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Ruthenium-Catalyzed [2 + 2] Cycloadditions between 7-Substituted Norbornadienes and Alkynes: An Experimental and Theoretical Study

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The ruthenium-catalyzed [2 + 2] cycloadditions of 7-substituted norbornadienes with an alkyne have been investigated. The cycloadditions were found to be highly regio- and stereoselective, giving only the *anti-exo* cycloadducts as the single regio- and stereoisomers in good yields. The results on the relative rate of different 7-substituted norbornadienes in the Ru-catalyzed [2 + 2] cycloadditions with an alkyne indicated that the reactivity of the alkene component decreases dramatically as the alkene becomes more electron deficient. Ab initio computational studies on the ruthenium-catalyzed [2 + 2] cycloadditions provided important information about the geometries and the arrangements of the four different groups on the Ru in the initial Ru−alkene−alkyne π-complex, **14**, and in the metallacyclopentene **15**. Based on our computational studies, we also found that the first carbon−carbon bond formed in the [2 + 2] cycloaddition is between the C^5 of the alkene and the C^b (the acetylenic carbon attached to the ester group) of the alkyne **8**. Our computational studies on the potential energy profiles of the cycloadditions showed that the activation energy relative to the reactants for the oxidative addition step is in the range of 9.3−9.8 kcal/mol. The activation energy relative to the metallacyclopentene for the reductive elimination step is much higher than for the oxidative addition step (in the range of 25.9−27.6 kcal/mol).

Introduction

Cycloaddition reactions are among the most powerful and most frequently used methods for the construction of rings.[1] Typically, cycloaddition reactions can be carried out using heat, light, or Lewis acids. However, cycloaddition reactions of unactivated alkenes, alkynes, and dienes usually require extreme reaction conditions such as high temperature and high pressure to achieve good yields of the cycloadducts. Transition-metal catalysts provide new opportunities for highly selective cycloaddition reactions since complexation of the metal to an alkene, alkyne, or diene significantly modifies the reactivity of this moiety, opening the way for enhanced reactivity and novel reactions.[2]

Recent developments in transition-metal-catalyzed [2 + 2 + 1],[3] [4 + 2],[4] [5 + 2],[5] [4 + 4],[6] and [6 + 2][7] cycloaddition reactions have provided efficient methods for the construction of 5- to 8-membered rings. We and others have studied various aspects of transition-metal-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne for the synthesis of cyclobutene rings, including development of novel catalysts, study of the intramolecular variant of the reaction, and investigation of chemo- and regioselectivity of unsymmetrical substrates.[8−12]

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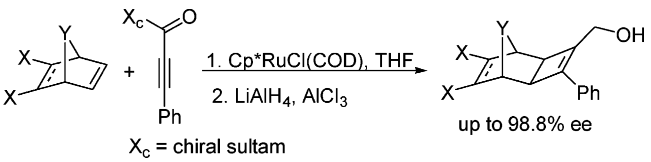
SCHEME 1



More recently, we have demonstrated the first examples of asymmetric induction studies in ruthenium-catalyzed [2 + 2] cycloadditions between symmetrical bicyclic alkenes and alkynes bearing a chiral auxiliary, and excellent levels of asymmetric induction (up to 98.8% ee, after removal of the recoverable chiral auxiliary) in the cycloadditions were achieved (Scheme 1).[12e]

To understand the mechanism of the Ru-catalyzed [2 + 2] cycloadditions thoroughly so that one can design more active catalysts for the cycloadditions, studies on the reactivity of both reaction partners are essential. To date, very little is known about the general course of reactivity in Ru-catalyzed [2 + 2] cycloadditions. Furthermore, very little is known as to whether electron-rich or electron-deficient alkenes and alkynes react faster or slower in the Ru-catalyzed [2 + 2] cycloadditions, and the steric requirements of the cycloaddition have yet to be determined. In this paper, we report our experimental and computational results on Ru-catalyzed [2 + 2] cycloadditions between 7-substituted norbornadienes and an alkyne. The experimental results of these studies provide important information on the reactivity of the alkene component in the cycloaddition and the computational studies give insights on the detailed mechanism of the cycloaddition. To our knowledge, no computational studies on any metal-catalyzed [2 + 2] cycloadditions have been reported in the literature.

Results and Discussion

Experimental Studies on Ru-Catalyzed [2 + 2] Cycloadditions between 7-Substituted Norbornadienes and an Alkyne. To investigate the reactivity of the alkene component and determine whether electron-rich or electron-deficient alkenes react faster or slower in the ruthenium-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne, we studied the ruthenium-catalyzed [2 + 2] cycloadditions between 7-substituted norbornadienes and an alkyne. We chose not to use alkenes with substituents directly attached to the olefinic carbons (**1**, Figure 1) as the alkene component in our study because the rate of the cycloaddition in this case will be governed not only by electronic effects but also by the steric effects of the X substituent. Experimental and theoretical studies on 7-substituted norbornadienes **2** have shown that as the electron-withdrawing power of the Y substituent increases the electron density of the *anti-π* bond decreases.[13] In other words, as the electronegativity of the Y substituent increases the *anti-π* bond becomes more electron deficient.

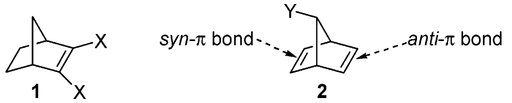
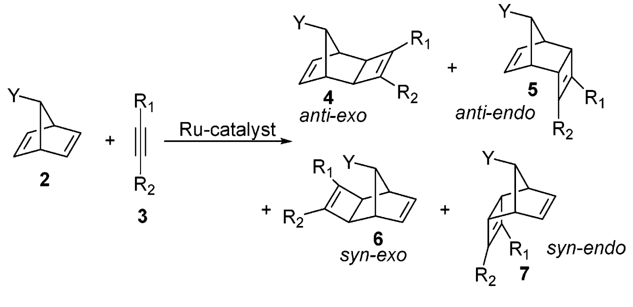


FIGURE 1. Bicyclic alkenes.

SCHEME 2. Possible Cycloadducts



Although four different [2 + 2] cycloadducts are theoretically possible in the cycloaddition between a 7-substituted norbornadiene and an alkyne (Scheme 2), we anticipated that the *anti-exo* cycloadduct would be produced preferentially. On the basis of previous work by our group and others,[9,11,12] Ru-catalyzed [2 + 2] cycloadditions of norbornenes or norbornadienes with alkynes produced only *exo* cycloadducts. Furthermore, the *exo* face of the *syn-π* bond is sterically shielded by the Y substituent, thus suggesting the Ru-catalyzed cycloaddition should occur preferentially on the *exo* face of the *anti-π* bond. This has proven to be true. The Ru-catalyzed [2 + 2] cycloadditions of all the 7-substituted norbornadienes **2a**−**f** with alkyne **8** are highly regio- and stereoselective, giving the *anti-exo* cycloadducts **9a**−**f** as the only regio- and stereoisomers in moderate to excellent yields (Tables 1 and 2).

When norbornadiene **2a** (Y = OAc) was treated with alkyne **8** in the presence of 5−10 mol % of Cp*RuCl(COD) in THF at room temperature, very little reaction was observed (Table 1, entry 1). At 60 °C in THF, only 13% of the cycloadduct **9a** was isolated and >80% of alkyne **8** was recovered (entry 2). Using Et$_3$N as the solvent, at 80 °C for 48 h, cycloadduct **9a** was produced in 50% yield; when the cycloaddition was carried out at 95 °C for 90 h, the yield increased to 68% (entries 3 and 4). Using diglyme as solvent at a higher temperature (110 °C) did not improve the yield further (entry 5). Unlike the cycloaddition of 7-substituted norbornadiene **2a** (when Y = OAc) which is very slow at room temperature (Table 1, entry 1), Ru-catalyzed [2 + 2] cycloadditions of 7-substituted norbornadienes **2c**−**f**, when Y = O^{t}Bu, H, alkyl group, or aryl group, are faster at room temperature, giving moderate yields of the cycloadducts (entries 6, 9, 11, and 13). Thus, 7-substituted norbornadienes **2c**−**f** are more reactive than 7-substituted norbornadiene **2a** in the Ru-catalyzed [2 + 2] cycloaddition with alkyne **8**.

To confirm these qualitative observations and to estimate the relative rate of the Ru-catalyzed [2 + 2] cycloadditions of different 7-substituted norbornadienes with alkyne **8**, competition experiments between 7-substituted norbornadiene **2a** (Y = OAc) and other 7-substituted norbornadienes **2b**−**f** were carried out. A typical

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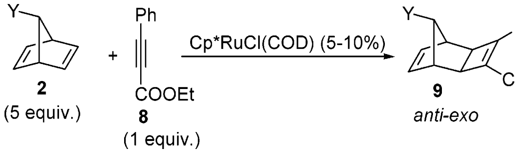
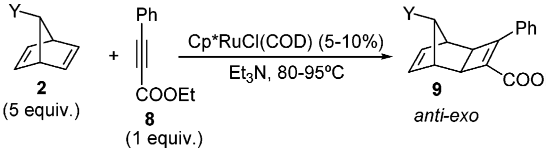
TABLE 1. Ruthenium-Catalyzed [2 + 2] Cycloadditions of 7-Substituted Norbornadienes and Alkyne 8 at Different Conditions



entry	norbornadiene	Y	cycloadduct	solvent/T (°C) /time (h)	yield[a] (%)
1	**2a**	OAc	**9a**	THF/25/48	<5[b]
2	**2a**	OAc	**9a**	THF/60/48	13[b]
3	**2a**	OAc	**9a**	Et_3N/80/48	50[b]
4	**2a**	OAc	**9a**	Et_3N/95/90	68[b]
5	**2a**	OAc	**9a**	Diglyme/110/48	66[b]
6	**2c**	O^{t}Bu	**9c**	THF/25/48	45[b]
7	**2c**	O^{t}Bu	**9c**	THF/60/48	50[b]
8	**2c**	O^{t}Bu	**9c**	Et_3N/80/67	88
9	**2d**	H	**9d**	THF/25/48	84
10	**2d**	H	**9d**	Et_3N/80/48	93
11	**2e**	Hexyl	**9e**	THF/25/48	54[b]
12	**2e**	Hexyl	**9e**	Et_3N/80/48	97
13	**2f**	Ph	**9f**	THF/25/48	44[b]
14	**2f**	Ph	**9f**	Et_3N/80/48	92

[a] Isolated yields after column chromatography. [b] 30-90% of unreacted alkyne **8** was recovered.

TABLE 2. Relative Rate of Different 7-Substituted Norbornadienes in Ru-Catalyzed [2 + 2] Cycloadditions with Alkyne 8



entry	norbornadiene	Y	cycloadduct	yield[a] (%)	relative rate[c]
1	**2a**	OAc	**9a**	68[b]	1
2	**2b**	OTBS	**9b**	89	4
3	**2c**	O^{t}Bu	**9c**	88	7
4	**2d**	H	**9d**	84	23
5	**2e**	hexyl	**9e**	97	31
6	**2f**	Ph	**9f**	92	53

[a] Isolated yields after column chromatography. [b] ~30% of **8** was recovered. [c] Measured from competition experiments, see text.The number indicated is the average number from three to five runs.

competition experiment employed 4 equiv of equimolar amounts of 7-substituted norbornadiene **2a** (Y = OAc) (a stock solution of known concentration was prepared for **2a**) and 7-substituted norbornadiene **2b** (Y = OTBS) with 1 equiv of alkyne **8** in the presence of 5 mol % of Cp*RuCl(COD) in Et_3N (large excesses of the norbornadienes were used in order to approach pseudo-first-order conditions).[13b] The reactivity of each 7-substituted norbornadiene was assessed by evaluation of the product ratio by capillary gas chromatography.[14] The results of these reactivity studies are shown in Table 2.

Replacement of the OAc group with an OTBS or an O^{t}Bu group at the 7-position of the norbornadiene leads to a 4- to 7-fold increase in the rate in the Ru-catalyzed [2 + 2] cycloaddition (Table 2, entries 2 and 3). Surprisingly, when the OAc group is replaced with a H, the parent norbornadiene **2d** reacts 23 times faster than the 7-OAc norbornadiene **2a** (entry 4) (in this case, for a fair comparison, the competition experiments were conducted using a mole ratio of **2a/2d** of 2:1 instead of 1:1, since norbornadiene contains two equivalent reactive double bonds). More interestingly, when Y = alkyl or aryl groups, the reactivities of the 7-substituted norbornadienes increase further. 7-Hexylnorbornadiene **2e** reacts 31 times faster than the 7-OAc norbornadiene **2a** and 7-Ph-norbornadiene **2f** reacts 53 times faster than the 7-OAc norbornadiene **2a** (entries 5 and 6). The relative rate values of Table 2 arise from three to five repetitions of each reaction.

In general, as the electronegativity of the Y substituent increases, the *anti-π* bond of the 7-substituted norbornadienes becomes more electron deficient. The results of our study on the relative rate of different 7-substituted norbornadienes in Ru-catalyzed [2 + 2] cycloadditions with alkyne **8** indicated that electron-deficient alkenes react more slowly than electron-rich alkenes.[15]

Computational Studies and Discussion of the Mechanism. We performed theoretical studies in order to examine the detailed mechanism of the Ru-catalyzed [2 + 2] cycloadditions between 7-substituted norbornadienes and alkyne **8**. All computations in this study were carried out with the Gaussian98 suite of programs.[16] The Becke three-parameter hybrid functional[17] combined with the Lee, Yang, and Parr (LYP) correlation functional,[18] B3LYP, was used. The LANL2DZ[19] basis set which uses effective core potentials for heavy elements was employed for all calculations. It includes some relativistic effects in its modeling of the core electrons of ruthenium.[20] All structures were computed as closed-shell molecules. Transition states (TS) were tested for electronic instabilities, where an instability would indicate a lower energy open-shell solution. All the transition states tested were stable to such perturbations and thus closed-shell structures. Transition-state structures are characterized by one imaginary frequency and are first-order saddle points. To ensure that the required transition states had

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[14] Since different cycloadducts may provide different response from the detector of the GC, an equimolar amount of two different cycloadducts may not provide exactly a 1:1 ratio of peak areas on the GC integration. Thus, equimolar amount of each cycloadduct was injected into the GC and their integration areas were compared. These numbers were then used to correct for the product ratios.

(15) As noted by a reviewer, the observed relative rate of cycloaddition may not be purely from an electronic effect. The coordinating ability of the 7-substutuent that competes with the *anti-π*-bond for the metal center could also be a factor in the observed rate difference.

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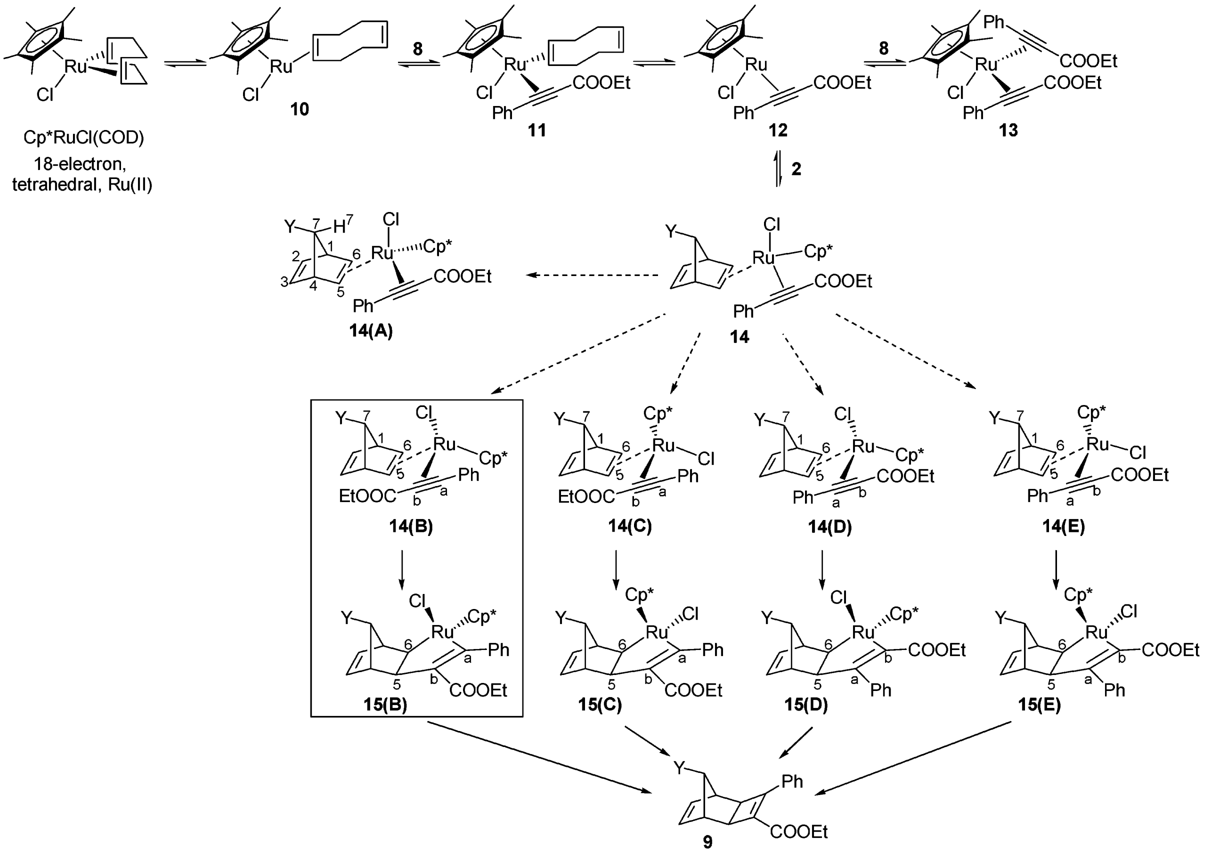
SCHEME 3. Proposed Mechanism



been found, the normal mode corresponding to the imaginary frequency was animated. From the transition states, the reactants and products were then located with a method similar to the intrinsic reaction coordinate (IRC) approach.[21] One descends from the transition states along the reaction coordinates to the appropriate minima. The reactant and product structures all exhibited zero imaginary frequencies and thus are minima.

Previous studies have shown that formation of a cationic [Cp*Ru]$^+$ species from Cp*RuCl(COD) by treatment with AgOTf decreased the catalytic activity, and low yields ($<$25%) of the cycloadditions were observed.[9,12] This result suggested that a neutral [Cp*RuCl] moiety is likely to be the active catalytic species in the cycloadditions. A proposed mechanism of the Ru-catalyzed [2 + 2] cycloadditions between 7-substituted norbornadienes and alkyne **8** is shown in Scheme 3. Dissociation of one of the double bonds of the cyclooctadiene (COD) ligand from the catalyst Cp*RuCl(COD) followed by ligand association with alkyne **8** will provide complex **11**. Upon dissociation of the COD ligand to form the coordinatively unsaturated complex **12**, either another molecule of alkyne **8** or norbornadiene **2** could complex with **12**. We noticed that the use of an excess of the alkene component (see Tables 1 and 2, 5 equiv of norbornadienes was used) improves the yields of the cycloadditions but on the other hand, the use of excess alkyne decreases the yield dramatically (e.g., when 5 equiv of the alkyne were used, less than 10% of the cycloadducts were obtained).[22] When an excess of alkyne **8** was used, complex **13** would form preferentially. Since Ru is known to form stronger π-complexes with alkynes than with alkenes,[23] the formation of complex **13** inhibits the cycloadditions. This explains why the use of an excess of the alkyne lead to low yields in the cycloadditions. When an excess of norbornadiene **2** was used, complexation of **12** to the *anti-*π bond on the *exo* face of norbornadiene **2** would give complex **14**. Since all the cycloadducts obtained in our experimental studies are *anti-exo* cycloadducts, in all the theoretical studies, we focused only on those complexes where the Ru is complexed to the *anti-*π bond on the *exo* face of the norbornadiene. In complex **14**, there are several ways that the four different groups (Cl, Cp*, alkene **2** and alkyne **8**) attached to Ru can be arranged. One of these groups (e.g., Cl) can be arranged such that the Ru−Cl bond is coplanar with the C^7-H^7 bond of the norbornadiene **2**, as in structure **14(A)**. On the other hand, two groups can be located above C^6 and C^5 of the norbornadiene **2** as in **14(B)**−**(E)**. For example, in structure **14(B)**, Cl is located above C^6, the alkyne is located above C^5 and the Ru−Cp* bond is coplanar with the C^7-H^7 bond of the norbornadiene. Due to steric hindrance of H^7 with Cl in **14(A)** (when the Ru−Cl bond is coplanar with the C^7-H^7 bond of the norbornadiene

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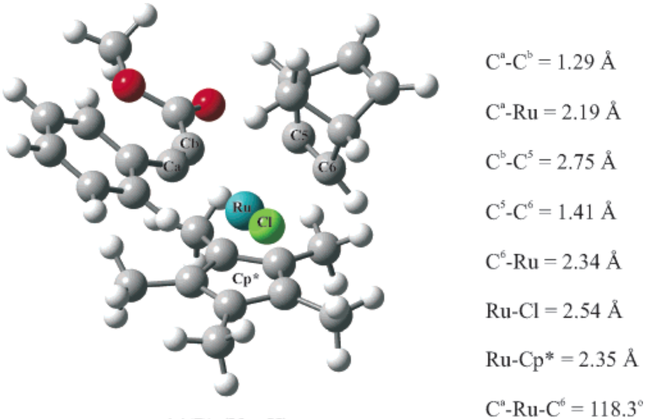

14(B) (Y = H)

FIGURE 2. Optimized structure of **14(B)** (when Y = H).

2), structure **14(A)** is of a much higher energy than **14-(B)**−**(E)**. The optimized structure of **14(B)**, with Y = H, is shown in Figure 2.[24] Oxidative addition of complexes **14(B)**−**(E)** would provide metallacyclopentenes **15(B)**−**(E)** which upon reductive elimination would give the cycloadduct **9**.

To gain insight on the detailed mechanism of the Ru-catalyzed [2 + 2] cycloadditions between 7-substituted norbornadienes and alkyne **8**, the computational studies were carried out. The first question we would like to address is how the four different groups (Cl, Cp*, alkene **2** and alkyne **8**) on the Ru in structure **14** (Scheme 3) are arranged before and after the oxidative addition to form the metallacyclopentenes **15**. In order for the oxidative addition to occur, the alkyne must be located above C^5 (or C,^{6} the bicyclic alkene has a symmetric structure and therefore C^5 and C^6 are "equivalent"). The remaining two groups Cl and Cp* can be arranged in two ways: either Cl is above C^6 and Cp* is pointing away from the bicyclic alkene (as in **14(B)** and **14(D)**) or Cp* is above C^6 and Cl is pointing away from the bicyclic alkene (as in **14(C)** and **14(E)**). In preliminary computations, we used a less complicated model (Y = H and replacing Cp* with Cp, and using methyl ester (COOMe) in the alkyne instead of the ethyl ester (COOEt)) to ascertain whether the Cl or the Cp* is located above C^6. Although the energy difference between the different structures of **14** is small, the energy difference between the different structures of **15** is significant. For example, for the model using Cp and COOMe, the energy difference between structure **14(D)** (with Cl above C^6) and structure **14(E)** (with Cp above C^6) is only 1.8 kcal/mol. On the other hand, structure **15(B)** (with Cl pointing toward the bicyclic framework and Cp pointing away from the bicyclic framework) is 9.0 kcal/mol more stable than structure **15(C)** (with Cp pointing toward the bicyclic framework and Cl pointing away from the bicyclic framework). These theoretical results show that formation of the metallacyclopentenes **15(B)** and **15(D)**, with Cl pointing toward the bicyclic framework and Cp pointing away from the bicyclic framework, is much more favorable than **15(C)** and **15(E)**.

TABLE 3. Comparison of Selected Bond Distances and Angles in Structures 14a−17a[a]

	14a	16a	15a	17a
C^a−C^b	1.29	1.32	1.45	1.47
C^a−Ru	2.20	2.10	1.91	1.93
C^b−C^5	2.76	2.05	1.54	1.53
C^5−C^6	1.41	1.46	1.56	1.56
C^6−Ru	2.32	2.16	2.15	2.42
Ru−Cl	2.53	2.51	2.49	2.50
Ru−Cp*	2.35	2.33	2.40	2.35
C^a−Ru−C^6	118.8	108.3	90.1	60.1

[a] Distances in angstroms. Angles in degrees.

Having determined the preferred arrangements of the four different groups on the Ru (**14(B)** and **14(D)**), the next two questions to address are as follows: (i) What is the preferred orientation of the unsymmetrical alkyne **8** in structure **14** (with the COOEt group adjacent to C^5 and Ph closer to the Ru as in **14(B)** or with Ph adjacent to C^5 and the COOEt group closer to the Ru as in **14-(D)**)? (ii) Which carbon−carbon bond is formed first between the symmetrical norbornadiene and the unsymmetric alkyne (with C^b, the acetylenic carbon attached to the ester group, to give metallacyclopentene **15(B)** or with C^a, the acetylenic carbon attached to the Ph group, to give metallacyclopentene **15(D)**)? To obtain more complete and more reliable results, we studied three different norbornadienes **2a** (Y = OAc), **2d** (Y = H), and **2f** (Y = Ph). The more realistic Cp* (C_5Me_5) ligand was used instead of Cp (C_5H_5) in these theoretical studies. The methyl ester (COOMe) in the alkyne instead of the ethyl ester (COOEt) was used in our computations. We compared the energy differences between **14(B)** and **14-(D)** in the three different cases (Y = OAc, H, and Ph). The **14(B)** structure, with the COOEt group adjacent to C^5 and Ph closer to the Ru, are always more stable (by 4.6−4.8 kcal/mol) than **14 (D)**. Thus, structure **14(B)** seems to be the preferred structure of the Ru complex before the oxidative addition. The difference in the activation energies in the oxidative addition step (**14(B)** and **14(D)** to their corresponding first transition states) is small (for example, when Y = OAc, the difference in the activation energies is only 0.4 kcal/mol), and the energy difference between the metallacyclopentenes **15-(B)** and **15(D)** is also very small (e.g., when Y = OAc, **15(B)** is only 0.1 kcal/mol more stable than **15(D)**). Since **14(B)** is ∼4.7 kcal/mol more stable than **14(D)**, it is likely that the first carbon−carbon bond formed in the [2 + 2] cycloaddition is between C^5 of the norbornadiene and C^b (attached to the electron-withdrawing ester group, COO-Et) of the unsymmetrical alkyne **8** leading to the formation of the metallacyclopentenes **15(B)**.[25]

The predicted potential energy profile for the Ru-catalyzed [2 + 2] cycloaddition between norbornadiene

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[24] Optimized geometries for all the structures mentioned in the text are reported in the Supporting Information.

[25] The regiochemistry of metallacyclopentenes **15(B)** and **15a**,**d**,**f** is opposite that proposed by Cheng and co-workers in the nickel-catalyzed coupling and cyclization reactions between oxanorbornenes and alkyl propiolates. The difference in regiochemistry could be due to the use of different metal catalyst (nickel vs ruthenium), and the oxygen in the oxanorbornenes used in Cheng's study could coordinate to the metal but not in our case with norbornadienes. Also, there are no theoretical calculations to support the proposed mechanism/structure by Cheng: (a) Rayabarapu, D. K.; Cheng, Cheng, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286. (b) Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2003**, *9*, 3164.

(Y=OAc) and alkyne **8**.

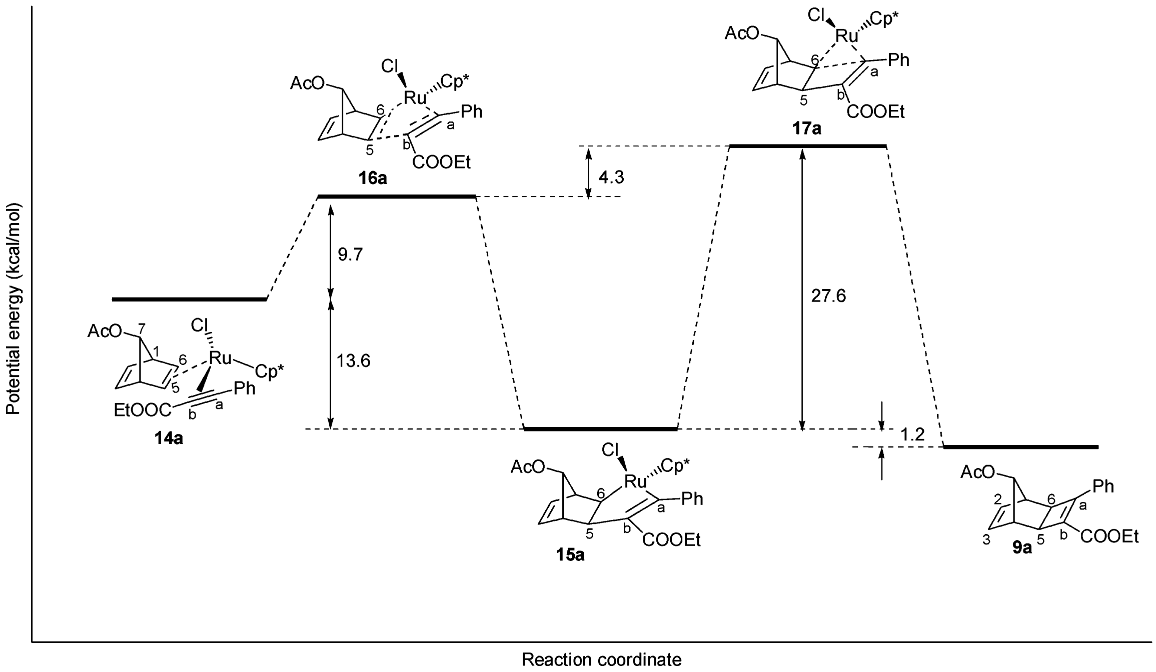

FIGURE 3. Potential energy profile for the Ru-catalyzed [2 + 2] cycloaddition between norbornadiene **2a** (Y = OAc) and alkyne **8**.

(Y = H) and alkyne **8**.

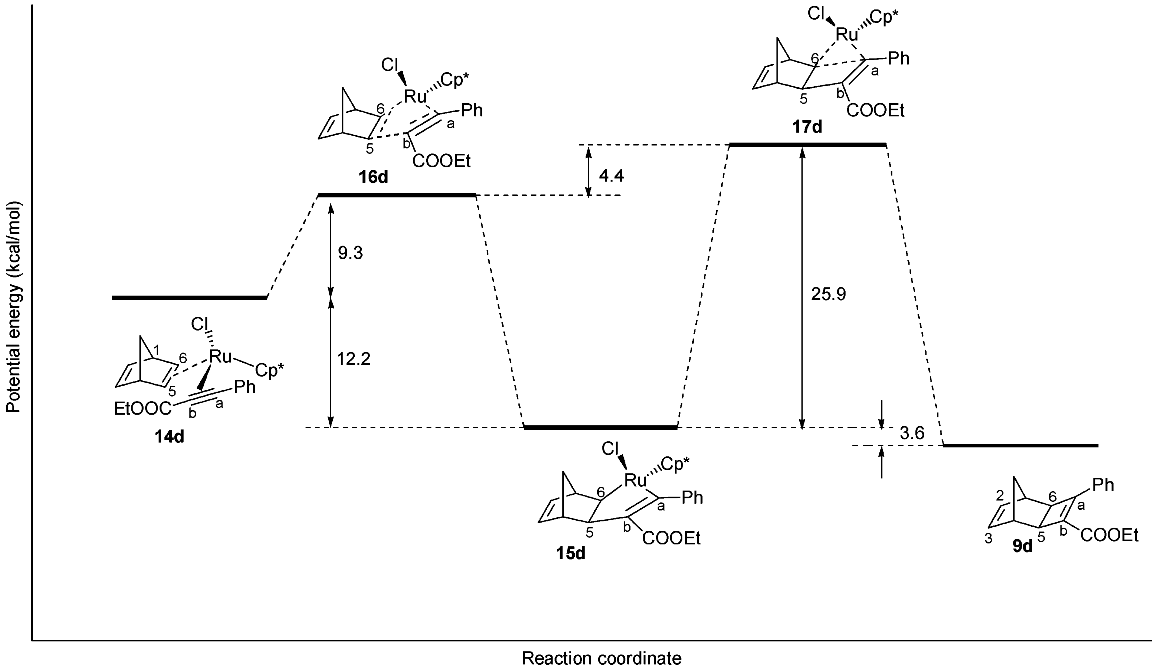

FIGURE 5. Potential energy profile for the Ru-catalyzed [2 + 2] cycloaddition between norbornadiene **2d** (Y = H) and alkyne **8**.

2a (Y = OAc) and alkyne **8** is shown in Figure 3, and the optimized geometries of the structures on the reaction path are illustrated in Figure 4 (Supporting Information). The activation energy for oxidative addition of the Ru π-complex **14a** to the first transition state **16a** is 9.7 kcal/mol, and the resulting metallacyclopentene **15a** is 13.6 kcal/mol more stable than **14a**. The activation energy for the reductive elimination of **15a** to the second transition state **17a** is much higher (27.6 kcal/mol) than the first step, and the resulting cycloadduct **9a** and the regenerated Cp*RuCl is 1.2 kcal/mol more stable than **15a**. A comparison of selected bond distances in structures **14a**-**17a** during the course of the reaction is shown in Table 3. For example, the bond length of the alkyne C^a-C^b bond increases from 1.29 Å in the Ru−alkyne π-complex **14a** (a typical C≡C bond length is 1.20 Å) to 1.32 Å in the

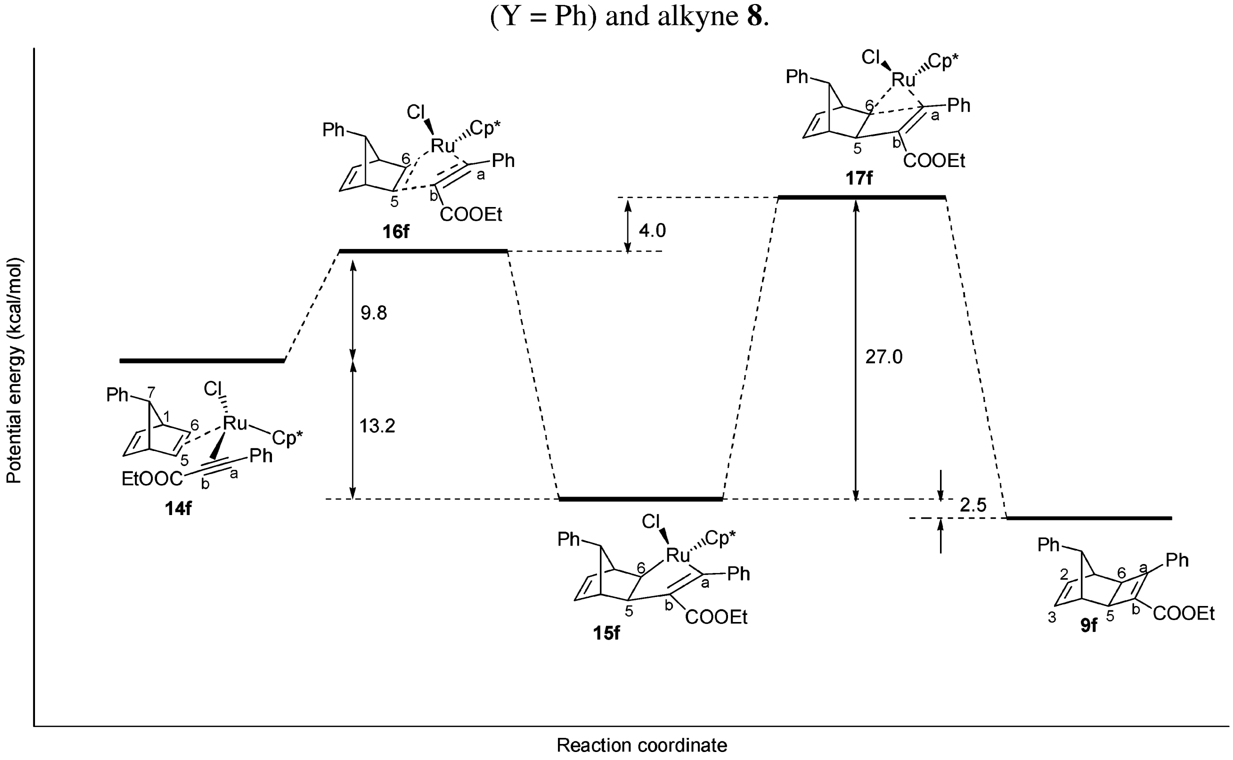

FIGURE 6. Potential energy profile for the Ru-catalyzed [2 + 2] cycloaddition between norbornadiene **2f** (Y = Ph) and alkyne **8**.

first transition state **16a** and increases further in the metallacyclopentene **15a** (1.45 Å) and the second transition state **17a** (1.47 Å) before decreasing back to 1.38 Å in the cyclobutene **9a**.

The potential energy profiles predicted for the Ru-catalyzed [2 + 2] cycloaddition between norbornadiene **2d** (Y = H) and alkyne **8**, and between norbornadiene **2f** (Y = Ph) and alkyne **8**, are shown in Figures 5 and 6. These potential energy profiles are very similar to the one in Figure 3 (with Y = OAc). No significant differences are observed in the activation energies for the first and second transition states **16** and **17** when the 7-substituents vary from Ph to H to OAc. The activation energy for the oxidative addition step to the first transition state **16** is in the small range of 9.3−9.8 kcal/mol, and the activation energy for the reductive elimination step to the second transition state is much higher than the first step but in a fairly small range of 25.9−27.6 kcal/mol.

Conclusions

We have reported the first study of the reactivity of the alkene component in ruthenium-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne. The Ru-catalyzed [2 + 2] cycloadditions of 7-substituted norbornadienes with an alkyne are highly regio- and stereoselective, giving the *anti-exo* cycloadducts as the only regio- and stereoisomers in good yields. The results of our study on the relative rate of different 7-substituted norbornadienes in Ru-catalyzed [2 + 2] cycloadditions with alkyne **8** indicate that reactivity of the alkene decreases dramatically as the alkene becomes more electron deficient. The theoretical studies provided important mechanistic information about the course of the reaction in the Ru-catalyzed [2 + 2] cycloaddition and represent the first ab initio studies on metal-catalyzed [2 + 2] cycloadditions. However, the trends in the reactivity of the different alkenes were not clearly revealed in the predicted activation energies. Among several possible arrangements of the four different groups (Cl, Cp*, alkene **2**, and alkyne **8**) on the Ru in the initial Ru−alkene−alkyne π-complex, **14**, and in the metallacyclopentene **15** (Scheme 3), **14(B)** and **15(B)** were found to be energetically more favorable. On the basis of the theoretical studies, the first carbon−carbon bond formed in the [2 + 2] cycloaddition is between the C^5 of the alkene and the C^b (the acetylenic carbon attached to the ester group) of the alkyne **8**. Our predictions of the potential energy profiles of the cycloadditions indicate that the activation energy for the oxidative addition step is in the range of 9.3−9.8 kcal/mol, and the activation energy for the reductive elimination step is much higher (in the range of 25.9−27.6 kcal/mol).

Experimental Section[26]

Materials. 7-Substituted norbornadienes **2a**−**f**,[27] Cp*RuCl(COD),[28] and alkyne **8**[29] were prepared according to literature procedures.

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[26] General methods were as described in a previous publication: Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113.

[27] 7-Substituted norbornadienes **2a**−**f** were prepared according to literature procedures: (a) Story, P. R.; Fahrenholtz, S. R. *J. Org. Chem.* **1963**, *28*, 1716. (b) Clarke, S. C.; Johnson *Tetrahedron* **1968**, *24*, 5067. (c) Story, P. R.; Fahrenholtz, S. R. *Org. Synth.* **1973**, 151. (d) Baxter, A. D.; Binus, F.; Javed, T.; Roberts, S. M.; Dalder, P.; Scheinmann, F.; Wakefield, B. J.; Lynch, M.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 5067.

[28] Cp*RuCl(COD) was prepared according to literature procedures: Fagan, P. J.; Mahoney, W. S.; Calabrese, J. C.; Williams, I. D. *Organometallics.* **1990**, *9*, 1843.

Typical Procedure for Ruthenium-Catalyzed [2 + 2] Cycloadditions between Alkene 2a−f and Alkyne 8. A mixture of norbornadiene **2** (1.0 mmol, 5 equiv) and acetylene **8** (0.2 mmol, 1 equiv) in an oven-dried vial was added via a cannula to an oven-dried screw-cap vial containing Cp*RuCl(COD) (weighed out from a drybox, 0.01 mmol, 5 mol %) under nitrogen. The oven-dried vial was rinsed with Et_3N (0.4 mL). The reaction mixture was stirred in the dark at 80−95 °C for 48−90 h. The crude product was purified by column chromatography (EtOAc−hexanes mixtures) to give the cycloadduct. Analytical and spectroscopic data of cycloadducts **9a−f** can be found in the Supporting Information.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all the cycloadducts and a listing of the Cartesian coordinates and total energies for the optimized geometries of calculated species. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Alkyne **8** was prepared according to literature procedures: Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 6133.