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Reactivity of the alkene component in the ruthenium-catalyzed [2+2] cycloaddition between an alkene and an alkyne. Part 2[†]

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Abstract—Ruthenium-catalyzed [2+2] cycloadditions of 2,3-disubstituted norbornadienes and 2-substituted norbornadienes with an alkyne were found to be highly chemo- and stereoselective with moderate level of regioselectivities and only small rate differences were observed with different substituents on the norbornadiene. © 2002 Elsevier Science Ltd. All rights reserved.

The [2+2] cycloaddition of an alkene with an alkyne represents an important strategy for the synthesis of cyclobutene derivatives.[2] This process is thermally forbidden by the Woodward–Hoffmann rules.[3] However, it can be achieved by photochemical methods,[4] by thermal reactions via biradical intermediates,[5] and by the use of Lewis acid catalysts.[6,7] To date, very few papers have addressed the transition metal catalyzed [2+2] cycloadditions of alkenes with alkynes.[1,8–11]

In order to effectively utilize Ru-catalyzed [2+2] cycloadditions a better understanding of the mechanism involved must be established. Examining the reactivity of both reaction components and the stereoelectronic environment involved are essential for the design of more active catalysts. 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. We have recently reported the study of the reactivity of the alkene component in the Ru-catalyzed [2+2] cycloaddition between an alkene and an alkyne with 7-substituent norbornadienes.[1] We found that the rate of Ru-catalyzed [2+2] cycloadditions of different 7-substituted norbornadienes with alkyne decreases dramatically as the alkene component becomes more electron deficient. In this paper, we report our initial results of the Ru-catalyzed [2+2] cycloadditions between 2,3-disubstituted norbornadienes and 2-substituted norbornadienes with alkyne **6**. There are several questions about the cycloaddition that we would like to address: (i) the chemoselectivity (the two different double bonds of substituted norbornadienes); (ii) the stereoselectivity (*exo* versus *endo* cycloadducts); (iii) the regioselectivity (for unsymmetrical 2-substituted norbornadienes **12**-**16**); and (iv) the relative reactivity, of different 2,3-disubstituted norbornadienes and 2-substituted norbornadienes.

Only very few examples of the study of chemo- and stereoselectivity of transition metal-catalyzed cycloadditions of substituted norbornadienes can be found in the literature, and in all cases, the only substituted norbornadiene that has been used in these studies was the 2,3-dicarbomethoxynorbornadiene **2**. For example, Pd-catalyzed [3+2] cycloaddition of palladium–trimethylenemethane (Pd–TMM) complex with **2** occurs exclusively on the electron-deficient, tetrasubstituted double bond (with stereoselectivity *exo*/*endo* = 80:20).[12] On the other hand, the opposite chemoselectivity was observed in the Co-catalyzed Pauson–Khand [2+2+1] cycloaddition of propyne and **2**,[13] in which the cycloaddition occurred exclusively on the less substituted, less electron-deficient double bond. To the best of our knowledge, no systematic study on the chemo-, stereo- and regioselectivity of Ru-catalyzed [2+2] cycloadditions of substituted norbornadienes has been reported in the literature.

In order to carry out this study, 2,3-disubstituted norbornadienes **2**–**5** and 2-substituted norbornadienes **12**–

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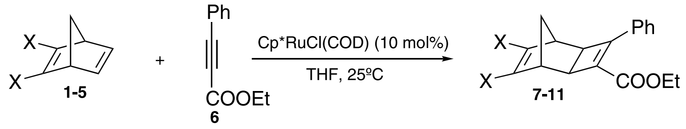
16 were prepared using the method that we recently developed,[15] and their Ru-catalyzed [2+2] cycloadditions with alkyne **6** were studied (Tables 1 and 2). The cycloadditions of 2,3-disubstituted norbornadienes **2**–**5** (Table 1) and 2-substituted norbornadienes **12**–**16** (Table 2) were found to be highly chemo- and stereoselective, giving single chemo- and stereoisomers in excellent yields. In all cases, cycloadditions only occur on the less substituted double bond of the substituted norbornadienes, regardless of the nature of the X substituent (whether it is electron-withdrawing substituents X = ester or Br, or silyl substituents X = TMS or TBS, or an alkyl group X = ^{n}hexyl) and only *exo* cycloadducts were formed. No other isomeric cycloadducts were detected by 400 MHz ^{1}H NMR in the crude reaction mixtures. In case of unsymmetrical 2-substituted norbornadienes **12**–**16**, two different regioisomers are possible. The substituent X on the norbornadienes (**12**–**16**, Table 2) can either end up *syn* (**17a**–**21a**) or *anti* (**17b**–**21b**) to the COOEt group of the alkyne. Moderate level of regioselectivities was observed with different X substituent on the norbornadiene and the highest regioselectivity was observed with X = OSiMe$_3$ (80:20). In all cases, the major regioisomers were found to have the X substituent *syn* to the COOEt group of the alkyne (**17a**–**21a**). The regiochemistry of the cycloadducts was determined by NMR techniques (COSY, HSQC, HMBC and NOESY) or chemical transformation to known cycloadducts that we have previously synthesized.[11,14]

The excellent chemoselectivities of the cycloadditions of 2,3-disubstituted norbornadienes and 2-substituted norbornadienes provided important information on the mechanism of the Ru-catalyzed [2+2] cycloadditions. A simplified possible mechanism is shown in Scheme 1. After dissociation of the cyclooctadiene (COD) ligand, the active Ru-catalyst (Cp*RuCl) would then associate

Table 1. Ru-catalyzed [2+2] cycloaddition of 2,3-disubstituted norbornadienes



Entry	Norbornadiene	X	Cycloadduct	Yield[a] (%)	Chemoselectivity[b,c]	Stereoselectivity[c,d]	Relative rate[e]
1	**2**	COOMe	**8**	88	100:0	100:0	1
2	**3**	SiMe$_3$	**9**	96	100:0	100:0	1.9
3	**4**	Br	**10**	93	100:0	100:0	2.3
4	**1**	H	**7**	80	n/a	100:0	2.3
5	**5**	^{n}Hexyl	**11**	92	100:0	100:0	2.5

[a] Isolated yields after column chromatography.

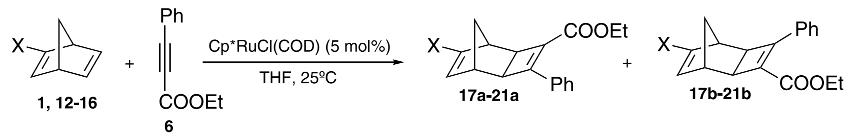
[b] Cycloadditions only occur on the less substituted double bond of the substituted norbornadienes, regardless of the nature of the X substituent.

[c] No other isomeric cycloadducts were detected by 400 MHz NMR in the crude reaction mixtures.

[d] Only *exo* isomers were formed.

[e] Measured from competition experiments, see text. The number indicated is the average of 4–6 runs.

Table 2. Ru-catalyzed [2+2] cycloaddition of 2-substituted norbornadienes



Entry	Norbornadiene	X	Cycloadducts	Yield[a] (%)	Chemoselectivity[b,c]	Stereoselectivity[c,d]	Regioselectivity (**a**:**b**)[e]	Relative rate[f]
1	**12**	COOEt	**17**	95	100:0	100:0	72:28	1
2	**1**	H	**7**	80	n/a	100:0	Na	2.1
3	**13**	SiMe$_2{}^t$Bu	**18**	98	100:0	100:0	52:48	2.2
4	**14**	^{n}Hexyl	**19**	94	100:0	100:0	57:43	2.6
5	**15**	Br	**20**	96	100:0	100:0	67:33	3.0
6	**16**	OSiMe$_3$	**21**	91[g]	100:0	100:0	80:20	7.5

[a] Isolated yields after column chromatography.

[b] Cycloadditions only occur on the less substituted double bond of the substituted norbornadienes, regardless of the nature of the X substituent.

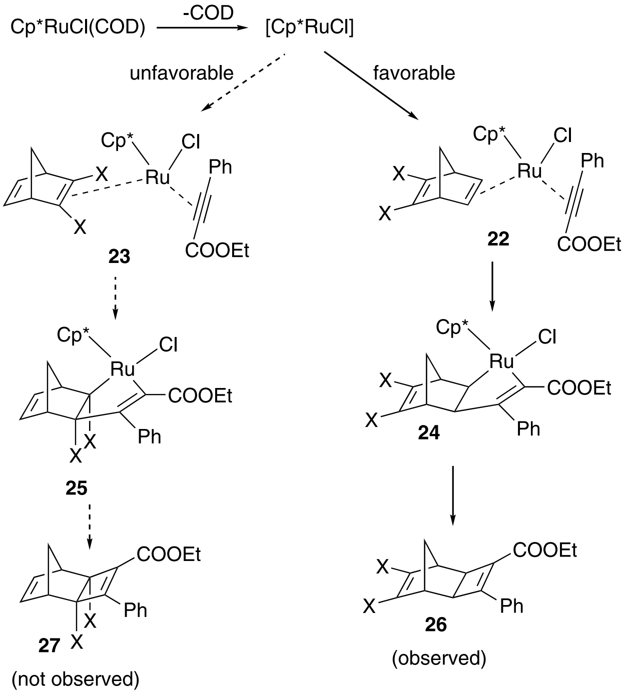
[c] No other isomeric cycloadducts were detected by 400 MHz NMR in the crude reaction mixtures.

[d] Only *exo* isomers were formed.

[e] Ratios measured by GC and/or by 400 MHz ^{1}H NMR.

[f] Measured from competition experiments, see text. The number indicated is the average of 4–6 runs.

[g] The corresponding ketone was isolated instead of the silylvinyl ether after acid hydrolysis.



Scheme 1. Possible mechanism.

to the alkene and the alkyne components. The [Cp*RuCl] could either coordinate to the less substituted double bond of the norbornadiene to form π-complex **22**, or coordinate to the more substituted double bond of the norbornadiene to form π-complex **23**. Oxidative cyclization of the π-complex **22** would lead to the formation of the metallacyclopentane **24** which upon reductive elimination would give the cycloadduct **26**. On the other hand, oxidative cyclization of the π-complex **23** would lead to the formation of the metallacyclopentane **25** which upon reductive elimination would give the cycloadduct **27**. Regardless of the electronic nature of the substituent X, in all cases that we examined, the cycloadditions were completely chemoselective and only cycloadducts **26** were formed. This observation may provide two important information about the mechanism of the Ru-catalzyed [2+2] cycloadditions: (i) the π-complexation of [Cp*RuCl] to the norbornadienes is governed mainly by steric effect of the X substituent but not by electronic effect; and therefore π-complex **22** was formed instead of the π-complex **23**; (ii) the metallacyclopentane **25** with the X substituents close to the Ru has a much higher energy than the metallacyclopentane **24** and is unfavorable to form.[16]

We have previously shown that Ru-catalyzed [2+2] cycloadditions of 7-substituted norbornadienes with alkyne **6** required a high reaction temperature (80–95°C),[1] however, all the Ru-catalyzed [2+2] cycloadditions of 2,3-disubstituted norbornadienes and 2-substituted norbornadienes with alkyne **6** occur readily at *room temperature*.[17] In order to determine the relative rate of the cycloadditions with different substituted norbornadienes, competition experiments between different substituted norbornadienes were carried out. A typical competition experiment employed 4 equiv. of equimolar amount of two different norbornadienes and 1 equiv. of alkyne **6** in the presence of 10 mol% of Cp*RuCl(COD) in THF (large excess of norbornadienes were used in order to approach pseudo-first-order conditions).[18] The reactivity of each substituted norbornadiene was assessed by evaluation of the product ratio by capillary gas chromatography.[19] Unlike the reactivity of 7-substituted norbornadienes,[1] in which we observed that electron-deficient double bonds react much slower than electron-rich double bond (7-OAc-norbornadiene reacts 53 times slower than 7-Ph-norbornadiene), as shown in Tables 1 and 2, the difference in the relative rate of the Ru-catalyzed [2+2] cycloadditions of 2,3-disubstituted norbornadienes and 2-substituted norbornadienes with alkyne **6** is very small with different X substituents. The greatest rate difference (7.5 times) was observed between **16** (X = $OSiMe_3$) with **12** (X = COOEt).

In conclusion, we have studied the Ru-catalyzed [2+2] cycloadditions of 2,3-disubstituted norbornadienes and 2-substituted norbornadienes with alkyne **6**. The cycloadditions occurred with excellent levels of chemo- and stereoselectivities, and moderate levels of regioselectivities were observed. Only small rate differences in the cycloaddition were observed with different 2,3-disubstituted norbornadienes and 2-substituted norbornadienes. Further investigations in this area, including the study of the reactivity of the alkyne component in the Ru-catalyzed [2+2] cycloadditions, MO calculations of possible metallocycles intermediates involved in the cycloaddition, as well as the intramolecular variant of the cycloaddition, are ongoing in our laboratory.

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16. Molecular modeling studies on the relative stability/energy of the π-complex **22** versus **23**, and the metallacyclopentenes **24** versus **25** are ongoing in our laboratory.
17. The higher strain energies in the bicyclic framework of 2,3-disubstituted norbornadienes and 2-substituted norbornadienes compared to 7-substituted norbornadienes may account for the higher reactivity and therefore lower possible reaction temperature of these 2,3-disubstituted norbornadienes and 2-substituted norbornadienes. Further investigations are required to verify this point.
18. For examples of the use of competition experiments to determine relative rates of different substrates in transition metal-catalyzed cycloadditions, see: (a) Lautens, M.; Edwards, L. G.; Tam, W.; Lough, A. J. *J*. *Am*. *Chem*. *Soc*. **1995**, *117*, 10276; (b) Gugelchuk, M. M.; Doherty-Kirby, A. L. *J*. *Org*. *Chem*. **1996**, *61*, 3490. See also Ref. 1.
19. 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.