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Study on the Reactivity of the Alkene Component in Ruthenium-Catalyzed [2 + 2] Cycloadditions between an Alkene and an Alkyne. Part 1†

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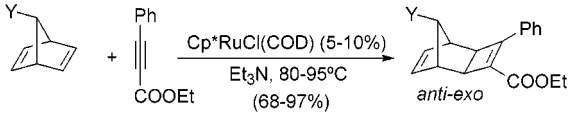
ABSTRACT



Relative rate of cycloaddition: Y=OAc < OTBS < O^{t}Bu < H < Hexyl < Ph

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.

The design and development of new transition metal-catalyzed reactions that are normally forbidden or difficult to achieve under ordinary conditions are important in organic synthesis.[1] Unlike transition metal-catalyzed [3 + 2],[2] [4 + 2],[3] and [2 + 2 + 2][4] cycloadditions which have been studied extensively,[5] there are only very few successful examples of transition metal-catalyzed [2 + 2] cycloadditions.[6]

The [2 + 2] cycloaddition of an alkene with an alkyne represents an important strategy for the synthesis of cyclobutene derivatives.[7] This process is thermally forbidden by the Woodward−Hoffmann rules.[8] However, it can be achieved by photochemical methods,[9] by thermal reactions via biradical intermediates,[10] and by the use of Lewis acid catalysts.[11] To date, very few papers have addressed the

† Dedicated to Professor Gord Lange on the occasion of his retirement.

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transition metal-catalyzed [2 + 2] cycloadditions of alkenes with alkynes.[6]

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 the 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 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 initial results of the reactivity of the alkene component in ruthenium-catalyzed [2 + 2] cycloadditions between an alkene 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

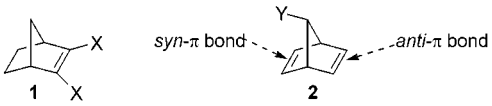
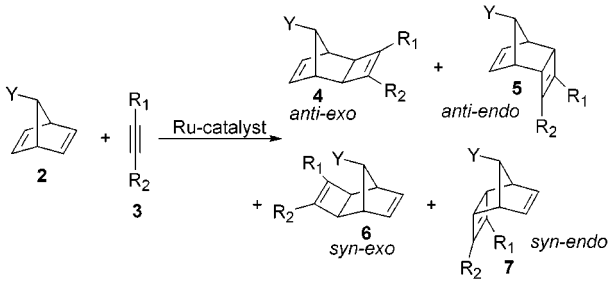


Figure 1.

our initial study because the rate of the cycloaddition in this case would have been governed by not only the electronic effects but also the steric effects of the X substituent. To study the electronic effects of the alkene component in the cycloaddition without taking steric effects into account, 7-substituted norbornadienes (**2**) were chosen for our initial study. 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.[12] In other words, as the electronegativity of the Y substituent increases the *anti*-π bond becomes more electron deficient.

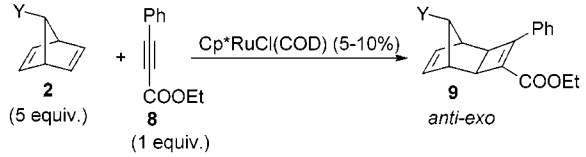
Although four different [2 + 2] cycloadducts are theoretically possible in the cycloaddition between a 7-substituted norbornadiene and an alkyne (Scheme 1), we anticipated that

Scheme 1. Possible Cycloadducts



the *anti-exo* cycloadduct would be produced preferentially. On the basis of our work and others,[6d,g] Ru-catalyzed [2 + 2] cycloaddition of norbornenes with alkynes produced only *exo* cycloadducts. As the *exo* face of the *syn*-π bond is sterically shielded by the Y substituent, 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**[13] with alkyne **8**[14] 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).[15]

Table 1. Ruthenium-Catalyzed [2 + 2] Cycloadditions of Some 7-Substituted Norbornadienes at Different Conditions



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

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

During our study on the regioselectivity of the Ru-catalyzed [2 + 2] cycloadditions between an unsymmetrical alkene and an unsymmetrical alkyne (Scheme 2),[6g] we

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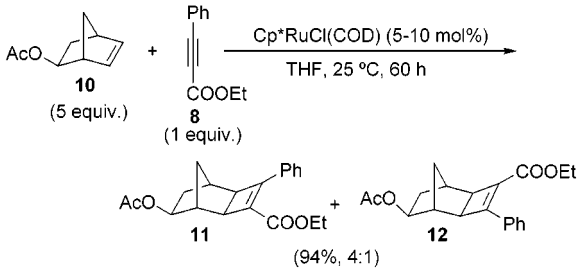
(12) (a) Mazzocchi, P. H.; Stahly, J. D.; Rondan, N. G.; Domelsmith, L. N.; Rozeboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482. (b) Lautens, M.; Tam, W.; Edwards, L. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2143.

(13) 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.

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

(15) No other regio- and stereoisomers were detected in the ^{1}H NMR spectra of the crude cycloaddition products. The regio- and stereochemistry of the cycloadducts were determined by various NMR techniques (NOE and GOESY experiments).

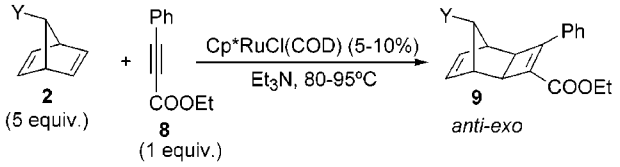
Scheme 2. Ru-Catalyzed [2 + 2] Cycloaddition of 2-Substituted Norbornene **10** with Alkyne **8**



noticed that the cycloadditions usually occur at room temperature. But when 7-OAc-norbornadiene **2a** (Y = OAc) was treated with alkyne **8** in the presence of 5−10 mol % of Cp*RuCl(COD)[16] 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_3N 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). Thus, 7-substituted norbornadiene **2a** is much less reactive than 2-substituted norbornene **10** in the Ru-catalyzed [2 + 2] cycloaddition with alkyne **8**. 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**−**2f**, 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**−**2f** 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-OAc norbornadiene **2a** with other 7-substituted norbornadienes **2b**−**2f** were carried out. A typical competition experiment employed 4 equiv of equimolar amounts of 7-OAc norbornadiene **2a** (a known concentration of stock solution of **2a** was prepared) and 7-OTBS norbornadiene **2b** with 1 equiv of alkyne **8** in the presence of 5 mol % of Cp*RuCl(COD) in Et_3N (large excess of the norbornadienes were used in order to approach pseudo-first-order conditions).[12b] The reactivity of each 7-substituted norbornadiene was assessed by evaluation of the product ratio by capillary gas chromatography.[17] 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, replacing the OAc group 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 molar ratio of **2a**:**2d** = 2:1 instead of 1:1, since norbornadiene contains two equivalent reactive double bonds). More interestingly, when Y = alkyl or aryl groups, the reactivity of the 7-substituted norbornadienes increases 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.

Table 2. Ru-Catalyzed [2 + 2] Cycloadditions of 7-Substituted Norbornadienes



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 3−5 runs.

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** indicate that electron-deficient alkenes react slower than electron-rich alkenes.

In conclusion, we have demonstrated the first study on the reactivity of the alkene component in ruthenium-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne. We have found that 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 component decreases dramatically as the alkene becomes more electron deficient. Further investigations on the reactivity of the alkene component with other alkenes such as **1** (Figure 1, in this case the rate of the cycloadditions will be governed by not only the electronic effects but also the steric effects of the

(16) 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.

(17) 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, an 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.

X substituent) and the study of the reactivity of the alkyne component in Ru-catalyzed [2 + 2] cycloadditions as well as investigations on an intramolecular variant of the cycloaddition and its application in the construction of spirocyclic frameworks are ongoing in our laboratory.

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Supporting Information Available: Experimental procedures, compound characterization data, and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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