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"Formal" and Standard Ruthenium-Catalyzed [2 + 2 + 2] Cycloaddition Reaction of 1,6-Diynes to Alkenes: A Mechanistic Density Functional Study

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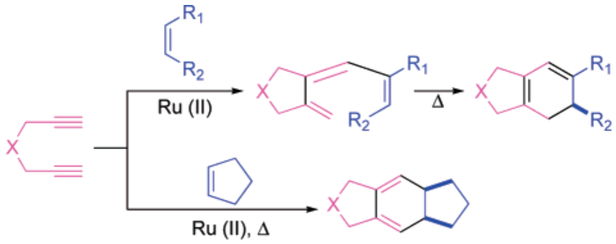

"Formal" and standard Ru(II)-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes **1** to alkenes gave bicyclic 1,3-cyclohexadienes in relatively good yields. The neutral Ru(II) catalyst was formed in situ by mixing equimolecular amounts of $[Cp^*Ru(CH_3CN)_3]PF_6$ and Et_4NCl. Two isomeric bicyclic 1,3-cyclohexadienes **3** and **8** were obtained depending on the cyclic or acyclic nature of the alkene partner. Mechanistic studies on the Ru catalytic cycle revealed a clue for this difference: (a) when acyclic alkenes were used, linear coupling of 1,6-diynes with alkenes was observed giving 1,3,5-trienes **6** as the only initial reaction products, which after a thermal disrotatory $6e^-\pi$ electrocyclization led to the final 1,3-cyclohexadienes **3** as probed by NMR studies. This cascade process behaved as a formal Ru-catalyzed [2 + 2 + 2] cycloaddition. (b) With cyclic alkenes, the standard Ru-catalyzed [2 + 2 + 2] cycloaddition occurred, giving the bicyclic 1,3-cyclohexadienes **8** as reaction products. A complete catalytic cycle for the formal and standard Ru-catalyzed [2 + 2 + 2] cycloaddition of acetylene and cyclic and acyclic alkenes with the Cp*RuCl fragment has been proposed and discussed based on DFT/B3LYP calculations. The most likely mechanism for these processes would involve the formation of ruthenacycloheptadiene intermediates **XXIII** or **XXVII** depending on the alkene nature. From these complexes, two alternatives could be envisioned: (a) a reductive elimination in the case of cyclic alkenes **7** and (b) a β-elimination followed by reductive elimination to give 1,3,5-hexatrienes **6** in the case of acyclic alkenes. Final $6e^-\pi$ electrocyclization of **6** gave 1,3-cyclohexadienes **3**.

Introduction

The elucidation of mechanistic aspects of homogeneous catalysis has been an ambitious scientific goal from the beginning of the awareness of organometallic catalysis. Recent progress in computational chemistry has shown that many important chemical and physical properties of the species involved in these reactions can be predicted from first principles by various computational techniques. This ability is especially important in those cases where experimental results are difficult to obtain.[1]

Metal-catalyzed cycloaddition reactions are excellent candidates to include in this reaction category.[2] For instance, a powerful method for the construction of three new bonds in a one-step process is the [2 + 2 + 2] metal-catalyzed cycloaddition of unsaturated moieties (such as three alkynes, two alkynes and an alkene, two alkynes and nitriles, etc.), allowing the synthesis of benzenes, 1,3-cyclohexadienes, and heterocyclic

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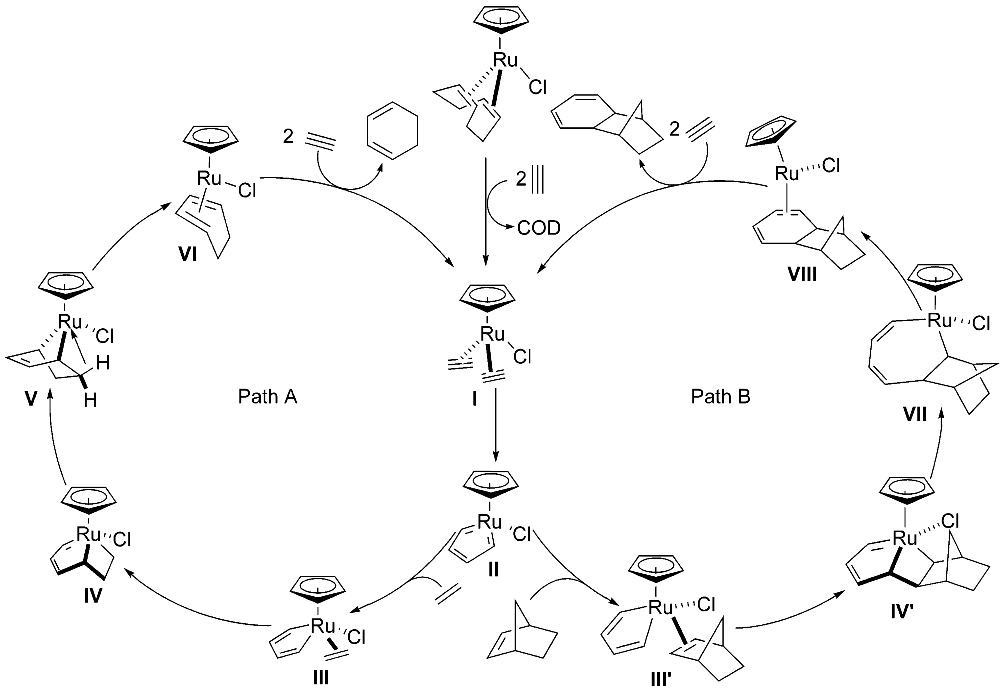
[1] For a review on reactions of transition metal, see: Niu, S.; Hall, M. B. *Chem. Rev.* **2000**, *100*, 353 and references therein.

[2] For reviews on metal-mediated reactions, see: (a) Soderberg, B. C. G. *Coord. Chem. Rev.* **2006**, *250*, 300. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

10.1021/jo702239v CCC: $40.75

SCHEME 1. Proposed Mechanism for the Standard CpRuCl-Catalyzed [2 + 2 + 2] Cycloadditions of Two Acetylenes to Ethylene and Norbornene



compounds such as pyridines, pyranes, pyrimidine diones, etc.[3] Theoretical attempts at understanding the mechanism of metal-catalyzed [2 + 2 + 2] cycloadditions of three alkynes to benzenes or two alkynes and one nitrile to pyridines are known for CpRuCl,[4] CpCo,[5] and CpRh.[6] However, the mechanism of the metal-catalyzed [2 + 2 + 2] cycloaddition between acetylenes and olefins to afford 1,3-cyclohexadienes has been less studied. Recently, two DFT studies on standard Ru(II)-catalyzed [2 + 2 + 2] cyclotrimerization of two acetylenes and norbornene[4a] or ethylene[4b] have been published. The first step in both studies is the replacement of labile cod in CpRu(cod)-Cl with two molecules of acetylene (Scheme 1).[4d] The resulting complex **I** easily forms the biscarbene **II**, which after coordination to the double bond of ethylene or norbornene affords the ruthenacyclopentadienes **III** and **III′**, respectively. Then, a formal [2 + 2] cycloaddition between the biscarbene **II** and ethylene or norbornene gives rise to ruthenabicyclo[3.2.0]-heptadienes **IV** and **IV′**, respectively. From this point, it seems that there are two different paths depending on the alkene used in the cyclization reaction: path A for ethylene and path B for norbornene. In path A, the most favorable step seems to be the reductive elimination from **IV** to give the Ru species **V** stabilized by an agostic interaction between a hydrogen and the ruthenium. Change of hapticity from η^2 to η^4 followed by decomplexation of the ruthenium affords the final cyclohexadiene. On the other hand, in the case of norbornene (path B), the most favorable step supposes the ring expansion of the ruthenabicycle **IV′** (via cleavage of the central Ru−C bond) to the ruthenacycloheptadiene **VII**, which is the key intermediate of the cocyclotrimerization of acetylene with norbornene. Reductive elimination and decomplexation affords the final cyclohexadiene (Scheme 1).

Also, a DFT study for the cobalt-mediated cocyclization of two acetylenes and ethylene to either 1,3-cyclohexadiene or 1,3,5-hexatriene has been recently published.[7] According to this

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(3) For reviews on metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. Cotrimerizations of Acetylenic Compounds. In *Organic Reactions*; RajanBabu, T. V., Ed.; John Wiley and Sons: Hoboken, NJ, 2007; Vol. 68, p 1. (b) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (c) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (d) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (e) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (f) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (g) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (h) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (i) Grotjahn, D. B. Transition Metal Alkyne Complexes: Transition Metal-Catalyzed Cyclotrimerization. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 741. (j) Bönnemann, H.; Brijoux, W. *Adv. Heterocycl. Chem.* **1990**, *48*, 177. (k) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (l) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. See also ref 2.

(4) Benzenes: (a) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143. (b) Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721. (c) Using cationic [RuCp$(CH_3CN)_3$]PF_6 as catalyst: Ruba, E.; Schmid, R.; Kirchner, K.; Calhorda, M. J. *J. Organomet. Chem.* **2003**, *682*, 204. Pyridines: (d) Dazinger, G.; Torres-Rodrigues, M.; Kirchner, K.; Calhorda, M. J.; Costa, P. J. *J. Organomet. Chem.* **2006**, *691*, 4434. (e) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605. (f) Dazinger, G.; Schmid, R.; Kirchner, K. *New J. Chem.* **2004**, *28*, 153.

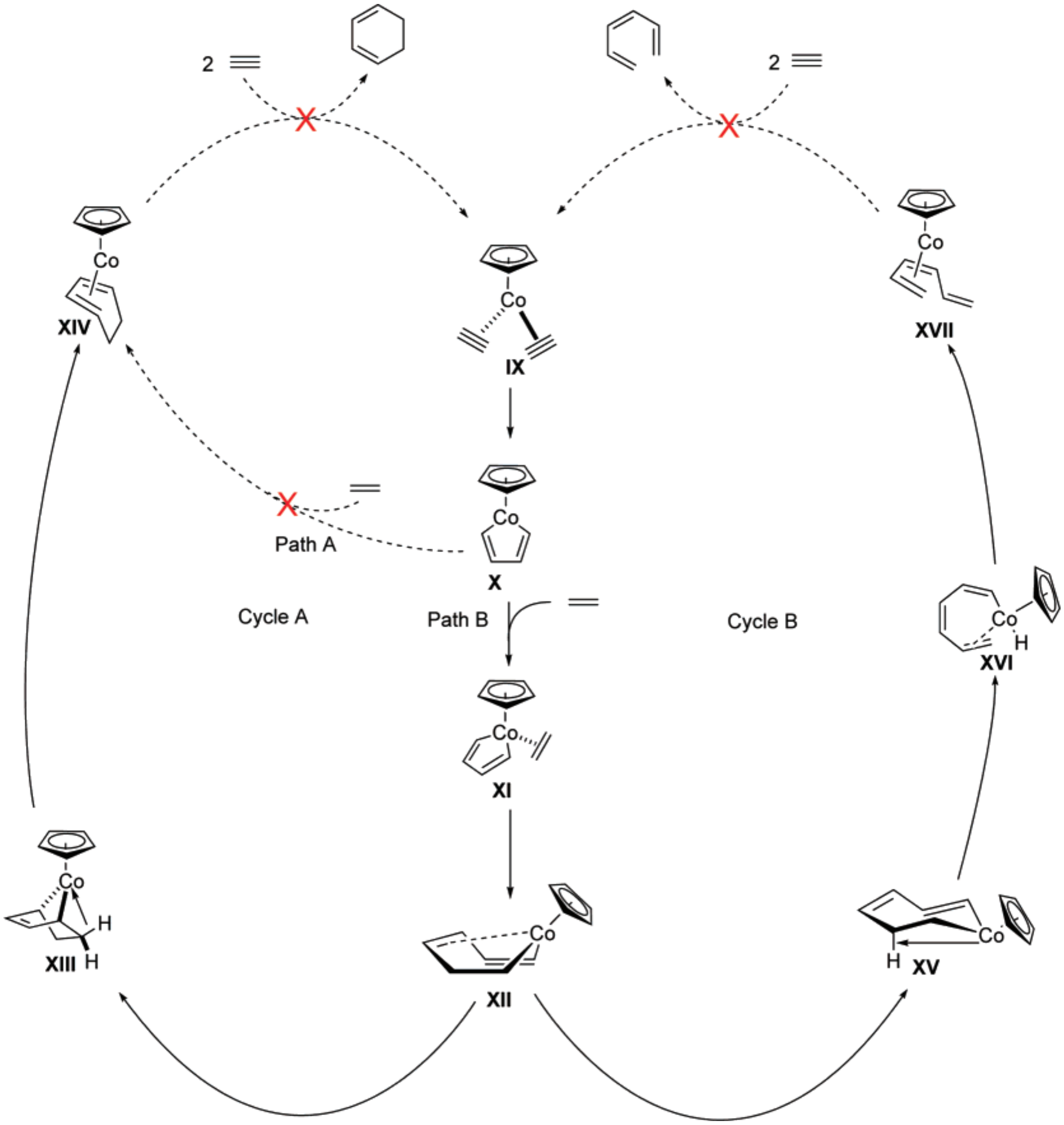
(5) Benzenes: (a) Agenet, N.; Gandon, V.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2007**, *129*, 8860. (b) Dahy, A. A.; Suresh, C. H.; Koga, N. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 792. (c) Dahy, A. A.; Koga, N. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 781. (d) Hardesty, J. H.; Koerner, J. B.; Albright, T. A.; Lee, G. Y. *J. Am. Chem. Soc.* **1999**, *121*, 6055. (e) Wakatsuki, Y.; Nomura, O.; Kitaura, K.; Morokuma, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 1907. Pyridines: see ref 4d.

(6) Orian, L.; vanStralen, J. N. P.; Bickelhaupt, F. M. *Organometallics* **2007**, *26*, 3816. For pyridines, see also ref 4d.

(7) (a) Aubert, C.; Gandon, V.; Geny, A.; Heckrodt, T. J.; Malacria, M.; Paredes, E.; Vollhardt, K. P. C. *Chem.—Eur. J.* **2007**, *13*, 7466. (b) Gandon, V.; Agenet, N.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2006**, *128*, 8509.

(8) Several examples of Co-catalyzed [2 + 2 + 2] cycloadditions of alkynes to alkenes have been reported: (a) Cammack, J. K.; Jalisatgi, S.; Matzger, A. J.; Negrón, A.; Vollhardt, K. P. C. *J. Org. Chem.* **1996**, *61*, 4798. (b) Duñach, E.; Halterman, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *107*, 1664. (c) Malacria, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1984**, *49*, 5010.

SCHEME 2. Proposed Mechanism of the CpCo-Mediated Cocyclization of Two Acetylenes and Ethylene



study, the mechanism of the cobalt-mediated [2 + 2 + 2] cycloaddition of two acetylenes to ethylene to give CpCo-complexed 1,3-cyclohexadiene proceeds via coordination of the alkene to **X** followed by insertion into a σ Co−C bond of resulting cobaltacyclopentadiene **XI** rather than inter- or intramolecular [4 + 2] cycloaddition between **X** and the alkene (path B vs path A, cycle A, Scheme 2). The resulting seven-membered cobaltacycle **XII** is the key intermediate which leads either to CpCo-complexed cyclohexadiene (cycle A) or to 1,3,5-hexatriene (cycle B). The metallacycle **XII** can be connected to the bicyclic intermediate **XIII** (with an agostic interaction analogous to intermediate **V** for the ruthenium) which leads, finally, to the CpCo-complexed cyclohexadiene **XIV** by breaking the agostic interaction and changing the hapticity of the ligand (cycle A). On the other hand, the metallacycle **XII** can

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(9) (a) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. (b) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630. (c) *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (d) Ruthenium Catalysts and Fine Chemistry. In *Topics in Organometallic Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Pergamon: Oxford, 2004; Vol. 11.

(10) Varela, J. A.; Rubín, S. G.; González-Rodríguez, C.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **2006**, *128*, 9262.

(11) (a) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 4310. (b) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Itoh, K. *J. Org. Chem.* **1998**, *63*, 9610.

(12) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 7376.

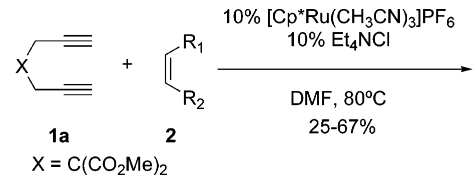
(13) The *trans* olefins such as dimethyl fumarate do not participate in the formal Ru(II)-catalyzed [2 + 2 + 2] cycloaddition reaction with terminal diynes **1**. See ref 10.

(14) Itoh and co-workers also reported excellent yields when an excess of benzyl allyl ether ($R_1 = CH_2OCH_2Ph$, $R_2 = H$) was used. See ref 11 for more details.

(15) This type of open trienes had been previously found when studying Ru-catalyzed cycloadditions involving 1,3-dienes. Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *5*, 2841.

(16) Open-chained hexatriene Co complexes have already been reported in Co-mediated reaction of alkynes with the 2,3-double bond in the following. (a) Indole: Boese, R.; Van Sickle, A. P.; Vollhardt, K. P. C. *Synthesis* **1994**, 1374. (b) Pyrimidine: Pelissier, H.; Rodriguez, J.; Vollhardt, K. P. C. *Chem.—Eur. J.* **1999**, *5*, 3549. (c) Furane and thiophene: Boese, R.; Harvey, D. F.; Malaska, M. J.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1994**, *116*, 11153. (d) Cyanoalkenes: Wakatsuki, Y.; Aoki, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1979**, *101*, 1123. (e) Benzene: Wakatsuki, Y.; Yamazaki, H. *J. Organomet. Chem.* **1978**, *149*, 385. Open-chained hexatrienes have been also reported in the Ru-catalyzed linear coupling reaction of acetylene and acrylonitrile: (f) Yi, C. S.; Torres-Lubian, J. R.; Liu, N.; Rheingold, A. L.; Guzei, I. A. *Organometallics* **1998**, *17*, 1257. (g) For Ni-catalyzed linear coupling reaction of α,β-unsaturated carbonyl compounds with alkynes, see: Sambaiah, T.; Li, L. P.; Huang, D. J.; Lin, C. H.; Rayabarapu, D. K.; Cheng, C. H. *J. Org. Chem.* **1999**, *64*, 3663.

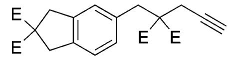
TABLE 1. Formal Ru-Catalyzed [2 + 2 + 2] Cycloaddition of Terminal 1,6-Diyne 1a with Acyclic Alkenes 2



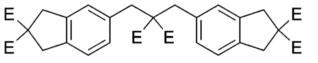
1a **2** **3**
X = C(CO$_2$Me)$_2$

entry	alkene		cyclohexadiene	yield[a,b]
1	**2a** R$_1$ = CO$_2$Me	R$_2$ = H	**3a**	62
2	**2b** R$_1$ = CO$_2$Me	R$_2$ = CO$_2$Me	**3b**	61
3	**2c** R$_1$ = CH$_2$OEt	R$_2$ = H	**3c**	52 (90)
4	**2d** R$_1$ = C$_5$H$_{11}$	R$_2$ = H	**3d**	67

[a] Isolated yields from reactions performed at 80 °C by slow addition, over 4 h, of 0.5 mmol of **1a** in DMF to a mixture of 3 equiv of **2**, 10% [Cp*Ru(CH$_3$CN)$_3$]PF$_6$, and 10% Et$_4$NCl in DMF (conditions A). Dimer **4a** (10−15%) and trimer **5a** (5%) are also observed as byproducts. [b] Yields in parentheses were isolated when using 10 equiv of **2** without slow addition of **1a** (conditions B).



4a E = CO$_2$Me



5a E = CO$_2$Me

undergo a conformational change to the more stable cobaltacycloheptadiene **XV** in which an agostic Co−H$_\beta$ interaction replaces a double bond coordination. Finally, β-hydride elimination followed by reductive elimination leads to the CpCo-complexed 1,3,5-hexatriene **XVII** (cycle B). The completion of both catalytic cycles requires the dissociation of the diene ligands followed by coordination of two acetylenes to regenerate complex **IX**. These processes have been calculated to be slightly exothermic,[7] which can explain why this reaction is catalytic only under specific conditions.[8]

In this article, we present a detailed mechanistic study of a new "formal" Ru(II)-catalyzed [2 + 2 + 2] cycloaddition between 1,6-diynes and acyclic alkenes based on experimental results and theoretical calculations. In addition, standard Ru(II)-catalyzed [2 + 2 + 2] cycloaddition between 1,6-diynes and cyclic alkenes will also be discussed.[9] Bicyclic and tricyclic 1,3-cyclohexadienes are the major products, respectively.

Results and Discussion

Formal Ru(II)-Catalyzed [2 + 2 + 2] Cycloaddition of Terminal 1,6-Diynes with Acyclic Alkenes. We have recently described a new formal [2 + 2 + 2] cycloaddition of terminal 1,6-diynes **1** with acyclic alkenes **2** in the presence of 10 mol % of [Cp*Ru(CH$_3$CN)$_3$]PF$_6$ and Et$_4$NCl to give 1,3-cyclohexadienes **3** (selected examples are shown in Table 1).[10]

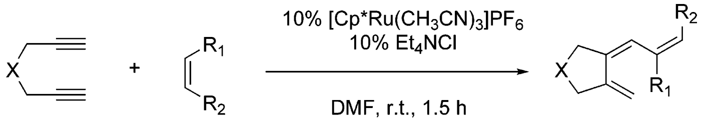
Strikingly, the double bonds in cyclohexadienes **3** are not in the position expected for a typical [2 + 2 + 2] cycloaddition reaction. This type of bond-migrated product **3** had previously been observed by Itoh[11] when using **1a**, benzyl allyl ether (R$_1$ = CH$_2$OCH$_2$Ph, R$_2$ = H), and Cp*Ru(cod)Cl as catalyst and was attributed to the occurrence of a 1,5-H shift after the expected [2 + 2 + 2] cycloaddition reaction.

To gain further insight into the scope and limitations and also into the mechanistic rationale of this new formal Ru-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes **1** with acyclic alkenes **2**, we have examined the reaction of **1a** with selected activated and nonactivated alkenes **2** using the combination of [Cp*Ru(CH$_3$CN)$_3$]PF$_6$/Et$_4$NCl as catalyst.[12] Thus, slow addition of a solution of **1a** in DMF to a heated mixture of DMF (80 °C) and methyl acrylate (**2a**) containing the catalytic mixture {10% [Cp*Ru(CH$_3$CN)$_3$]PF$_6$ plus 10% Et$_4$NCl} afforded the cyclohexadiene **3a** (R$_1$ = CO$_2$Me, R$_2$ = H) in reasonably good yield (Table 1, entry 1, conditions A). Small amounts of the dimer (**4a**, 10%) and trimer (**5a**, 10%) were also present. *cis*-Disubstituted electron-poor olefins such as dimethyl maleate (**2b**) also participate in the formal [2 + 2 + 2] cycloaddition, affording a 61% yield of the more functionalized cyclohexadiene **3b** (Table 1, entry 2).[13] Alkenes with metal-coordinating heteroatoms such as allyl ether **2c** afforded quite good yields of the expected cyclohexadiene **3c** (Table 1, entry 3). Excellent yields were obtained when an excess of 10 equiv of allyl ether **2c** was used (Table 1, entry 3, conditions B).[14] Surprisingly, nonactivated olefins such as 1-heptene (**2d**) gave cyclohexadiene **3d** in a good yield (Table 1, entry 4). This result indicates that, under the reaction conditions, the presence of a heteroatom in the allylic position in the alkene is not required for the formal cycloaddition to take place as had been suggested,[11] but it appears to be significant for better yields.

Interestingly, a smooth conversion into the linear coupled products, the open trienes **6b** and **6c**, was observed when the diyne **1a** was added at room temperature to a solution of 10 equiv of alkenes **2b** and **2c** in DMF containing the catalytic mixture (Scheme 3).[15]

NMR Studies on Hexatrienes 6. The isolation of hexatrienes **6b**,**c** when the reaction was performed at room temperature clearly indicates that they are the initial products of the Ru(II)-catalyzed reactions.[16] Most likely, when the reaction is performed at 80 °C, the observed products, cyclohexadienes **3**, would arise from a thermal disrotatory 6e$^-\pi$ electrocyclization of the initially formed hexatrienes **6**. In fact, smooth conversion of **6** into **3** was observed when hexatrienes **6b** and **6c** were heated at 50 °C in an NMR tube for 1 h and monitored every 5 min (Figures 1 and 2). The conversion was almost quantitative after 35 min for **6b** and after 1 h for **6c**, proving that the relative position of the double bonds in the final cyclohexadienes **3** is the result of a thermal disrotatory 6e$^-\pi$ electrocyclization instead of a [1,5]-hydrogen shift of the initial [2 + 2 + 2] cycloadduct as had been previously suggested.[11]

SCHEME 3. Ru-Catalyzed Linear Coupling of 1a with Alkenes 2b and 2c to 1,3,5-Hexatrienes 6b,c



1a
2b R$_1$,R$_2$ = CO$_2$Me
2c R$_1$ = CH$_2$OEt, R$_2$ = H
X = C(CO$_2$Me)$_2$
6b R$_1$,R$_2$ = CO$_2$Me; 47%
6c R$_1$ = CH$_2$OEt, R$_2$ = H; 66%

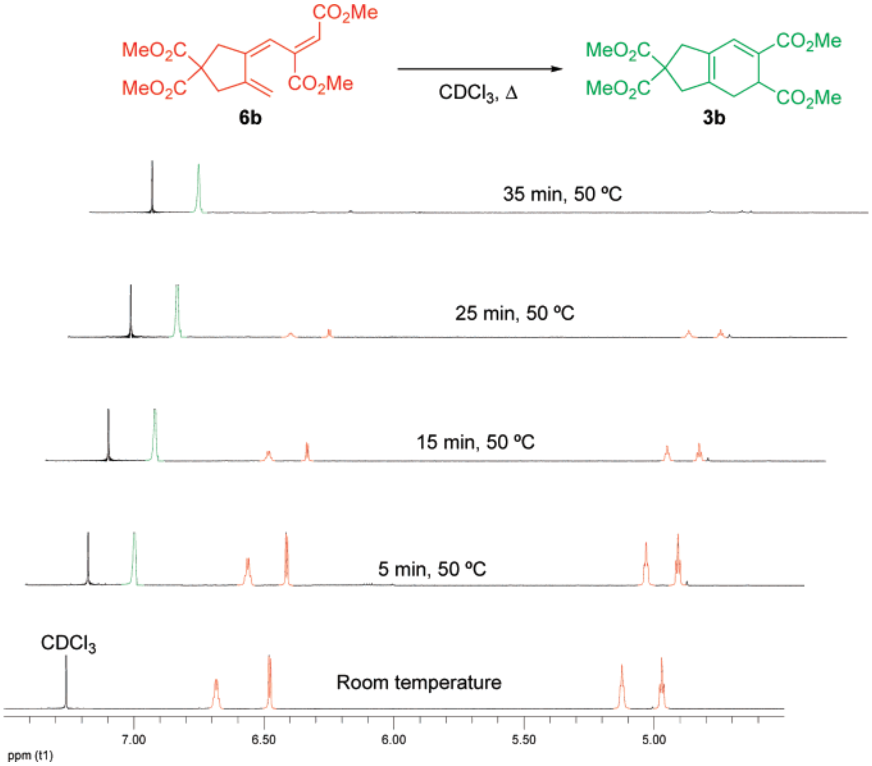


FIGURE 1. NMR studies on the thermal disrotatory 6e$^-\pi$ electrocyclization of **6b**.

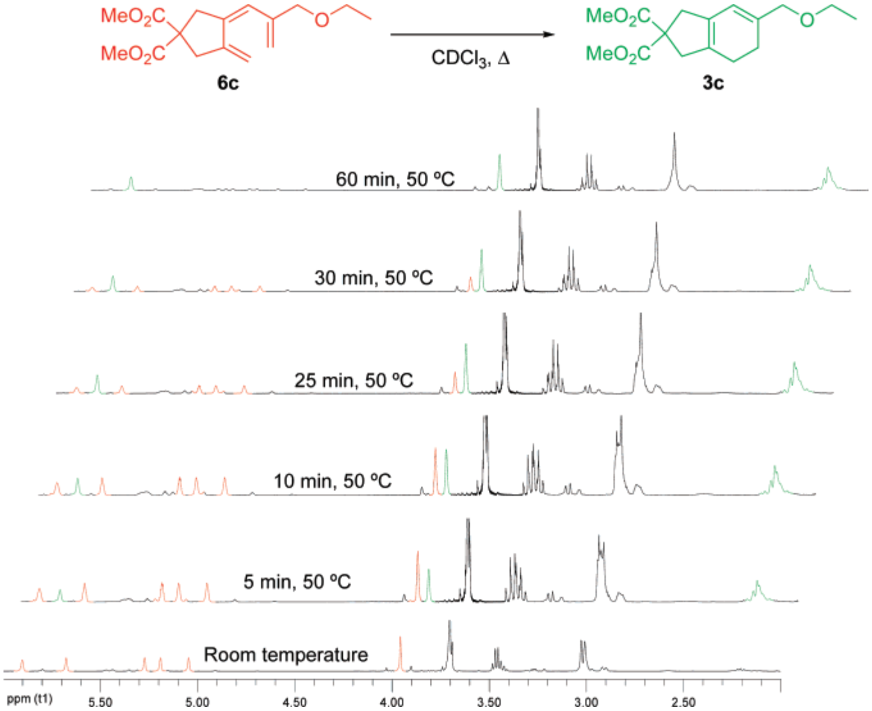


FIGURE 2. NMR studies on the thermal disrotatory 6e$^-\pi$ electrocyclization of **6c**.

Standard Ru(II)-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes with Cyclic Alkenes. As expected, like Itoh,[11] we found that addition of 2,5-dihydrofurane (**7a**) to diyne **1a** afforded the tricyclic 1,3-cyclohexadiene **8a** in an excellent yield (Table 2, entry 1). Interestingly, we have also found that nonactivated cycloalkenes **7b** and **7c** gave the expected tricyclic cyclohexadienes **8b** and **8c**, although in low yields (entries 2 and 3).[17] These last two results, like their acyclic analogues,

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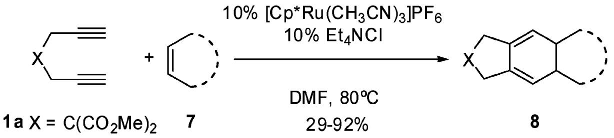
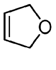
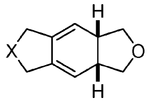
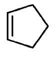
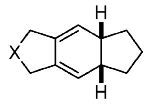
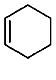
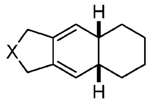
(17) For more examples, see ref 10.

(18) All attempts to isolate the corresponding open hexatriene analogue to **6** were unfruitful (reaction performed at room temperature or excess of cyclic alkene).

TABLE 2. Standard Ru(II)-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes 1 with Cyclic Alkenes 7



entry	cyclic alkene	cyclohexadiene	yield[a]
1	 **7a**	 **8a**	92
2	 **7b**	 **8b**	29
3	 **7c**	 **8c**	32

[a] Isolated yields following conditions A as in Table 1. Same byproducts are also observed.

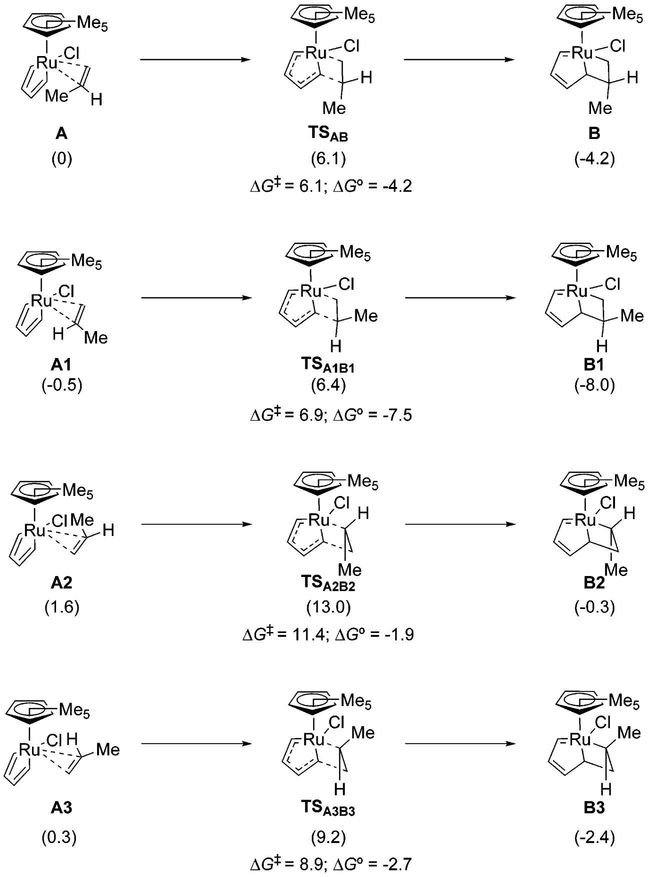
show that the presence of a heteroatom in the allylic position of the alkene is not required for the reaction to take place, although its presence seems to favor the process. Unlike bicyclic cyclohexadienes **3**, the double bonds in tricyclic cyclohexadienes **8** are in the position expected for a [2 + 2 + 2] cycloadduct;[18] that means that the course of the reaction changes from using acyclic or cyclic alkenes. To understand this mechanistic change, we performed theoretical calculations.

Density Functional Study on Formal and Standard Ru-Catalyzed [2 + 2 + 2] Cycloadditions between Alkynes and Alkenes.[19] Regarding our experimental results, the two paths shown in Scheme 1 are able to explain the formation of tricyclic cyclohexadienes **8** expected for a standard Ru-catalyzed cocyclization between two acetylenes and one cyclic alkene. However, none of them explains the formation of the open 1,3,5-hexatrienes of type **6** obtained when using acyclic alkenes.

For a better understanding of our own results and having in mind the theoretical studies with ruthenium[4a,b] and cobalt[7] with ethylene and norbornene as alkene models, we decided to perform new DFT/B3LYP calculations[20,21] of formal and standard Ru-catalyzed [2 + 2 + 2] cycloadditions between two acetylenes and propene and cyclopentene as models for acyclic and cyclic alkenes. We started our study from the ruthenacyclopentadiene(alkene) complexes of type **III** and **III′** (Scheme 1), with all the energy values referring to these complexes.

Density Functional Study on the Acetylene−Propene Reaction. The main difference between our model system and those of Ru and Co shown in Schemes 1 and 2 is the use of propene, an asymmetric alkene as a partner (Scheme 4), which opens the possibility of formation of two regioisomers (α and *β*) and two stereoisomers (*endo* and *exo*). Thus, the first step is the evaluation of which those regio- and stereoisomers begins the catalytic cycle. For this purpose, energies of initial alkene−ruthenacyclopentadiene regio- and stereoisomers **A** (*β*, *endo*), **A1** (*β*, *exo*), **A2** (α, *endo*), and **A3** (α, *exo*) were computed together with the facile C−C coupling between them featuring the fused 5,4-membered bicyclic ring systems **B**, **B1**, **B2**, and **B3** (Scheme 4).

SCHEME 4. Possible Regio- and Stereoisomers Resulting from the Coordination of Ruthenacyclopentadiene with Propene and Energy Profile for the C−C Coupling between Them (*G* in kcal mol−1 at 298 K and 1 atm, in brackets *G* values refer to A)



Note that, whereas all the propene−ruthenacyclopentadiene complexes of type **A** have very similar stability, the bicyclic Ru complexes of type **B** have different energies with the most stable being **B1** (methyl group in *exo* and *β* to the ruthenium) and the less stable being **B2** (methyl group in *endo* and α to the ruthenium). On the other hand, looking at the activation energy for each process, the one with a higher energy cost is the transformation of **A2** to **B2** via $\mathbf{TS_{A2B2}}$ ($\Delta G^{\ddagger} = 11.4$ kcal mol^{-1}, $\Delta H^{\ddagger} = 10.6$ kcal mol^{-1}), followed by **A3** to **B3** via

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(19) Initial results were presented as a poster in the 1st European Chemistry Congress at Budapest, Hungary, August 2006.

(20) Parr, R. G.; Wang, Y. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

(21) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Miehlich, B.; Savin, A.; stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200. (c) Lee, C.; Yang, W.; Parr, G. *Phys. Rev. B* **1988**, *37*, 785.

(22) The same kind of intermediate as **B** was also proposed in the Ru-catalyzed cyclization of two acetylenes with ethylene (see ref 4b, Scheme 1), norbornene (see ref 4a, Scheme 1), and in the Co-mediated cyclization of pyrazinediones with alkynes (see ref 7a). While the direct reductive elimination was proposed as the more likely pathway for the Ru-catalyzed reaction with ethylene and for the Co-mediated reaction, the electrocyclic opening of the analogues of **B** was the preferred pathway for the Ru-catalyzed reaction with norbornene.

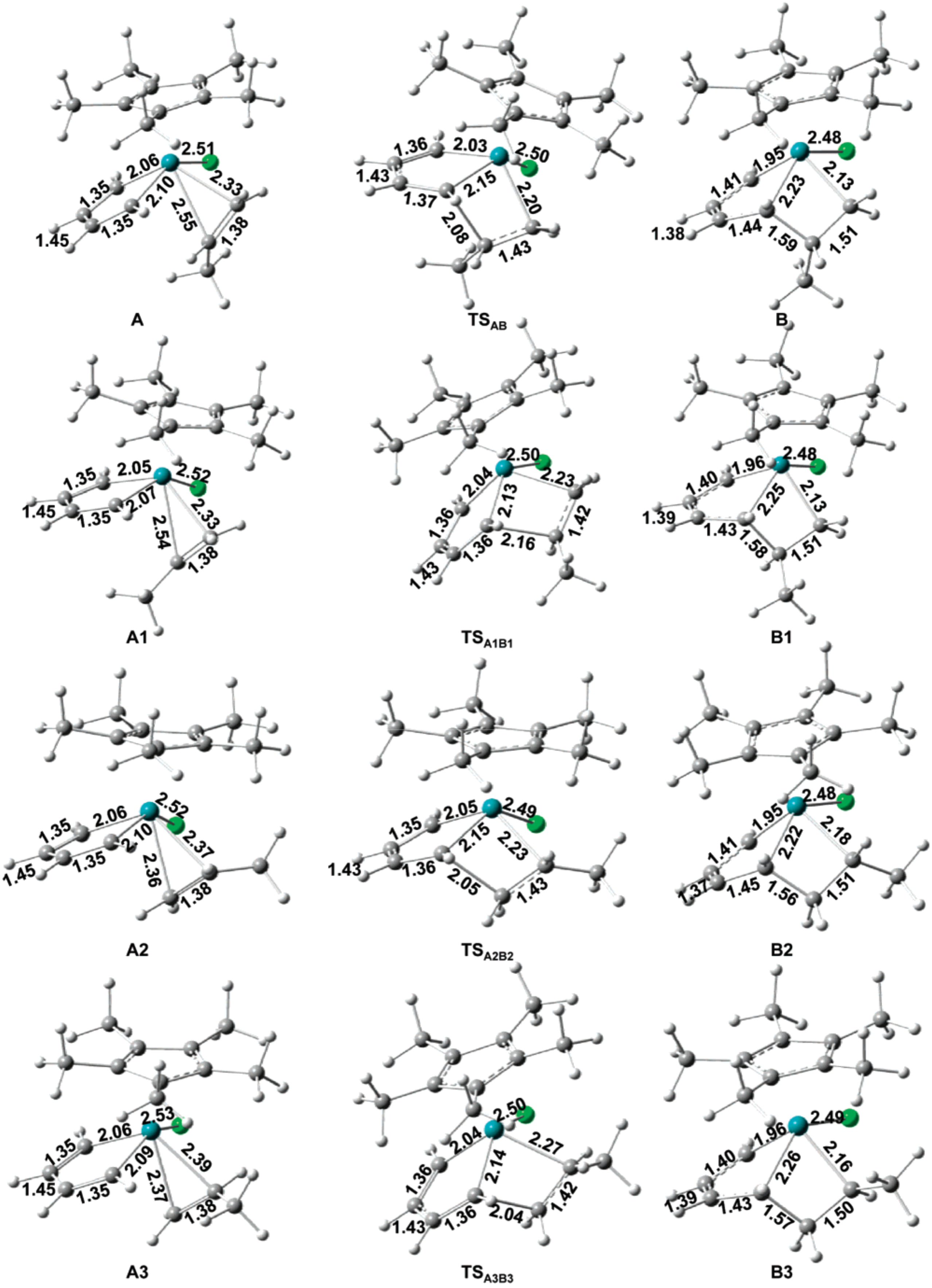


FIGURE 3. Structures for the four regio- and stereoisomers of the ruthenacyclopentadiene−propene complexes of type **A** and their corresponding ruthenabicyclic complexes of type **B**.

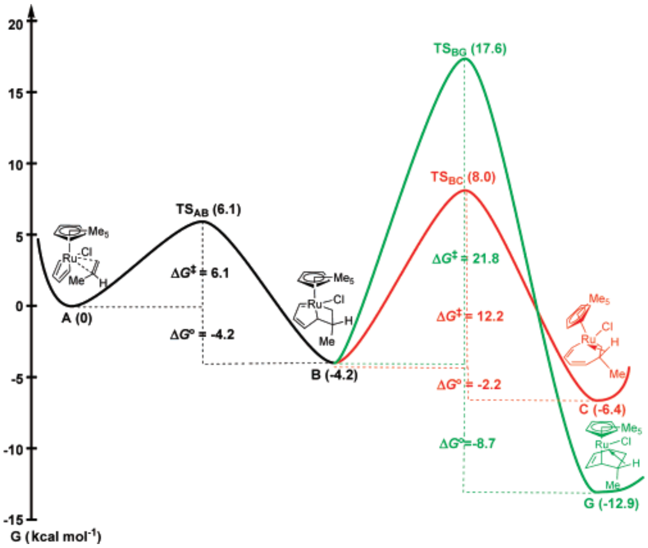
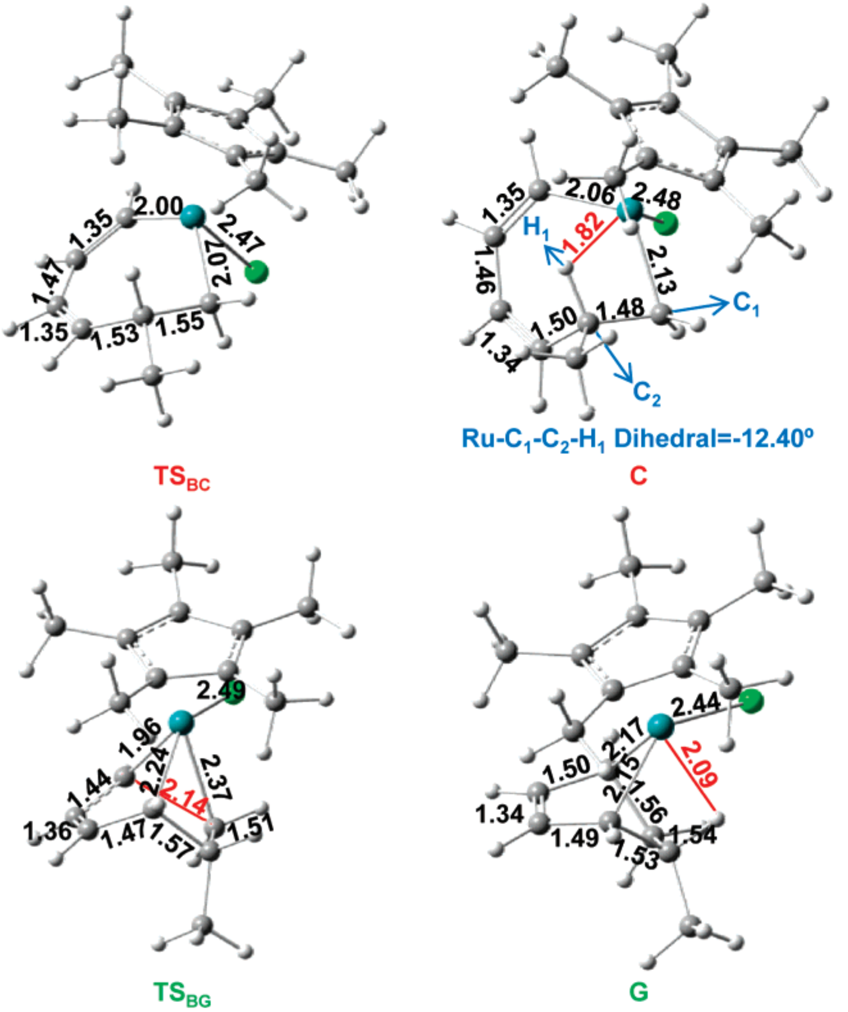


FIGURE 4. Energy profile (G in kcal mol^{-1} at 298 K and 1 atm) for the formation of ruthenacycles **C** and **G** from complex **A**.

TS$_{\mathbf{A3B3}}$ ($\Delta G^{\ddagger} = 8.9$ kcal mol^{-1}, $\Delta H^{\ddagger} = 6.9$ kcal mol^{-1}), **A1** to **B1** via **TS$_{\mathbf{A1B1}}$** ($\Delta G^{\ddagger} = 6.9$ kcal mol^{-1}, $\Delta H^{\ddagger} = 6.1$ kcal mol^{-1}), the one with lower energy cost being the transformation of **A** to **B** via **TS$_{\mathbf{AB}}$** ($\Delta G^{\ddagger} = 6.1$ kcal mol^{-1}, $\Delta H^{\ddagger} = 4.2$ kcal mol^{-1}). Some selected bond distances for the structures depicted in Scheme 4 are shown in Figure 3.

Therefore, as shown in Figure 4, the first step would be the facile C−C coupling between the coordinated alkene with the ruthenacyclopentadiene in complex **A** (*endo*, β) via **TS$_{\mathbf{AB}}$** leading to the fused 5,4-membered bicyclic ring system **B** with a $\Delta G^{\ddagger} = 6.1$ kcal mol^{-1} ($\Delta H^{\ddagger} = 4.2$ kcal mol^{-1}) and $\Delta G^{\circ} = -4.2$ kcal mol^{-1} ($\Delta H^{\circ} = -5.8$ kcal mol^{-1}).

From the ruthenabicyclo[3.2.0]heptadiene complex **B**, two different pathways can be now envisaged: the first one, shown as a green line in Figure 4, supposes a C−C bond formation and a Ru−C bond break, assisted now by the H_{β} agostic interaction (2.09 Å) which prevents the Ru center from being unsaturated to afford the η^2 complex **G** through the transition state **TS$_{\mathbf{BG}}$** with a $\Delta G^{\ddagger} = 21.8$ kcal mol^{-1} ($\Delta H^{\ddagger} = 21.3$ kcal mol^{-1}) and $\Delta G^{\circ} = -8.7$ kcal mol^{-1} ($\Delta H^{\circ} = -9.6$ kcal mol^{-1}); the second pathway, shown as a red line in Figure 4, is an electrocyclic opening of the ruthenabicyclo[3.2.0]heptadiene **B** via **TS$_{\mathbf{BC}}$** to give rise to the ruthenacycloheptadiene **C**, which also presents a H_{β} agostic interaction (1.82 Å) with $\Delta G^{\ddagger} = 12.2$ kcal mol^{-1} ($\Delta H^{\ddagger} = 12.6$ kcal mol^{-1}) and $\Delta G^{\circ} = -2.2$ kcal mol^{-1} ($\Delta H^{\circ} = -2.1$ kcal mol^{-1}).[22] Note that, although the red pathway is thermodynamically less favorable than the green one, it is kinetically preferred. Therefore, we have followed all the



TS$_{BC}$

C

TS$_{BG}$

G

FIGURE 5. Structures of intermediates and transition states for the transformation of **B** into **C** and **G**, with selected bond distances (Å) and angles (deg).

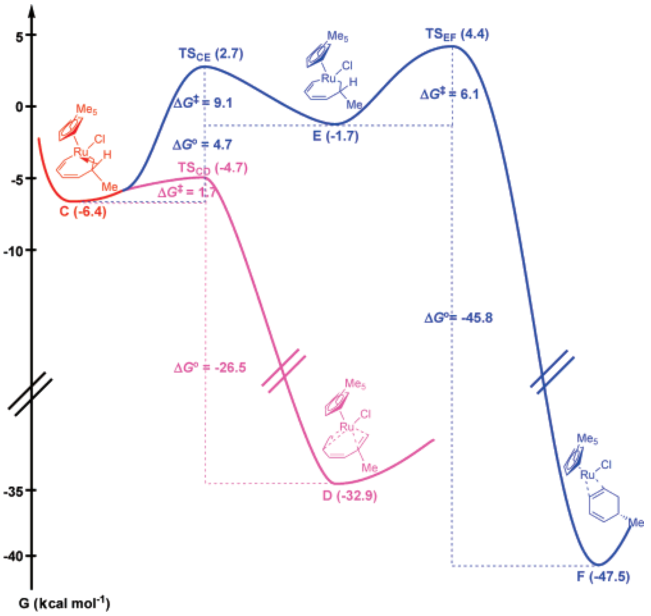
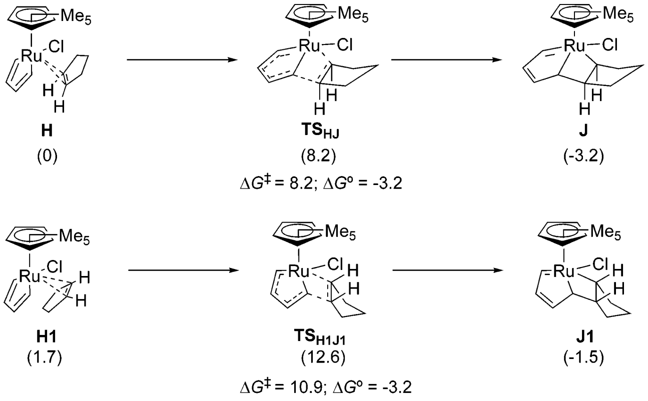


FIGURE 6. Energy profile (G in kcal mol^{-1} at 298 K and 1 atm) from **C** for the reductive elimination (blue line) and β-hydride/reductive elimination (purple line).

subsequent calculations from the intermediate **C**. Some selected bond distances for the structures of intermediates and transition states for the transformation of **B** into **C** and **G** are shown in Figure 5.

SCHEME 5. Possible Stereoisomers from the Coordination of Ruthenacyclopentadiene to Cyclopentene and Energy Profile for the C−C Coupling between Them (G in kcal mol^{-1} at 298 K and 1 atm, in brackets G values refer to H)



From **C**, two different paths can also be envisaged, as shown in Figure 6: path A, a reductive elimination to afford the cyclohexadiene **F** which coordinates η^2 to the ruthenium **F** (blue line); path B, a β-hydride elimination followed by a reductive elimination of the ruthenium hydride formed to afford the complex **D** in which the triene coordinates η^4 to the ruthenium (purple line).

In the case of path A (blue line), it was not possible to find any transition state connecting directly **C** with **F**, a necessary initial conformational change between ruthenacycloheptadienes **C** and **E** through **TS$_{CE}$** ($\Delta G^‡ = 9.1$ kcal mol^{-1}, $\Delta H^‡ = 9.7$

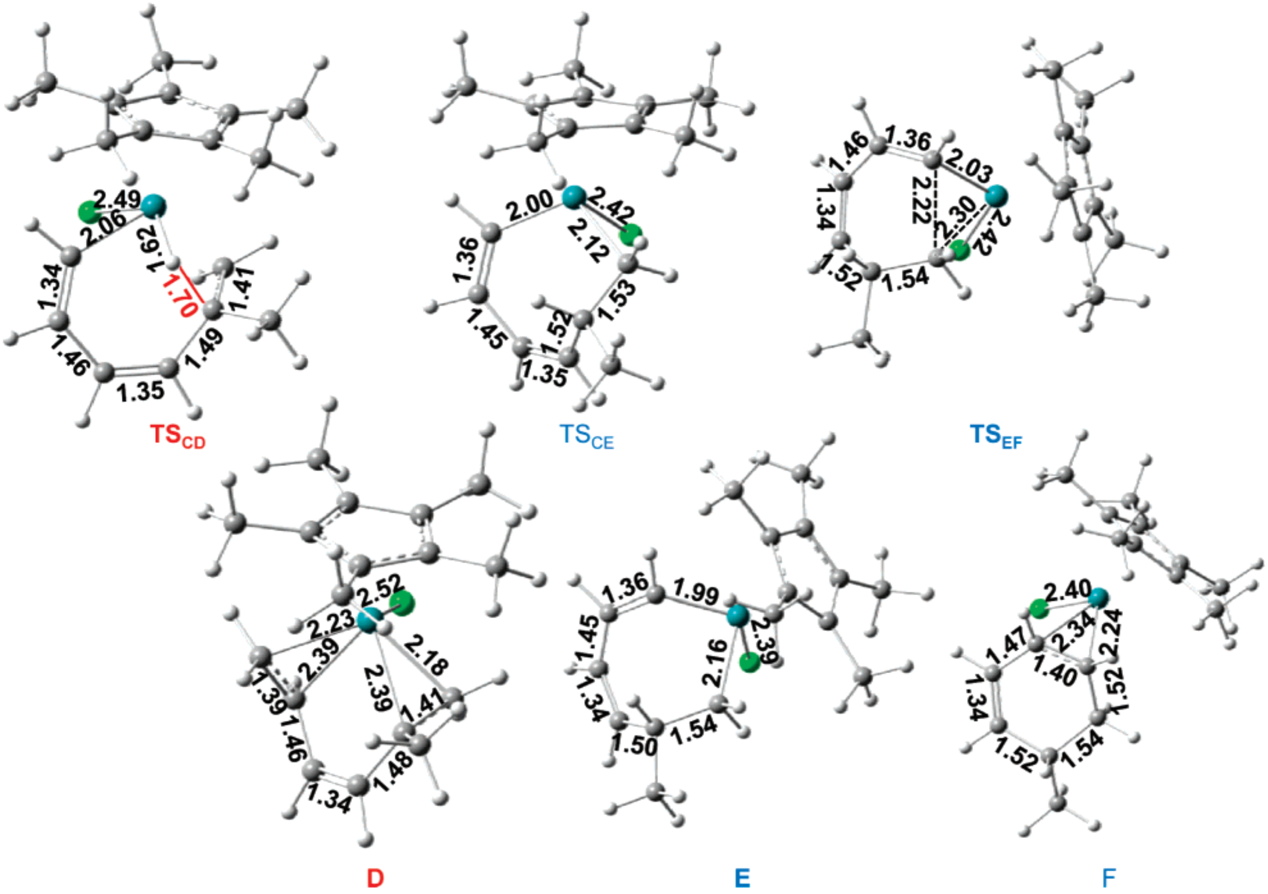


FIGURE 7. Structures of intermediates and transition states for the transformation of **C** into **D** and **F**, with selected bond distances (Å).

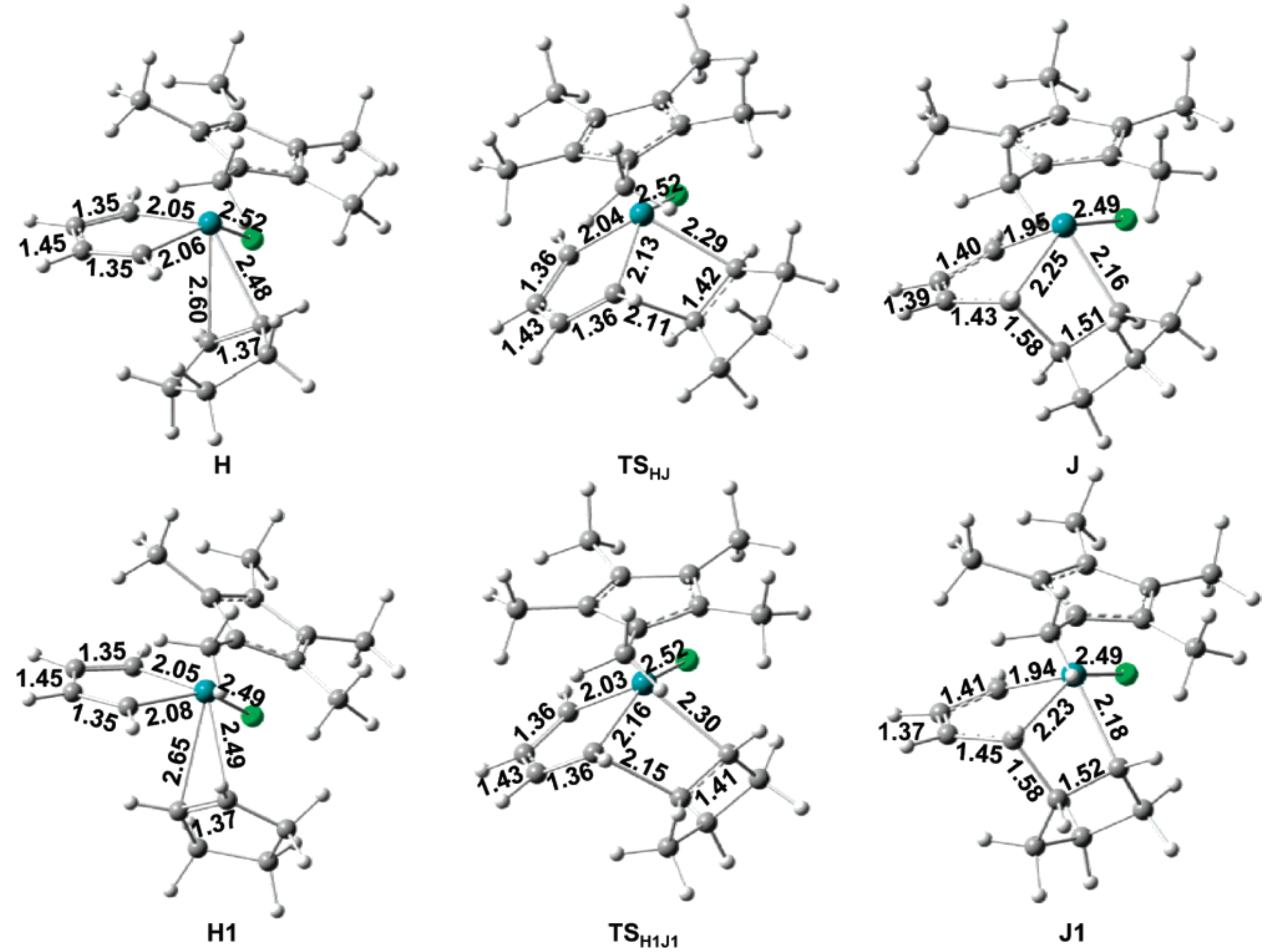


FIGURE 8. Structures for the stereoisomers of the ruthenacyclopentadiene−cyclopentene complexes of type **H** and their corresponding ruthenium tricyclic complexes of type **J**.

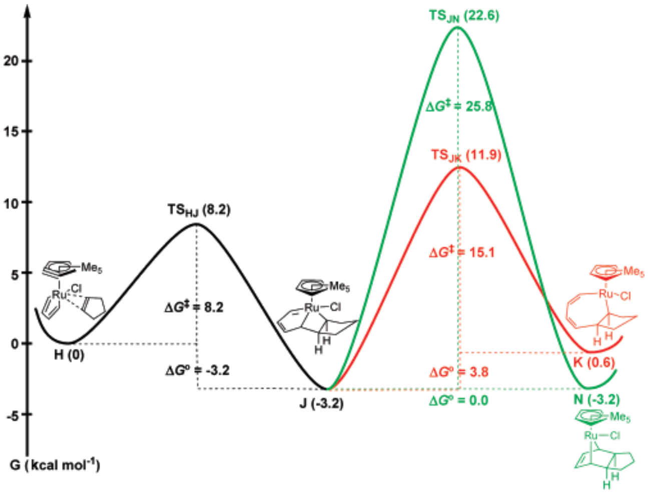


FIGURE 9. Energy profile (G in kcal mol^{-1} at 298 K and 1 atm) for the formation of ruthenacycles **K** and **N** from complex **H**.

kcal mol^{-1}; $\Delta G^\circ = 4.7$ kcal mol^{-1}, $\Delta H^\circ = 6.3$ kcal mol^{-1}), which now has an adequate conformation for a reductive elimination via **TS$_{EF}$** to form the η^2-cyclohexadiene Ru complex **F** ($\Delta G^\ddagger = 6.1$ kcal mol^{-1}, $\Delta H^\ddagger = 6.7$ kcal mol^{-1}; $\Delta G^\circ = -45.8$ kcal mol^{-1}, $\Delta H^\circ = -45.1$ kcal mol^{-1}). In the case of path B (purple line), due to the agostic interaction between H_β and the ruthenium (dihedral angle Ru−C−C−H of −12.40°), the complex **C** directly evolves via **TS$_{CD}$** to the η^4-triene Ru complex **D** with a very low activation barrier ($\Delta G^\ddagger = 1.7$ kcal mol^{-1}; $\Delta H^\ddagger = 2.1$ kcal mol^{-1}) and is thermodynamically very favorable ($\Delta G^\circ = -26.5$ kcal mol^{-1}; $\Delta H^\circ = -26.0$ kcal mol^{-1}). So, *path B is kinetically favored against path A, which satisfactorily explains why the Ru-catalyzed reaction of 1,6-diynes with monosubstituted acyclic alkenes affords exclusively the open 1,3,5-hexatrienes **6***. The completion of the catalytic cycle requires the displacement of the 1,3,5-hexatriene by two acetylenes to regenerate the catalytic species. This process is quite exothermic ($\Delta G^\circ = -8.2$ kcal mol^{-1}; $\Delta H^\circ = -14.6$ kcal mol^{-1}), which could explain why this reaction is catalytic in ruthenium.

Some selected bond distances for the structures of intermediates and transition states for the transformation of **C** into **D**, **E**, and **F** are shown in Figure 7.

Density Functional Study on the Acetylene−Cyclopentene Reaction. Following a similar procedure as for the case of propene, we begin our study evaluating which of the two possible initial complexes **H** (*exo*) or **H1** (*endo*) begins the catalytic cycle (Scheme 5). For this purpose, the energies of the initial complexes and their conversions to the tricyclic ruthenium species **J** and **J1** were computed.

From the results summarized in Scheme 5, the transformation from **H** to **J** (*exo* approach) is kinetically more favorable ($\Delta G^\ddagger$

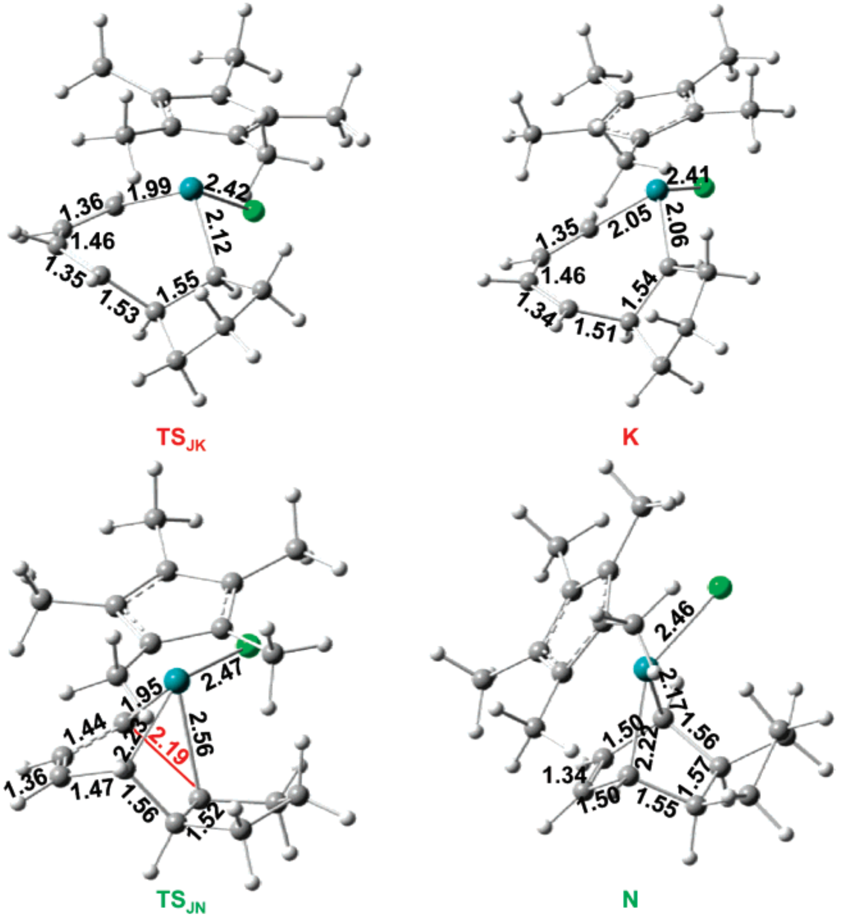


FIGURE 10. Structures of intermediates and transition states for the transformation of **J** into **K** and **N** with selected bond distances (Å) and angles (deg).

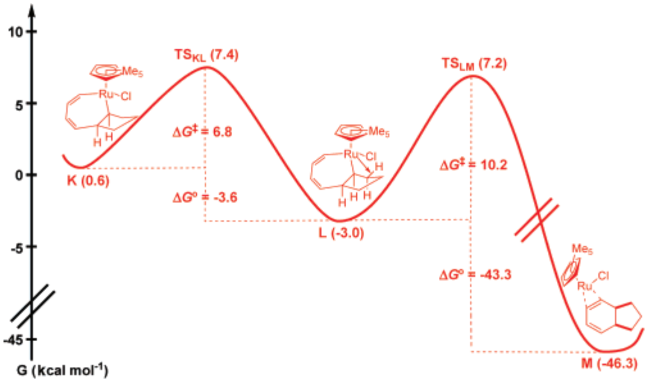


FIGURE 11. Energy profile (G in kcal mol^{-1} at 298 K and 1 atm) for the reductive elimination from **K**.

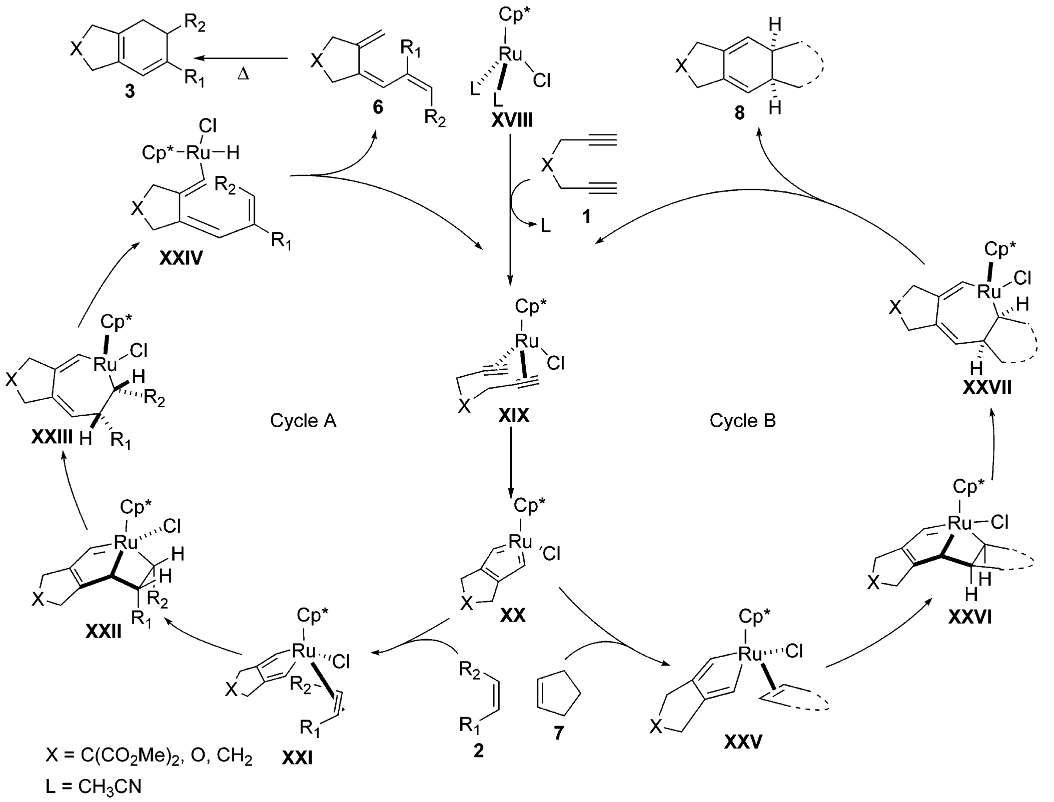
$= 8.2$ kcal mol^{-1}, $\Delta H^{‡} = 5.9$ kcal mol^{-1}). Some selected bond distances from the structures depicted in Scheme 5 are shown in Figure 8.

Therefore, we started the new DFT calculations from the ruthenacyclopentadiene(cyclopentene) complex **H**, with all the energy values referring to this complex (Figure 9). The first step, as in the reaction with acyclic alkenes, is the C−C coupling between the coordinated cycloalkene with the ruthenacyclopentadiene in complex **H** leading to the fused 5,4,5-membered tricyclic complex **J** via **TS$_{HJ}$** with $\Delta G^{‡} = 8.2$ kcal mol^{-1} ($\Delta H^{‡} = 5.9$ kcal mol^{-1}) and $\Delta G° = -3.2$ kcal mol^{-1} ($\Delta H° = -5.5$ kcal mol^{-1}). The energy profile for the first step of the catalytic cycle is very similar to those obtained for the propene in terms of energy values.

Two possible paths, as in the case of propene, were then evaluated (Figure 9): path A, shown as a green line, where the ruthenabicyclo[3.2.0]heptadiene complex **J** evolves to the η^2 complex **N** via **TS$_{JN}$** with a $\Delta G^{‡} = 25.8$ kcal mol^{-1} ($\Delta H^{‡} = 25.7$ kcal mol^{-1}) and $\Delta G° = 0.0$ kcal mol^{-1} ($\Delta H° = -1.0$ kcal mol^{-1}), and path B, shown as a red line, where the ruthenacycloheptadiene **K** is formed by an electrocyclic opening of the ruthenabicyclo[3.2.0]heptadiene **J** via **TS$_{JK}$** with a $\Delta G^{‡} = 15.1$ kcal mol^{-1} ($\Delta H^{‡} = 16.0$ kcal mol^{-1}) and $\Delta G° = 3.8$ kcal mol^{-1} ($\Delta H° = 5.2$ kcal mol^{-1}).

Compared with the energy profile of acyclic alkenes (Figure 4), both path B (red line) and path A (green line) for cyclic alkenes are both kinetically and thermodynamically less favorable ($\Delta G^{‡} = 15.1$ vs 12.2 kcal mol^{-1} and $\Delta G° = 3.8$ vs -2.2 kcal mol^{-1} for path B and $\Delta G^{‡} = 25.8$ vs 21.8 kcal mol^{-1} and $\Delta G° = 0.0$ vs -8.7 kcal mol^{-1} for path A). For path B, the ruthenacycloheptadiene **K** (Figure 9) is 7.0 kcal mol^{-1} less stable than ruthenacycloheptadiene **C** (Figure 4) due to the lack of an agostic interaction (present in complex **C**) that prevents the Ru(IV) in **K** from having 18 electrons.[23] As in the case of propene, the way in red is kinetically more favorable than the one in green; therefore, mechanistic studies continue from intermediate **K**.

SCHEME 6. Proposed Mechanisms for the Formal and Standard Ru-Catalyzed [2 + 2 + 2] Cycloadditions of Terminal 1,6-Diynes with Acyclic and Cyclic Alkenes



Some selected bond distances for the structures of intermediates and transition states for the transformation of **J** into **K** and **N** are shown in Figure 10.

Due to the *exo* approach for the coordination of cyclopentene to the Ru biscarbene to generate complex **H** (Schemes 1 and 5), there is no suitable hydrogen in **K** to give a β-hydride elimination to afford an open η^4-triene coordinated to the ruthenium as for **D** (Figure 6). Therefore, a path involving reductive elimination from **K** would probably now be favorable (Figure 11).

First, a conformational change of the cyclopentane ring in **K** to the more stable conformer **L** in which the Ru(IV) has now 18 electrons due to the agostic interaction (1.96 Å) with a hydrogen of the cyclopentane occurs.[24] The energy barrier for this change via $\mathbf{TS_{KL}}$ is relatively low, $\Delta G^\ddagger = 6.8$ kcal mol^{-1}, $\Delta H^\ddagger = 5.6$ kcal mol^{-1}, with a $\Delta G^\circ = -3.6$ kcal mol^{-1}, $\Delta H^\circ = -4.1$ kcal mol^{-1}. The ruthenacycloheptadiene **L** is now suitable for a reductive elimination to afford the Ru$-\eta^2$-cyclohexadiene **M** through the transition state $\mathbf{TS_{LM}}$, with a relatively low barrier of $\Delta G^\ddagger = 10.2$ kcal mol^{-1} ($\Delta H^\ddagger = 9.0$ kcal mol^{-1}), and is thermodynamically favored, $\Delta G^\circ = -43.3$ kcal mol^{-1} ($\Delta H^\circ = -41.2$ kcal mol^{-1}). As in the case of the formation of the 1,3,5-hexatriene, to complete the catalytic cycle, it is necessary to displace the η^2-cyclohexadiene ligand by two acetylenes. This process is much more exothermic ($\Delta G^\circ = -8.6$ kcal mol^{-1}; $\Delta H^\circ = -18.3$ kcal mol^{-1}) than the Co-mediated [2 + 2 + 2] cycloaddition of two acetylenes and ethylene,[7] which could explain why this cycloaddition is catalytic in Ru and stoichiometric in Co.

Some selected bond distances for the structures of intermediates and transition states for the transformation of **K** into **L** and **M** are shown in Figure 12.

Mechanistic Proposal. Our mechanistic hypothesis for the Ru-catalyzed reaction of alkynes and alkenes supposes two possible pathways depending on the alkene partner (Scheme 6). When mixed with Et$_4$NCl, the cationic catalyst [Cp*Ru(CH$_3$CN)$_3$]PF$_6$ probably generates the neutral complex Cp*RuL$_2$Cl (**XVIII**, L = CH$_3$CN), as is suggested by changes in the ^{1}H NMR spectrum.[12] Coordination to the diyne **1** followed by oxidative coupling would form the biscarbene species **XX**, which after coordination to the alkene would give rise to the ruthenacyclic species of type **XXI** for acyclic alkenes (*endo* approach) or **XXV** for cyclic alkenes (*exo* approach). Formation of Ru bicyclic complexes **XXII** and **XXVI** followed by electrocyclic opening would afford ruthenacycloheptadienes **XXIII** and **XXVII**, from which two alternatives could be envisioned depending on the nature of the alkene: (a) the well-established reductive elimination to cyclohexadienes **8**, in the case of cyclic alkenes;[11b] (b) a new β-elimination leading to the ruthenium hydride **XXIV** followed by a reductive elimination to give the open hexatrienes **6**, in the case of acyclic alkenes. Hexatrienes **6** undergo a pure thermal disrotatory 6e$^-\pi$ electrocyclization to give the observed cyclohexadienes **3**.

In summary, the course of the Ru(II)-catalyzed [2 + 2 + 2] cycloaddition between 1,6-diynes and alkenes to give 1,3-cyclohexadienes varies with the nature of the starting alkene: (a) with cyclic alkenes as partners, standard 1,3-cyclohexadienes **8** are obtained (from the reductive elimination of intermediate

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(23) Most likely, 2,5-dihydrofuran, with oxygen in the allylic position, is able to coordinate to the ruthenium lowering the energy of intermediates of type **K**, just favoring the reaction as noticed experimentally with better yields. See also ref 11.

(24) It has not been possible to find a transition state from ruthenacycloheptadiene **L** leading to the Ru−H from the β-elimination of the hydrogen of the cyclopentane ring.

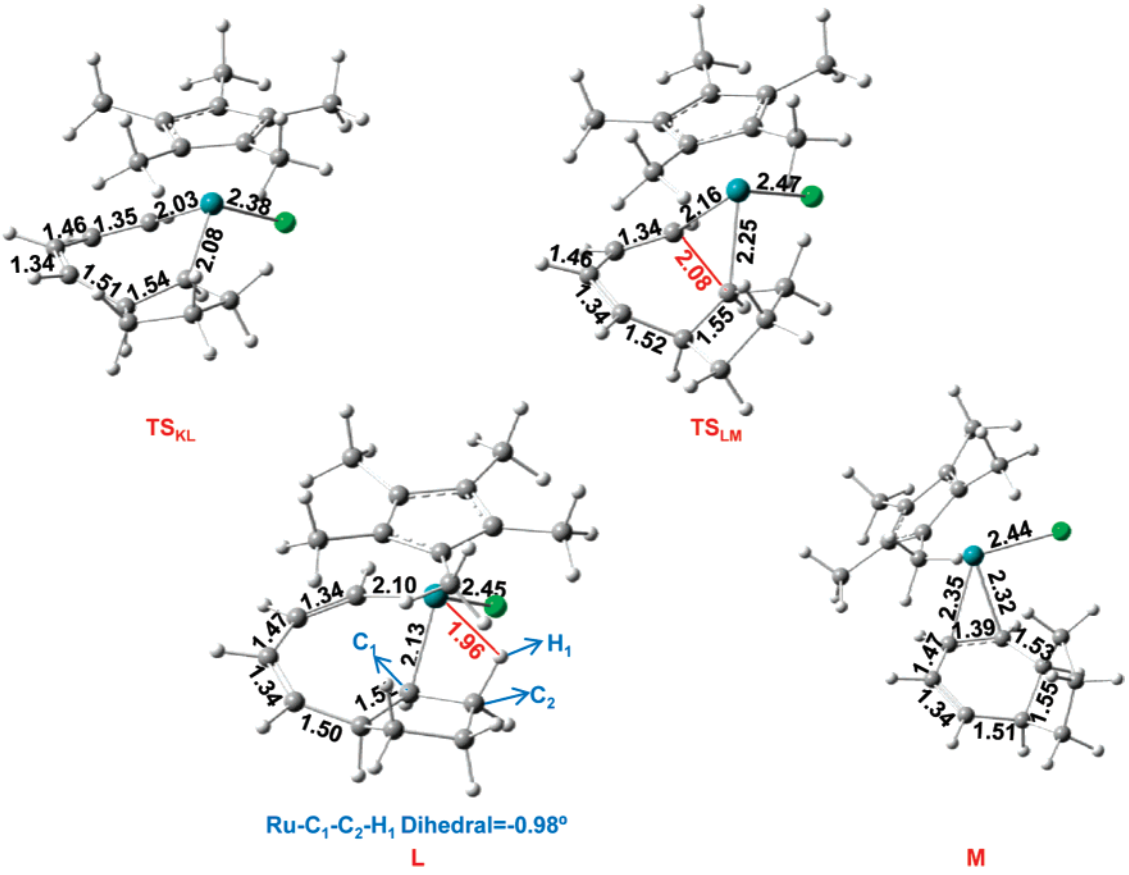

FIGURE 12. Structures of intermediates and transition states for the transformation of **K** into **L** and **M** with selected bond distances (Å).

XXVII); (b) with acyclic alkenes as partners, a tandem process is observed which involves a linear coupling of 1,6-diynes and alkenes to 1,3,5-hexatrienes (from a β-elimination of intermediate **XXIII** followed by a reductive elimination) followed by a pure thermal 6e$^-\pi$ electrocyclization of **6** to give 1,3-cyclohexadienes **3**. The whole cascade process could be considered as a formal [2 + 2 + 2] cycloaddition of alkynes to alkenes. Experimental observations and DFT calculations support the mechanism proposed.

Experimental Section

Computational Details: All calculations were performed using the Gaussian 03 software package[25] using the CESGA facilities. The geometry and energy of the model complexes and the transition states were optimized at the B3LYP level[21] with the double-ζ LANL2DZ[26] basis set to describe the electrons of the ruthenium atom. For all other atoms, the 6-31G* basis set was employed.[27] Frequency calculations were performed to confirm the nature of the stationary points, yielding one imaginary frequency for the transition states and none for the minima. Each transition state was further confirmed by following its vibrational mode downhill on both sides and obtaining the minima presented on the reaction energy profile. All geometries were optimized without constraints (C_1 symmetry), and all the relative Gibbs free energies (ΔG values) and enthalpies (ΔH values) were obtained by taking into account zero-point energies, thermal motion, and entropy contribution (for the case of ΔG) at standard conditions (temperature 298 K, pressure 1 atm). The reaction profiles were built up in terms of ΔG, although the pathway was calculated in terms of E.

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Supporting Information Available: Optimized geometric parameters for all the calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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