alkyl−allyl ligand, which favors reductive elimination rather than metathesis.

Results and Discussion

The reaction of the diazoalkane N$_2$CHSiMe$_3$ with alkynes in the presence of RuCl(COD)Cp* (**I**) as catalyst precursor leads to the double addition of a related carbene to the triple bond to selectively generate silylated 1,3-dienes[19] (eq 2). This reaction reveals the potential biscarbene character of a triple bond for coupling with external carbene. It also suggests the intermediate formation of RuCl(=CHSiMe$_3$)Cp* from RuCl(COD)Cp* and N$_2$CHSiMe$_3$.
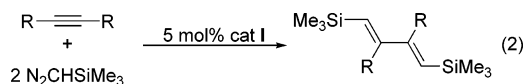
As the neutral 16-electron ruthenium(II)−carbene intermediate RuCl(=CHY)Cp* is isoelectronic with the Grubbs catalysts RuCl$_2$(=CHR)(PCy$_3$)L (L = PCy$_3$ or imidazolinylidene, IMes), one might expect that the intermediate RuCl(=CHY)Cp* would catalyze the enyne metathesis to give the corresponding alkenylcycloalkene.[3] Thus, the enyne **1a** would lead to the 1,3-diene **2a** (path (a), eq 3).

| A: 2M in hexane (2.4 eq) dioxane / 60°C / 1 h | 95%, Z/E = 4/1 |
| B: 2M in ether (1.1 eq) ether / r. t./ 5 min | 86%, Z/E = 4/1 |

Actually, the initial attempt at transformation[13] of the enyne **1a** with 2.4 equiv of N$_2$CHSiMe$_3$ (2 M in hexane) and 5 mol
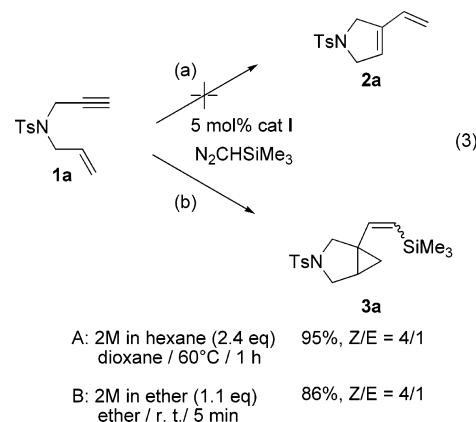
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% of RuCl(COD)Cp*, after 1 h at 60 °C in dioxane (reaction conditions A), to allow for complete conversion of **1a**, did not lead to the enyne metathesis product **2a** but instead gave a 95% yield of **3a** with a *Z/E* ratio of 4/1 (path (b), eq 3).

The effect of reaction conditions on the reaction efficiency and yields led us to choose instead N₂CHSiMe₃ 2 M in diethyl ether, as the reaction takes place more rapidly at room temperature (complete conversion in 5 min) and uses only 1.1 equiv of N₂CHSiMe₃ (reaction conditions B). Furthermore, complete conversion of the enyne can be carried out in various polar and nonpolar solvents (dioxane, diethyl ether, methylene chloride, pentane, toluene, and even water), diethyl ether and dioxane giving the best solubility. The catalyst is used in 5 mol % rather than in 3 and 1 mol %, as the reaction conversion is respectively 100% (5 min), 100% (35 min), and 30% (24 h). The reaction can take place at 0 °C with 5 mol % of catalyst but leads to only 76% conversion of **1a** after 5 min.

The best conditions for the transformation of **1a** into **3a**, with 5 mol % of RuCl(COD)Cp* and 1.1 equiv of N₂CHSiMe₃ in diethyl ether at room temperature, have been used to study the generality of the reaction with a variety of terminal triple-bond-containing enynes (eq 4). These results are summarized in Table 1.
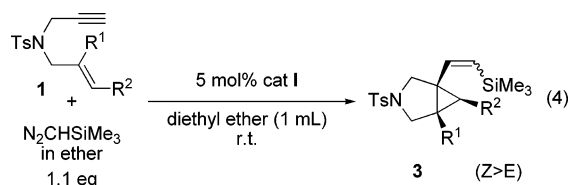
The results show that the reaction takes place with good yields, except in the case of **1i**, containing an electron-withdrawing group at the double bond. The nature of the protecting group (Ts or Cbz) seems to have no influence on reaching good yields (entries 1 and 2). The alkene chain of **3** possesses preferentially the *Z*-configuration regardless of the reaction temperature (entries 1−3). However, only the *Z*-isomer is obtained with enynes **1** containing *a substituent on the C=C bond terminal carbon* (entries 4−6).

Enynes containing a terminal allylic alcohol function also lead to bicyclic products (entries 7 and 8), although the reaction is much slower than with other substituted C=C bond enynes **1d**−**f**. Only the α-disubstituted product **1h** leads to a good yield of **3h** (95%; *Z/E* = 90/10).

It is noteworthy that the disubstitution on the terminal carbon of the alkene bond in **1j** disfavored the formation of the bicyclic compound **3j** (11%; *Z/E* = 30/70) (entry 10) to the profit of the "alkene metathesis" products **4** (20%) and **5** (20%). This observation suggests that this disubstitution disfavors the reductive elimination step (cyclopropanation) to the profit of metathesis with equal formation of CH=CHSiMe₃ (**4**) and CH= CMe₂ (**5**) groups. This also means that, after each metathesis step giving **4**, the released Ru=CMe₂ moiety is efficient only to perform the metathesis reaction leading to **5**, not the bicyclization.

The diastereoselectivity of the reaction depends on the alkene stereochemistry. The transformation of **1d** (*E/Z* = 85/15) gives two diastereoisomers of **3d** (85/15). The X-ray structure of the isolated major diastereoisomer establishes the *cis* arrangement

Table 1. Catalytic Transformation of Substituted-C=C-Bond Enynes **1** with N₂CHSiMe₃

a Reaction conditions: A, 2.4 equiv of N₂CHSiMe₃ (2 M in hexane) in dioxane (1 mL), 60 °C, 5 mol % RuCl(COD)Cp*; B, 1.1 equiv of N₂CHSiMe₃ (2 M in ether) in diethyl ether (1 mL), room temperature, 5 mol % RuCl(COD)Cp*. *b* Isolated product yields obtained after complete conversion and purification by silica gel chromatography.

of the alkenyl and methyl groups in **3d**. Thus, the double-bond *E*-configuration favors the selective formation of the diastere-

Table 2. Catalytic Transformation of Propargyl Allyl Ethers with N$_2$CHSiMe$_3$

Entry	Enynes	Reaction conditions[a]	Products, yields%[b] (Z/E)
1	**6a**	B, 30 min	**7a** 28 %, (83/13)
2	**6b**	B, 30 min	**7b** 35 %, (100/-) **8b** 21 %
3	**6c**	A, 30 h B, 4.5 h	**7c** 40 %, (-/100) 47 %, (-/100) dr=90/10
4	**6d**	A, 20 h B, 30 min	**7d** 85 %, (75/25) 20 %, (83/13) **9d** 35% B conditions

[a] Reaction conditions: A, 2.4 equiv of N$_2$CHSiMe$_3$ (2 M in hexane) in dioxane (1 mL), 60 °C, 5 mol % RuCl(COD)Cp*; B, 1.1 equiv of N$_2$CHSiMe$_3$ (2 M in ether) in diethyl ether (1 mL), room temperature, 5 mol % RuCl(COD)Cp*. [b] Isolated product yields obtained after complete conversion and purification by silica gel chromatography.

Table 3. Catalytic Transformation of Carbon-Chain Enynes[a]

Entry	Enynes	Products, yields%[b] (Z/E)
1	**10a**	**11a** 62 %, (85/15)
2	**10b**	**11b** 70 %, (100/-)

[a] Reaction conditions: 1.1 equiv of N$_2$CHSiMe$_3$ (2 M in ether) in diethyl ether (1 mL), room temperature, 1 h, 5 mol % RuCl(COD)Cp*. [b] Isolated product yields obtained after complete conversion and purification by silica gel chromatography.

Table 4. Catalytic Transformation of 1,7-Enynes

Entry	Enynes	Reaction conditions[a]	Products, yields%[b] (Z/E)
1	**12a**	30 min	**14a** 78 %, (83/17)
2	**12b**	24 h	**14b** 27 %, (100/-)
3	**13**	r.t. or 60°C 24 h	No reaction

[a] Reaction conditions: 1.1 equiv of N$_2$CHSiMe$_3$ (2 M in ether) in diethyl ether (1 mL), room temperature, 5 mol % RuCl(COD)Cp*. [b] Isolated product yields obtained after complete conversion and purification by silica gel chromatography.

oisomer with *cis* alkenyl and R^2 groups (**1d** → **3d**). The Z-configuration favors the formation of the diastereoisomer with *trans* alkenyl and alkyl (R^2) groups in the transformation of **1f** into **3f**. This was established by the X-ray structure of **3f**.

The catalytic transformation of easily accessible enynes arising from terminal propargylic alcohols and allyl bromides was performed, and the results obtained with both types of conditions, A and B, are presented in Table 2.

It first appears that the bicyclization of oxygenated enynes **6** into derivatives **7** is more difficult to perform than that of enynes **1**, in either conditions A or B. The best results are obtained for α-disubstituted propargyl ethers (entries 3 and 4).

It is noteworthy that, from the enyne **6b**, only a small amount of the product **8b**, corresponding to the double carbene addition to the triple bond, was observed (entry 2) and that from **6d**, besides the bicyclo[3.1.0.]hexane **7d** (20%), the bicyclo[4.1.0]-heptane derivative **9d** (35%) was obtained.

The reaction applied to 1,6-enynes **10**, containing only a carbon chain, led at room temperature to alkenylbicyclo[3.1.0]-hexanes **11a** (62%) and **11b** (70%) with high Z-stereoselectivity of the alkenyl chain (Table 3).

Attempts were then made to apply the previous bicyclization reaction to 1,7- and 1,8-enynes in order to produce larger rings and bicyclo[4.1.0]heptane and -[5.1.0]octane derivatives. The

results are shown in Table 4. The transformation of 1,7-enynes **12a,b** takes place and **14a,b** are obtained. However, under similar conditions, the 1,8-enyne **13** did not lead to the formation of eight-membered cycle and was recovered (Table 4).

Enynes with a disubstituted triple bond or a disubstituted propargylic carbon disfavor the previous catalytic reaction, to the profit of two reactions leading to either derivative **17** or **18** (eq 5, Table 5).

(5)
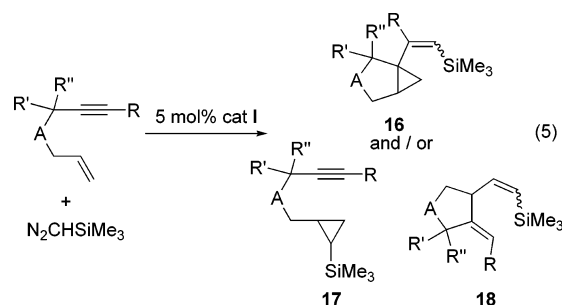
When the alkyne C(1) carbon atom is linked to a bulky substituent, such as a phenyl (**6e**) or a trimethylsilyl (**15a**) group, the interaction with the triple bond is obviously disfavored and classical cyclopropanation of the double bond takes place,

Table 5. Catalytic Transformation of Enynes with Substituted Triple Bonds or Disubstituted Propargylic Carbon


^{a} Reaction conditions: A, 2.4 equiv of $N_2CHSiMe_3$ (2 M in hexane) in dioxane (1 mL), 60 °C, 5 mol % RuCl(COD)Cp*; B, 1.1 equiv of $N_2CHSiMe_3$ (2 M in ether) in diethyl ether (1 mL), room temperature, 5 mol % RuCl(COD)Cp*. ^{b} Isolated product yields obtained after complete conversion and purification by silica gel chromatography.

leading to derivatives **17** (Table 5, entries 1 and 2). For other alkyne substituents, R = Me (**15b**) and $CH_2CH=CH_2$ (**15c**), besides the expected derivative **16**, which is obtained only in low yield, formation of derivative **18** as the major product is observed (Table 5, entries 3 and 4). Derivatives **18**, at first, appear to result from an inhibited cyclopropanation reaction (reductive elimination process), to the profit of a β-elimination process. When the enyne possesses propargylic α,α-disubstituents and a terminal triple bond (**15d,e**, entries 5 and 6), the derivatives **18** or the bicyclo[4.1.0]heptane **9e** (entry 6), analogous to **9d** (Table 2, entry 4), are obtained as minor products, in addition to the formation of the expected bicyclic products **16**.

The direct desilylation of 2-trimethylsilylvinylbicyclo[3.1.0]-hexanes appeared not to take place under classical conditions. The treatment of **3a** with either KOH in methanol or KF in tetrahydrofuran did not lead to desilylation.

The *in situ* formation of diazomethane from $N_2CHSiMe_3$ in methanol was performed and gave much more easily the vinylbicyclo[3.1.0]hexanes (eq 6, Table 6). This reaction avoids the preliminary diazomethane preparation.
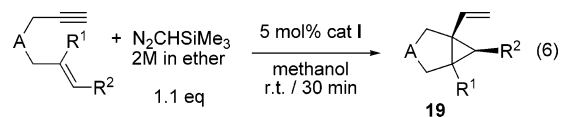
Reaction of the enynes **1a−e** and **10b** with a slight excess of $N_2CHSiMe_3$ in methanol at room temperature for only 30 min led to the vinyl derivatives **19a−f** in 60−80% yield (Table 6).

As the double bond of the enyne major isomer has *E*-configuration, the major products contained the vinyl group and the cyclopropane substituent in the *cis* arrangement (**19d,e**).

It is noteworthy that the catalytic enyne bicyclization can be performed in water. Thus, the enyne **1a** was reacted with N_2-$CHSiMe_3$ (1.2 equiv, 2 M in ether) and RuCl(Cp*)COD in 2 mL of water for only 5 min at room temperature to reach 100% conversion and avoid desilylation or decomposition. The deriva-

**Table 6.** Synthesis of Non-silylated Vinylbicyclo[3.1.0]hexanes

Entry	Enynes	Products, yields%[b]
1	**1a**	**19a** 60 %[c]
2	**1c**	**19c** 66 %
3	**1d** E/Z : 85/15	**19d** 55 % dr : 85/15
4	**1e**	**19e** 78 % dr : 100/-
5	**10b**	**19f** 81 %

a Reaction conditions: 1.1 equiv of N₂CHSiMe₃ (2 M in ether) in methanol (1 mL), room temperature, 5 mol % RuCl(COD)Cp*, 30 min. *b* Isolated product yields obtained after complete conversion and purification by silica gel chromatography. *c* 15 mol % of RuCl(COD)Cp* (with 5 mol %, the conversion never reached completion).

tive **3a** was obtained in 78% yield (eq 7). This result shows that the catalyst precursor and the intermediate catalytic species are stable in water and that the reaction in water of diazoalkane is possible on the condition that the related catalytic reactions are fast.

1a
+
N₂CHSiMe₃
2M in ether
1.2 eq

5 mol% cat I
———————
r.t. / water

3a
78%   (7)
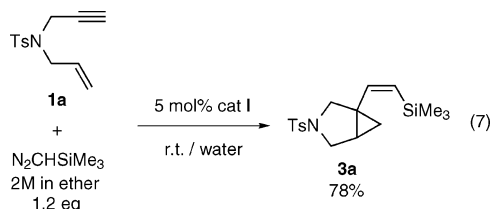
The catalytic transformation of enynes with other diazoalkanes (eq 8), such as N₂CHCO₂Et (Table 7) and N₂CHPh (Table 8), was performed and shows that the reaction proceeds as for N₂CHSiMe₃. More drastic conditions are required with N₂CHCO₂Et, 100 °C in dioxane for 1−24 h, to obtain complete conversion and good yield. No conversion takes place under 60 °C for N₂CHCO₂Et.

5 mol% cat I
———————
dioxane

20-24   (8)

Y = CO₂Et   100 °C
Y = Ph, in toluene   20, 60 and 100 °C
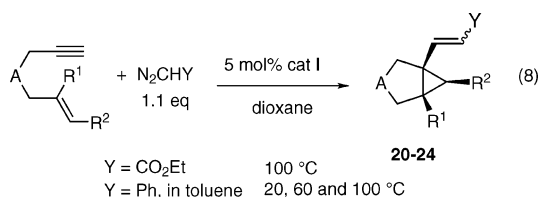
The *E*-configuration of the double bond is always observed for the derivatives **20−22** formed from enynes **1a−h**, **10b**, and **6d** with N₂CHCO₂Et (Table 7). This was shown by the X-ray structure of **20e** obtained from the *E*-enyne **1e**, which also

Table 7. Catalytic Transformation of Enynes with Diazoacetate

Entry	Enynes	Reaction conditions[a]	Products, yields%[b] (Z/E)
1	**1a**	5 h	**20a** 65 %, (-/100)
2	**1c**	24 h	**20c** 65 %, (-/100)
3	**1e**	24 h	**20e** 60 %, (-/100) dr : 100/- X-ray structure
4	**1g**	24 h	**20g** 91 %, (-/100) dr : 100/-
5	**1h**	24 h	**20h** 84 %, (-/100) dr : 100/-
6	**10b**	1 h	**21** 71 %, (-/100)
7	**6d**	24 h	**22** 75 %, (-/100)

a Reaction conditions: 1.1 equiv of N₂CHCO₂Et in dioxane (1 mL), 5 mol % RuCl(COD)Cp*, at 100 °C. *b* Isolated product yields obtained after complete conversion and purification by silica gel chromatography.

Table 8. Catalytic Transformation of Enynes with Phenyldiazomethane

Entry	Enynes	Reaction conditions[a]	Products, yields%[b] (Z/E)
1	**1a**	r.t., 5 h 60°C, 5 h 100°C, 5 h	**23** 80 %, (30/70) 84 %, (20/80) 65 %, (25/75)
2	**6d**	60°C, 24 h	**24** 50 %, (45/55)

a Reaction conditions: 1.1 equiv of N₂CHPh, conditionned in toluene (2 mL), room temperature, 60 °C, or 100 °C, 5 mol % RuCl(COD)Cp*. *b* Isolated product yields obtained after complete conversion and purification by silica gel chromatography.

established the *cis* arrangement of the alkenyl and phenyl groups. With N₂CHPh, the reaction takes place at lower temperature than with N₂CHCO₂Et, from room temperature to 100 °C (Table 8). This transformation with **1a** allows us to monitor the variations in *Z/E* ratio for formation of compound **23** according
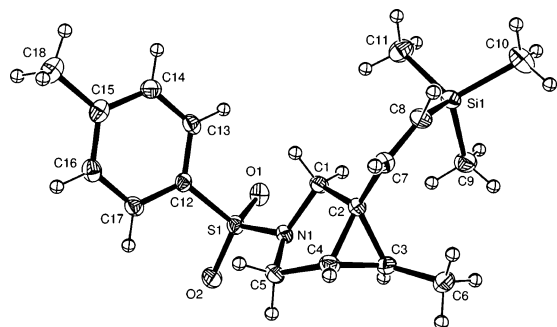
Figure 1. ORTEP drawing of the molecular structure of **3d**. Thermal ellipsoids are set at the 50% probability level.

to temperature. By increasing the reaction temperature from room temperature (Z/E = 30/70) to 60 °C (Z/E = 20/80), only a slight increase in the formation of the *E*-isomer is observed. Comparison of the reaction of **1a** at room temperature with N_2-CHSiMe$_3$ and N_2CHPh shows that the nature of the diazoalkane does influence the configuration of the alkenyl bond. From the N_2CHSiMe$_3$ product, an hypervalence interaction between the silicon and the (Ru)chlorine atoms can occur.

X-ray Diffraction Study of the Alkenylbicyclo[3.1.0]-hexanes 3d, 3f, and 20e

To elucidate the nature of diastereoisomers arising from the bicyclization of enynes, the relative positions of substituents on the cyclopropane moiety were confirmed by X-ray structure analysis of compounds **3d** (isolated major diastereoisomer), **3f**, and **20e**.[20] Each compound was purified by chromatography on silica gel, and crystals were obtained in a mixture of pentane and diethyl ether. These structures are presented in Figures 1−3.

The ORTEP drawing of the major diastereoisomer of the compound **3d** (Figure 1) shows the *Z*-stereochemistry (C$_7$−C$_8$ bond) of the double bond with a SiMe$_3$ group and the *cis* arrangement of the alkenyl and methyl groups on C$_2$ and C$_3$ of the cyclopropane moiety, respectively. This major diastereoisomer was isolated from a mixture of compounds **3d** obtained in an 85:15 ratio, arising from an *E/Z*-enyne **1d** mixture (*E/Z* : 85/15) (Table 1). The X-ray-established stereochemistry shows that the enyne with *E*-configuration leads to the diastereoisomer with *cis* alkenyl and methyl (at C$_3$ of the initial double bond) groups.

The structure of compound **3f** (Figure 2) clearly shows the three rings at the core of the molecule: a cyclopropane ring (C$_5$−C$_6$−C$_8$), a heterocycle (N$_1$−C$_1$−C$_8$−C$_6$−C$_7$), and a cyclohexyl ring (C$_1$−C$_2$−C$_3$−C$_4$−C$_5$−C$_8$). It confirms the *Z*-stereochemistry (C$_9$−C$_{10}$ bond) of the double bond with the SiMe$_3$ group and shows the *trans* relative positions between the alkenyl group on the cyclopropane linked at the C$_6$ carbon atom and the substituent on the cyclopropane linked at C$_5$. This diastereoselectivity is imposed by the *Z*-stereochemistry of the cyclohexenyl substitutent of the enyne **1f** (*Z*-C$_5$−C$_8$ bond).

The structure of compound **20e** (Figure 3) was determined to show the structural variation with a N_2CHCO$_2$Et reaction product. It shows the *E*-stereochemistry (C$_{13}$−C$_{14}$ bond) of the double bond with the CO$_2$Et group. The ORTEP drawing
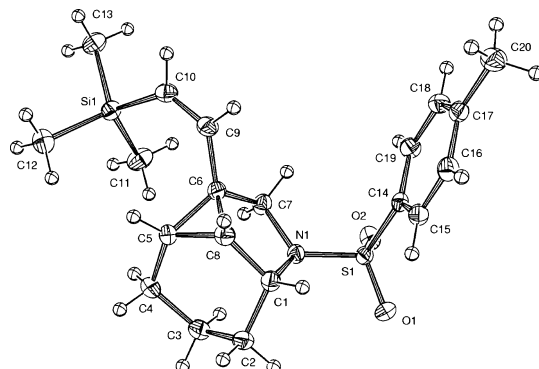

Figure 2. ORTEP drawing of the molecular structure of **3f**. Thermal ellipsoids are set at the 50% probability level.
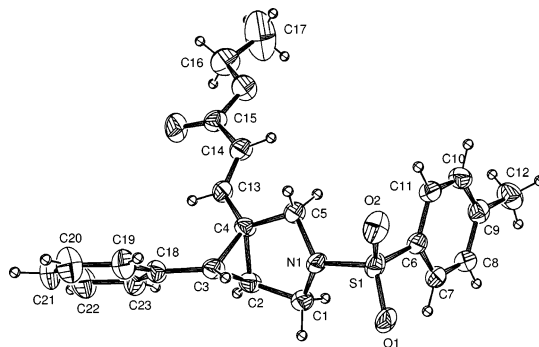

Figure 3. ORTEP drawing of the molecular structure of **20e**. Thermal ellipsoids are set at the 50% probability level.

demonstrates the *cis* arrangement on the cyclopropane moiety (C$_2$−C$_3$−C$_4$) of the phenyl group (on C$_3$) and the alkenyl group (on C$_4$) of the obtained product. This diastereoselectivity results from the *E*-stereoselectivity of the starting enyne. It confirms that, whatever the diazoalkane derivative, an *E*-configuration of the enyne-substituted (R) alkene bond favors the formation of the diastereoisomer with *cis* alkenyl and R groups.

Proposed Mechanism

Related Stoichiometric Reactions. This catalytic reaction of enyne bicyclization has some resonance with stoichiometric reactions of metal−carbene complexes containing an unsaturated chain.[21] The first related reaction involved the interaction of an alkene chain containing a stabilized alkoxycarbene−tungsten complex with an alkyne to give a bicyclo[4.1.0]heptene derivative (eq 9).[22]


(9)
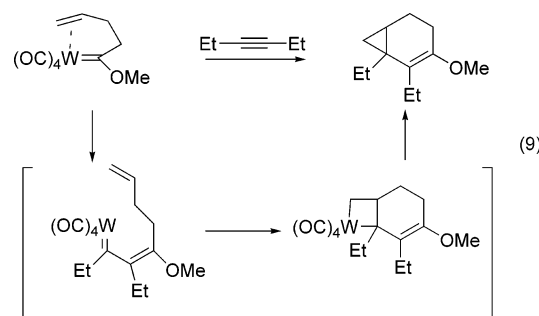
This reaction involved the coupling of the alkyne and M=C bonds to give the alkenylcarbene intermediate, followed by

(20) Crystal structure analysis of **3d**, **3f**, and **20e** is presented in the Supporting Information. Crystallographic data (excluding structure factors) for **3d**, **3f**, and **20e** have also been deposited with the Cambridge Crystallographic Data Center as CCDC 215613, 239959, and 634214. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Rd., Cambridge CB2 1EZ, UK (fax (+44) 1223-336-033; E-mail deposit@ccdc.cam.ac.uk).

(21) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271.
(22) Parlier, A.; Rudler, H.; Platzer, N.; Fontanille, M.; Soum, A. *J. Organomet. Chem.* **1985**, *287*, C7−C8.

internal [2+2] coupling of the metal—carbene with the C=C bond and reductive elimination. This stoichiometric reaction has been developed by Hoye et al.[23] and was revealed to be useful for natural product synthesis. Actually, Hoye was the first to react an enyne with a manganese—carbene complex and obtained the stoichiometric version of the present catalytic reaction.[24] This reaction was transferred to Cr, Mo, and W metal—carbene derivatives and was shown to give, on reaction with 1,6-enynes, alkenylbicyclo[3.1.0]hexanes.[25] At the same time, Mori et al. demonstrated that the reaction of $(OC)_5Cr=C(OMe)Me$ with 1,6-enynes led to bicyclization of the enyne and/or metathesis reaction products, depending on the nature of the C(1) double-bond substituent[26] (eq 10), via the same metallacyclobutane intermediate, for which the nature of the R group favored either reductive elimination with an electron-withdrawing substituent ($R = p\text{-}O_2NC_6H_4-$) or metathesis reaction ([2+2] retrocycloaddition) with an electron-donating group ($R = p\text{-}MeC_6H_4-$).


(10)
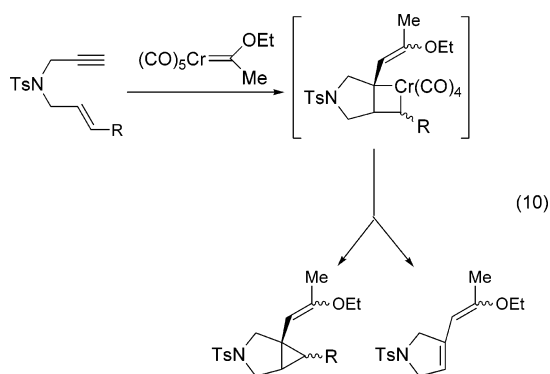
Proposed Mechanism with Initial Interaction with the C≡CH Bond. Our reaction performed with **1a** containing a deuterium atom at the alkyne bond C≡CD shows that the terminal alkyne carbon is involved in the $CD=CHSiMe_3$ bond formation (eq 11).

(11)
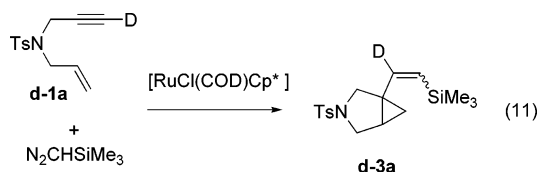
The catalytic transformation of enynes with diazoalkane in the presence of the catalyst precursor RuClCp*(COD) can be understood by the initial formation of RuCl(=CHY)Cp* as the catalytic species, which first reacts with the terminal triple bond to give the intermediate **A**, leading to the ruthenium vinylcarbene **B**. The intramolecular interaction of the Ru=C bond with the C=C bond of **B** gives back **A** or produces the metallacyclobutane **C**, which is subject to reductive elimination to give the bicyclic products **3** and **7** (Scheme 1).

The catalytic enyne metathesis has been shown by Mori[3b] to easily proceed with Grubbs catalyst, and the proposed mechanism involves the interaction of the Ru=C bond with the triple bond via a mechanism similar to that in Scheme 1, with [Ru]=

(23) Hoye, T. R.; Vyvyan, J. R. *J. Org. Chem.* **1995**, *60*, 4184.
(24) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1990**, *9*, 3014.
(25) Hoye, T. R.; Suriano, J. A. *Organometallics* **1992**, *11*, 2044.
(26) Mori, M.; Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1082.

Scheme 1. Proposed Mechanism for the Selective Transformation of Enynes and Diazoalkanes into Alkenylbicyclo[3.1.0]hexanes
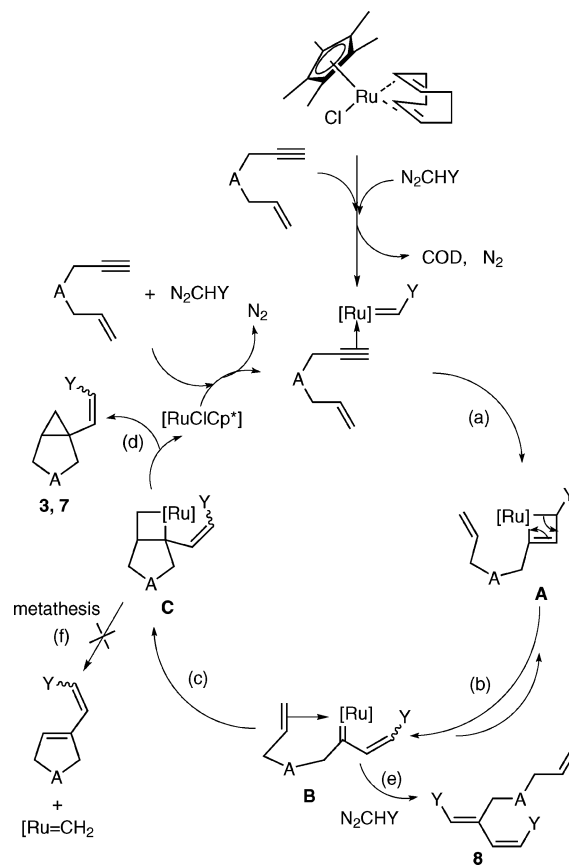
$CHY = (L)Cl_2Ru=CHPh$ ($L = Cy_3P$, IMes), *except for the last step.* In this latter case, the intermediate **C** exclusively leads to the metathesis process and alkenylcycloalkene and ruthenium—carbene formation (Scheme 1, step f). Thus, the present reaction differs from enyne metathesis only by the ability of the RuClCp* moiety to favor reductive elimination (step d).

This may result from both the electronic influence and the geometry of the RuClCp* moiety with respect to those of the $(L)Cl_2Ru$ moiety, with no obvious answer. Thus, a computational study has been undertaken from intermediate **B** (see the discussion on DFT calculations below).

The $RuCl(=CHSiMe_3)Cp*$ intermediate was proposed in the double carbene addition to alkyne (eq 2).[19] Thus, in the bicyclization reaction, the intramolecular reaction (step c) should be faster than step e, which was observed only with one enyne **6b**, giving **8b** in low yield (Table 2 and Scheme 1).

Actually, enyne metathesis with the Grubbs catalyst has led in a specific case to a parallel minor stoichiometric cyclopropanation,[3b] generating a non-carbene ruthenium system. Alternatively, Diver et al., using the Grubbs II catalyst with a dienyne, leading to ring constraint, have shown the formation of a tricyclic compound via a vinylcyclopropane intermediate.[12]

In some specific cases, enyne metathesis can take place by an initial interaction of the (carbene)C=Ru bond with an enyne double bond.[27] However, according to the product nature arising from the RuCl(COD)Cp*/N2CHY system, for which the enyne double bond is incorporated in the cyclopropane, this initial

(27) Lloyd-Jones, G. C.; Margue, R. G.; De Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7442.

Scheme 2. Stereochemichal Aspects of Intermediate **A**
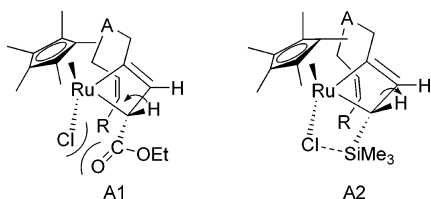
C=C bond interaction does not take place, at least for enynes containing a terminal alkyne bond (Scheme 1 and Table 1). It takes place only with disubstituted triple bonds (Scheme 3, below).

Another initial process could be considered. The electrophilic activation of the enyne by ruthenium(II)[12] or by platinum(II)[10] has been proposed to generate a bicyclo[3.1.0]carbene−metal intermediate. This process does not take place with the RuClCp* system, as the stoichiometric reaction of enyne **1a** with RuCl-(COD)Cp* rather leads to enyne oxidative addition and further addition of N₂CHSiMe₃ does not lead to the bicyclic product.

Stereochemistry of the Alkenyl Chain. The stereochemistry in the intermediate **B** (Scheme 1) depends on the nature of the substituent of diazoalkane. When Y = SiMe₃, a *Z*-stereochemistry is obtained, while Y = CO₂Et produces an *E*-stereochemistry. Phenyldiazomethane leads to a mixture of *Z* and *E* double bonds.

Simple models show that the formation of intermediate **A** requires the anti-positioned Cp* and Y groups to decrease steric interactions (Scheme 2). Thus, the stereochemistry of the double bond results from the opening of the metallacyclobutene **A**. With Y = CO₂Et, electronic repulsion between Cl and CO₂Et groups (**A1**), or at least the absence of attraction, favors the opening, such that these groups are pushed away, lowering steric hindrance and offering alkenyl *E*-configuration. For Y = SiMe₃, a strong (hypervalence) interaction between SiMe₃ and Cl groups is expected and can be responsible for the opposite opening in spite of steric interactions (**A2**).

However, in this latter case, the stereoselectivity depends also on the double-bond substitution (R) of the A-allyl arm. The enynes bearing an alkyl or aryl substituent on the C(1) of the double bond (R ≠ H) induced in all cases a total *Z*-stereoselectivity (see Table 1, entries 4−6), whereas with R = H the *Z*-isomer was the major one (see Table 1, entries 1−3). The allyl double bond can coordinate to ruthenium in **A** only if it is a terminal double bond (R = H). The opening bringing the SiMe₃ group near the Cl group can then be disturbed by the presence of the allyl arm and leads to a *Z/E* mixture with a *Z > E* stereochemistry. If R ≠ H, steric hindrance does not allow the coordination of the double bond, and thus only the expected *Z*-stereochemistry is obtained. Finally, the study with phenyldiazomethane shows an *E/Z* mixture for all reaction temperatures, suggesting that the phenyl substituent has no real interactions with the Cl group.

Alternative Mechanism with C≡CR-Containing Enynes. When the triple-bond substituent is bulky, such as Ph (**6e**) or SiMe₃ (**15a**), interactions with the triple bond are likely disfavored, and in that case the [2+2] cycloaddition of the Ru= C bond to the CH=CH₂ bond takes place, with the unique formation of cyclopropanes **17** (Table 5). When this alkyne substituent is smaller, R = CH₃ (**15b**) and CH₂CH=CH₂ (**15c**), the prefered formation of five-membered cycles with an

Scheme 3. Proposed Mechanism for the Selective Transformation of Enynes and Diazoalkanes into Alkenyl Alkylidene Cyclopentanes
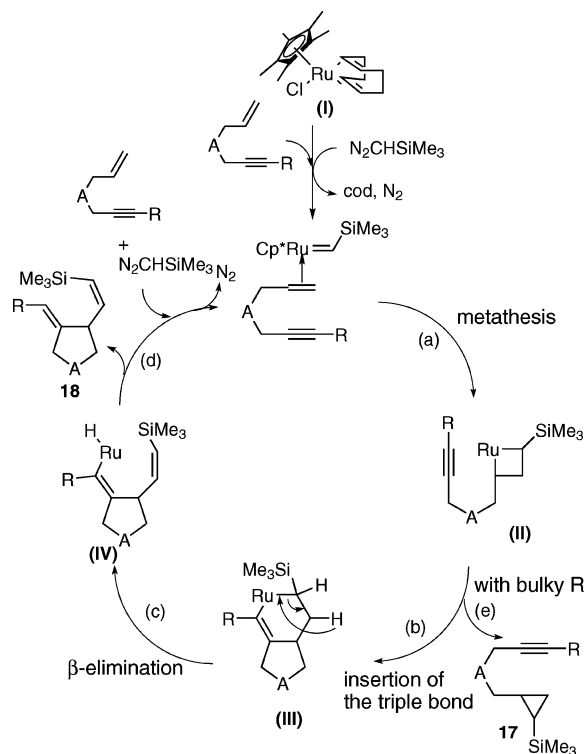
alkylidene group, arising from the C≡CR group, takes place (**18b,c**). Scheme 3 accounts for the catalytic cycle. Initial double-bond coordination can lead to metallacyclobutane **II**. With a bulky triple bond (R = Ph, SiMe₃), in the absence of its coordination, reductive elimination takes place (step e), giving the products **17**. With a smaller substituent (R = Me, CHCH= CH₂), the triple bond can be coordinated, and its insertion into the metallacyclobutane Ru−C bond can lead to the intermediate **III**. β-Elimination (step c), formation of intermediate **IV**, and reductive elimination (step d) are expected to generate the observed cyclic products **18** and [RuClCp*], the RuClCp*(= CHY) precursor.

Theoretical Study of the Selective Transformation of Enynes and Diazoalkanes into Alkenylbicyclo[3.1.0]-hexanes

Since the RuClCp* moiety favors reductive elimination from the metallacyclobutane **C** (step d in Scheme 1) rather than metathesis (step f), DFT calculations were performed in order to rationalize such a different behavior. The analysis proceeds from the intermediate **B**, since an initial interaction of the Ru−carbene unit with the enyne double bond, rather than with the enyne alkyne bond, would not lead to the main compounds **3** and **7**. Both possibilities have already been analyzed by Straub[28] and Lloyd-Jones[27] and do not represent our main goal here.

For the sake of simplicity, the Cp* ligand was replaced by the unsubstituted Cp precursor, while the alkyne and alkene functions of the enyne have been considered as separate HC≡CH and H₂C=CH₂ units, always in *cis* positions in the starting model RuCl(HC≡CH)(H₂C=CH₂)(C₅H₅). A number species were optimized by DFT calculations, including various transition

(28) Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444.
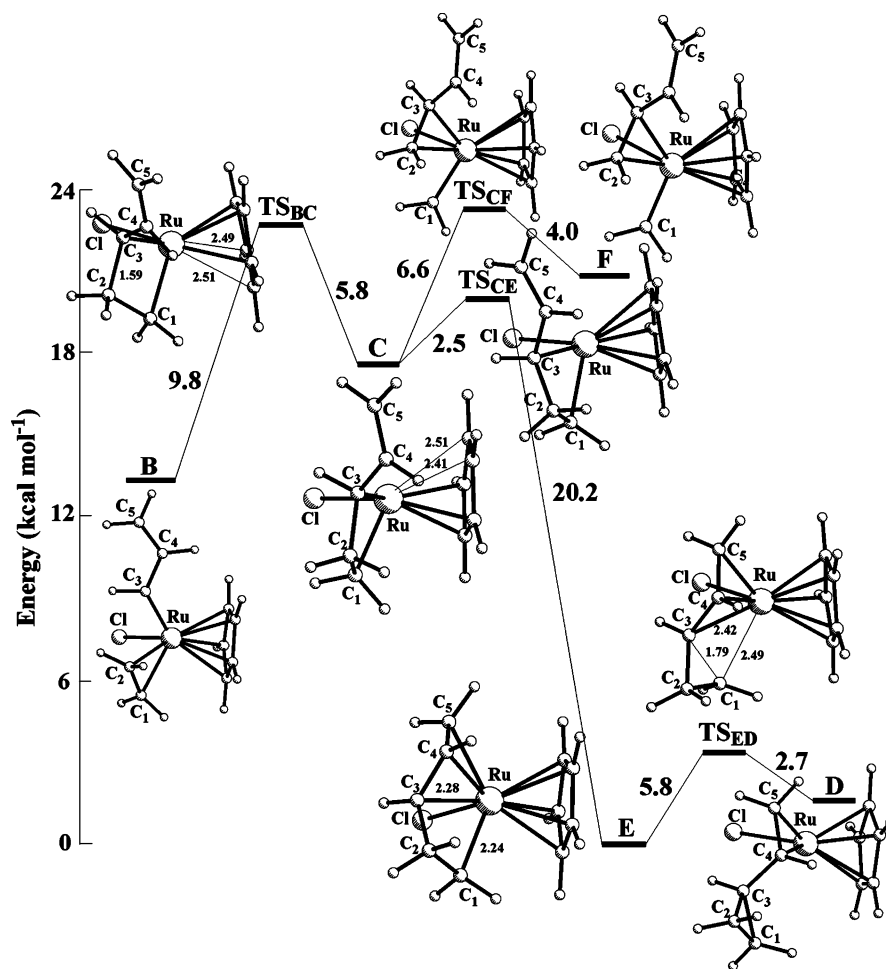
Figure 4. Stationary points on the potential energy surface relative to the possible evolution of the *cis* carbene/ethylene model **B**, which corresponds to the analogous intermediate **B** in Scheme 1.
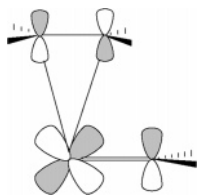

Figure 5. Coplanarity of critical orbitals at the transition state **TS**$_{BC}$.

states. Figure 4 provides a diagram of the energies and the stereochemical features of the various stationary points. The precise nature of each transition state has been validated by intrinsic reaction coordinate (IRC) calculations.

The starting species **B** is a d^6 pseudo-octahedral complex which contains two *cis*-coordinated carbene and ethylene units and has the formal 18-electron configuration. The relative orientation of the carbene and ethylene units (the dihedral angle RuC$_1$C$_2$/RuC$_3$C$_4$ is 50°) indicates that two filled "t$_{2g}$" orbitals ensure sufficient back-donation to both ethylene and carbene. The reorientation of the latter ligands in two orthogonal planes, already at the transition state **TS**$_{BC}$, forces key orbitals to lie coplanar (Figure 5) and promotes C−C coupling. The energy barrier is not very high (only 9.8 kcal·mol^{-1}), while the metallacyclobutane derivative **C** lies only 4 kcal·mol^{-1} above **B**.

Surprisingly, the transformation **B** → **C** affects the structure of the ancillary fragment CpClRu, while the now oxidized d^4

metal is far from being pseudo-octahedral. In this case, a small splitting of the t$_{2g}$ level would correspond to a small highest occupied molecular orbital−lowest unoccupied molecular orbital (HOMO−LUMO) gap, while in **C** the gap is >1 eV. This is most likely the consequence of a significant Jahn−Teller distortion. In particular, two features must be underlined. First, the Cp ring has no regular η^5 coordination, but it is closer to η^3 (allylic type), since two adjacent Ru−C distances are as long as 2.41 and 2.51 Å. Interestingly, a Walsh diagram based on extended Hückel molecular orbital (EHMO) calculations shows that the rearrangement of the Cp ligand from the observed η^3 to the more regular η^5 coordination causes a significant decrease of the HOMO−LUMO gap, associated with a decrease of the thermodynamic stability. The second distortional effect is highlighted by the direction of the Ru−Cl bond, which is not symmetrically displaced with respect to the MC$_1$C$_2$C$_3$ ring. Essentially, the geometry of **C** is similar to that of a d^4-L$_4$MCp piano-stool species, with one missing leg in this case.

Importantly, the metal unsaturation, implicit in **C**, appears mitigated in the optimized model RuCl(HC≡C−CH$_2$CH$_2$CH$_2$−CH=CH$_2$)(C$_5$H$_5$) (**C′**), which contains the enyne unit. In fact, the latter (see Figure 6) features an evident agostic interaction between the metal and one CH$_2$ group of the chain which cannot exist in the simplest model **C**. The involved C−H bond approximately occupies the position of the missing piano-stool ligand.
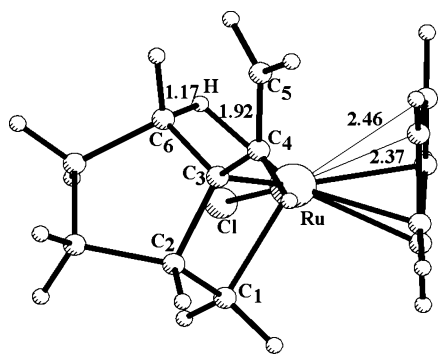
Figure 6. Geometry of the model RuCl(HC≡C−CH₂CH₂CH₂−CH=CH₂)-(C₅H₅) (**C'**), derived from a complete enyne unit.

In any case, the metal has significant electrophilicity in **C** and **C'**, which can be quenched by the donor capabilities of the free dangling olefin group (C_4 and C_5 atoms) and the return of the Cp ligand to the classic η^5 coordination. The resulting product **E** can be considered as a stable 18-electron eptacoordinated species of the type L₄MCp, where two adjacent L ligands correspond to an *in situ*-formed allyl moiety. Model **E** lies at zero energy in the diagram in Figure 4, being 17.7 kcal·mol⁻¹ more stable than the precursor **C**. Moreover, there is a very small barrier for the conversion of **C** into **E** (2.5 kcal·mol⁻¹), as indicated by the optimization of the transition state **TS_CE**. Complex **E** is also the most immediate precursor of the final vinyl-substituted cyclopropane product **D**. The attainment of the latter implies a reductive elimination step and the restoring of the d⁶ metal configuration, but it seems energetically facile. In fact, the barrier (**TS_ED**) is small (5.8 kcal·mol⁻¹), and although **D** is less stable than **E** by 3.1 kcal·mol⁻¹, its formation may be favored if the organic alkene−cyclopropane derivative behaves as a good leaving molecule.

Concerning the mechanism leading to cyclopropane, the calculations show that the C_1−C_3 bond is not formed in one step from the two equivalent C atoms of the metallacyclobutane unit (complex **C**). Rather, at the intermediate **E**, the atoms C_1 and C_3 have different electronic natures, being alkylic and allylic, respectively. Their non-equivalence is also reflected by the transition state **TS_ED**, where the elongation of the Ru−C_1 bond (2.49 Å) proceeds faster that that of the Ru−C_3 one (2.42 Å). The difference is not sufficiently large to exclude a concerted electron transfer between the carbon atoms and the metal, but still it suggests that separation of the carbon charges can facilitate the reductive elimination process. In the final product **D**, the electron count is 16, which is not unusual for classic and stable L₂MCp complexes (M = d⁶).

Figure 4 also shows the alternative metathesis route, which leads from **B** to **F** through **C**. The last barrier toward **F** (**TS_CF**) implies the cleavage of the olefinic C_1−C_2 linkage and the formation of Ru=C_1 and Ru−(η^2-C_2=C_3) bonds, but it is not particularly high (6.6 kcal·mol⁻¹). The most remarkable result is that **F** is definitely less stable than the alternative product **E** (by 20.2 kcal·mol⁻¹). This was not the case with the Grubbs catalyst (LCl₂(PMe₃)Ru, L = N-heterocyclic carbene), which was previously analyzed by Lippstreu and Straub.[28] These authors calculated reaction steps analogous to those of Figure 4, so we highlight in Figure 7 the most relevant differences between the two systems. For convenience, the species of the Grubbs system are named as in the original publication,[28] and
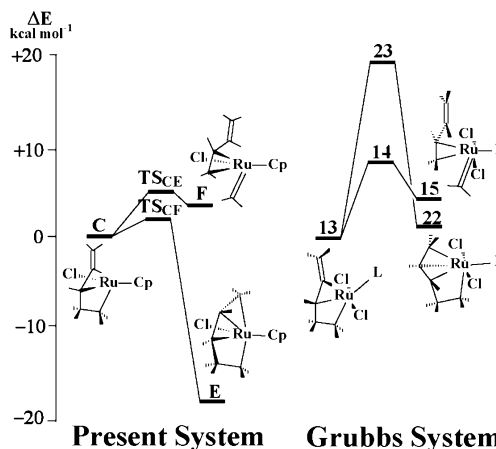

Figure 7. Comparison of key reaction steps in the present system and in the Grubbs one. For the latter, the nomenclature used is that originally reported in ref 28. The ΔE values are relative to the metallacyclobutane intermediate in each case.
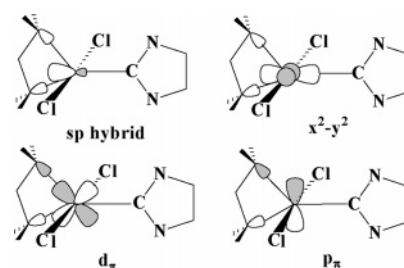

Figure 8. Dative orbital interactions which stabilize the 14-electron metallacyclobutane intermediate in the Grubbs-type mechanism.

the zero point on the common ΔE scale refers to the metallacyclobutane intermediate (**C** and **13**, respectively).

We first observe that, with respect to the metallacyclobutane precursor, the model **E** is much more stabilized than the analogous species **22** (by about 18 kcal·mol⁻¹). Also, the barrier at the transition state **23** is much higher than that at **TS_CE** (18.1 vs 2.6 kcal·mol⁻¹). On the other hand, the energies involved in the metathesis process are rather similar in the two cases, although this route is followed only by the Grubbs system. In fact, for the latter, the formation of cyclopropane is difficult due to both the high barrier to the allylic coordinated species and the scarce stabilization of the latter. The situation is reversed in the present system.

Given the significantly different energy profiles, it is interesting to explore their electronic causes. The latter are found in the MO structures of the intermediate metallacyclobutane species **13** and **C**, which contain different ancillary fragments (i.e., T-shaped LCl₂Ru and CpClRu, respectively). In the former case, the dialkyl chelate [RHC−CH₂−CH₂]²⁻ completes a trigonal bypyramidal structure, which is rather stable in spite of its electron count of 14. This is because the symmetrical environment allows the two coordinated alkyl groups to donate electron density into four different and empty metal orbitals. As shown in Figure 8, the *in-phase* combination of carbon lone pairs is dative toward both a σ hybrid and the x^2-y^2 d orbital, while the *out-of-phase* combination donates into one p$_\pi$ orbital and one d$_\pi$ orbital. The orbital interactions are not equally efficient in **C**, which also has 14 electrons (by assuming that Cp is only a four-electron donor) but is much less "organized". The great difference in the strengths of the orbital interactions is highlighted by the Ru−C distances at the metallacyclobutane rings.

In fact, the values of 2.14 Å (average), optimized for **C**, are much longer than those in **13** (2.00 Å),[28] where bonding is definitely stronger.

Under these circumstances, it is also reasonable that, in the Grubbs system, any distortion from the stable trigonal bipyramidal species "**13**"[28] has a significant energy cost. For instance, the transformation into a square pyramid, which characterizes the transition state toward "**22**",[28] frees a coordination site at which the nucleophilic attack of the free olefin arm may be directed (as occurs between **C** and **E**), but the barrier is large (18 kcal·mol^{-1}). Also, the formation of a coordinated allyl group in "**22**"[28] does not produce the same stabilization found in **E**. In this case, there is no possibility of restoring the full donor capabilities of the Cp ligand, and in the hexacoordinated product, the d^4 metal reaches at most the 16- and not the 18-electron configuration. A closer inspection at the geometry of "**22**"[28] shows that the coordination geometry is not even pseudo-octahedral and that, trans to the alkylic carbon atom, there remains a free coordination site. Most likely, this is protected by the bulky substituent at one of the N atoms of the heterocyclic carbene ligand.

In conclusion, the present theoretical analysis has quantitatively confirmed that the catalyst, based on the CpClRu fragment, favors the formation of a cyclopropanation product and inhibits the enyne metathesis. This is mainly due to the large stabilization of a d^4 heptacoordinated allyl/alkyl intermediate (**E**), which is the precursor for the reductive elimination process and the formation of a cyclopropane unit. Conversely, the analogous intermediate in the Grubbs process "**22**"[28] remains unsaturated at the metal center and does not attain an equivalent amount of stabilization.

General Conclusion

The RuCl(COD)Cp*-catalyzed transformation of C≡CH-containing 1,6-enynes with N$_2$CHSiMe$_3$ into alkenylbicyclo-[3.1.0]hexanes appears to be a general reaction for which a *Z*-stereoselectivity of the alkenyl chain and a *cis* arrangement of cyclopropane alkenyl and R groups are observed for an *E*-configuration of the initial double bond. For C≡CR-containing enynes, with bulky R groups simple cyclopropanation of the enyne double bond takes place, and with less hindered R groups mixed 1-alkenyl-2-alkylidene five-membered heterocycles are selectively produced. By contrast, with N$_2$CHCO$_2$-Et, the analogous alkenylbicyclo[3.1.0]hexanes are produced under slightly more drastic conditions with an *E*-configuration of the alkenyl group.

DFT analysis of a simplified model system, RuCl(HC≡CH)-(CH$_2$=CH$_2$)(C$_5$H$_5$), in which the alkene and alkyne groups of the enyne reactant are kept separated, has provided some satisfactory answers to the question of the difference between the catalytic enyne transformations performed either by the present CpRuCl-based catalyst (favoring cyclopropanation) or the Grubbs catalyst (favoring metathesis). In the present case, a rearrangement of the η^5-C$_5$H$_5$ ligand toward the allylic η^3-type coordination mode is observed, which confers extra electrophilicity to the metal. From the latter ruthenacyclobutane species **C**, a rather stable allyl/alkyl key intermediate (**E**) is formed through a barrier, which is quantitatively smaller with respect to that of the analogous Grubbs catalyst. Eventually, the non-equivalence of the allylic C$_1$,C$_3$ carbon atoms in **E**

promotes their coupling and the easy formation of the cyclo-propane unit.

Experimental Section

All catalytic reactions were carried out under inert atmosphere in Schlenk tubes. The complex RuCl(COD)Cp* was prepared according to the reported method.[29] ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 3000 WB and DPX 200 spectrometers in deuterated chloroform solutions at 298 K. ΔCH$_n$ refers to cyclopropane nuclei. IR spectra were recorded on a Bruker IFS28 instrument. Mass spectra were obtained on a Varian MATT 311 high-resolution spectrometer at the Centre Regional de Mesures de l'Ouest (CRMPO) of the University of Rennes 1. Characterization data are presented in the Supporting Information.

Computational Details. All the calculations were performed using the hybrid density functional theory with Becke's three-parameter hybrid exchange-correlation functional,[30] containing the non-local gradient correction of Lee, Yang, and Parr[31] (B3LYP), using the Gaussian03 suite of programs.[32] All the structures were fully optimized, and the vibrational frequencies were calculated to confirm their nature as stationary points or as transition states. The reaction pathways were followed using the IRC method.[33] For the ruthenium metal, the effective core potential of Stuttgart/Dresden[34] was used, and the basis set used for the remaing atomic species was the 6-31G(d,p).[35] The qualitative MO arguments have been developed with the EHMO method[36] using the CACAO package.[37]

Typical Procedure for Enynes Synthesis. Enynes **1g** and **1h** were prepared according to the reported method.[38] For the others, a typical procedure was used. In a Schlenk tube under an inert atmosphere, a solution of tosyl aminoethynyl (1 equiv) in distilled dimethylformamide was brought to 0 °C, and 60 wt % of sodium hydride was added (1.2 equiv). The reaction mixture was stirred for 1 h at 0 °C, and the substituted allyl bromide was added (1.2 equiv). After coming to room temperature, the reaction mixture was stirred for 16 h and hydrolyzed by addition of 1 N chloridric acid. The organic phase was washed two times with brine, dried under magnesium sulfate, and concentrated under reduced pressure to give an oil, which was purified by silica gel chromatography (eluent, pentane−diethyl ether mixture) to give the enyne as a solid.

Typical Procedure for Method A. In a Schlenk tube under an inert atmosphere, to a solution of the enyne in degassed dioxane (1.5 mL) was added 2.4 equiv of the 2.0 M (trimethylsilyl)diazomethane solution in hexane. Next, 5 mol % of the precatalyst RuCl(COD)Cp* was introduced. The mixture was stirred at 60 °C. Reaction completion was monitored using gas chromatography (GC) or thin-layer chromatography (TLC) techniques. The products were obtained after purification by silica gel chromatography with an ether/pentane eluting mixture.

Typical Procedure for Method B. In a Schlenk tube under an inert atmosphere, to a solution of the enyne in distilled diethyl ether (1.5 mL) was added 1.1 equiv of the 2.0 M (trimethylsilyl)diazomethane

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solution in diethyl ether. Next, 5 mol % of the precatalyst RuCl(COD)-Cp* was introduced. The mixture was stirred at room temperature. Reaction completion was monitored using GC or TLC techniques. The products were obtained after purification by silica gel chromatography with an ether/pentane eluting mixture.

Supporting Information Available: Complete ref 32, Cartesian coordinates of the optimized structures, characterization data for **3a**−**j**, **4**, **5**, **7a**−**d**, **8b**, **9d,e**, **11a,b**, **14a,b**, **16b**−**e**, **17a,e**, **18b**−**e**, **19a,c**−**f**, **20a,c,e,g,h**, **21**−**24**, and crystal structure analysis of **3d**, **3f**, and **20e** (PDF); X-ray crystallographic files for **3d**, **3f**, and **20e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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