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

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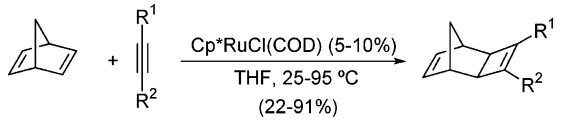

Relative rate of cycloaddition (R^1=Ph):

R^2 = Cl > Br > SO_2Ph > COOEt > COMe > COOH >> CH_2OH > CH_2OTBS > CH_3

The ruthenium-catalyzed [2 + 2] cycloadditions of norbornadiene with a variety of alkynes have been investigated. Electronic effect of the alkyne component has shown to play an important role on the rate of the cycloaddition, and the reactivity of the alkyne component increases dramatically as the alkyne becomes more electron deficient. Increase in the steric bulk of the alkyne component decreases the reactivity of the alkyne component. It was also found that chelation effect of propargylic alcohols greatly enhanced the reactivity of the alkyne component in the ruthenium-catalyzed [2 + 2] cycloadditions.

Cycloaddition reactions are among the most powerful and most frequently used methods for the construction of rings.[1] We have studied various types of cycloaddition reactions of bicyclic alkenes and are especially interested in those catalyzed by transition metals.[2,3] Transition-metal-catalyzed cycloadditions have demonstrated their usefulness in the formation of rings and complex molecules.[4] The use of transition metal catalysts provides new opportunities for highly selective cycloaddition reactions since complexation of the metal to an unactivated alkene, alkyne, or diene significantly modifies the reactivity of this moiety, opening the way for enhanced reactivity and novel reactions. Recent developments in transition-metal-catalyzed [2 + 2 + 1],[5] [4 + 2],[6] [5 + 2],[7] [4 + 4],[8] and [6 + 2][9] cycloaddition reactions have provided efficient methods for the construction of five- to eight-membered rings. We and others have studied various aspects of transition-metal-catalyzed [2 + 2] cycloadditions of an alkene and an alkyne for the synthesis of cyclobutenes, including development of novel catalysts, study of the intramolecular variant of the reaction, investigation of the chemo- and regioselectivity of unsymmetrical substrates, and asymmetric induction studies using chiral auxiliaries on the alkyne component.[3,10−12] 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. 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 our studies on the reactivity of the alkene component in ruthenium-catalyzed [2 + 2] cycloadditions

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(2) For our recent contributions on non-metal-catalyzed cycloaddition reactions of bicyclic alkenes, see: (a) Yip, C.; Handerson, S.; Jordan, R.; Tam, W. *Org. Lett.* **1999**, *1*, 791. (b) Tranmer, G. K.; Keech, P.; Tam, W. *Chem. Commun.* **2000**, 863. (c) Mayo, P.; Hecnar, T.; Tam, W. *Tetrahedron* **2001**, *57*, 5931. (d) Yip, C.; Handerson, S.; Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 276. (e) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113. (f) Tranmer, G. K.; Tam, W. *Org. Lett.* **2002**, *4*, 4101.

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SCHEME 1. Reactivity of the Alkene Component

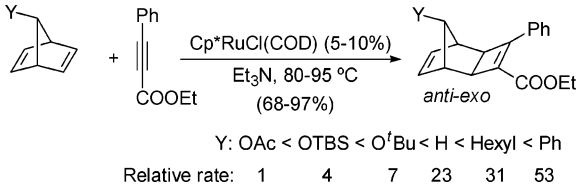
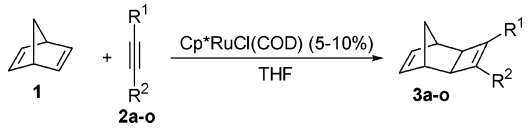


TABLE 1. Ru-Catalyzed [2 + 2] Cycloadditions of Norbornadiene 1 with a Variety of Alkynes



entry	R^1	R^2	cycloadduct	temp (°C)	time (h)	yield (%)[a]
1	Ph	COOH	**3a**	60	80	86
2	Ph	COMe	**3b**	60	48	90
3	Ph	COOEt	**3c**	60	48	90
4	Ph	SO_2Ph	**3d**	95	80	91
5	Ph	Br	**3e**	60	48	83
6	Ph	Cl	**3f**	60	48	82
7	Ph	CH_3	**3g**	95	90	22[b]
8	Ph	CH_2OTBS	**3h**	95	90	34[b]
9	Ph	CH_2OH	**3i**	95	80	48[b]
10	COOEt	^{n}Bu	**3j**	60	70	89
11	COOEt	Cy	**3k**	95	90	88
12	COOEt	^{t}Bu	**3l**	95	144	0[b]
13	COOEt	CH_2OH	**3m**	65	48	88
14	COOEt	CHMeOH	**3n**	25	72	90
15	COOEt	CMe_2OH	**3o**	65	48	85

[a] Yield of isolated cycloadducts after column chromatography. [b] 45−88% of the starting alkynes were recovered.

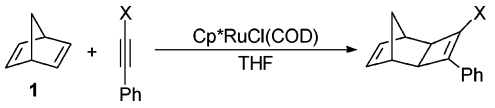
between an alkene and an alkyne.[3f] Our results indicated that reactivity of the alkene component decreases dramatically as the alkene becomes more electron deficient (Scheme 1). To the best of our knowledge, no study on the reactivity of the alkyne component has been reported in the literature. In this paper, we report our results of the reactivity of the alkyne component in ruthenium-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne.

The variety of alkynes employed thus far in the Ru-catalyzed [2 + 2] cycloadditions is very limited, and only substituents with primary alkyl groups, aryl groups, esters, and amides have been used. To expand the scope of the cycloaddition, we investigated the Ru-catalyzed [2 + 2] cycloadditions of norbornadiene **1** with a variety of alkynes, which are shown in Table 1.

To our delight, alkynes attached to various functional groups, such as carboxylic acid (Table 1, entry 1), ketone (entry 2), sulfone (entry 4), halides (entries 5 and 6), and propargylic alcohols (entries 9, 13−15), are all compatible with the Ru catalyst, giving the corresponding [2 + 2] cycloadducts as single stereoisomers (*exo* cycloadducts) in moderate to good yields.[13] It can be seen from Table 1 that alkynes attached to an electron-withdrawing group are more reactive than those without an electron-withdrawing group (compare entries 1−6 with entries 7−9). Complete consumption of the electron-deficient alkynes (**2a**−**2f**) was observed within 48−80 h when reacted with

(13) For determination of *exo* and *endo* stereochemistry of [2 + 2] cycloadducts, see our previous work in ref 3.

TABLE 2. Electronic Effect on the Relative Rate of Cycloaddition



entry	alkyne	X	relative rate[a]
1	**2g**	Me	0.16
2	**2h**	CH_2OTBS	1
3	**2i**	CH_2OH	4
4	**2a**−**2f**	Cl, Br, SO_2Ph, COOEt, COMe, COOH	>100

[a] Measured from competition experiments; see text. The number indicated is the average number from 3 to 5 runs.

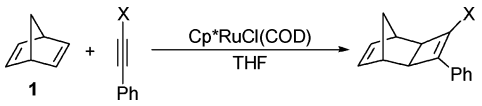
norbornadiene **1** in the presence of the Ru catalyst (Cp*RuCl(COD)), giving the corresponding [2 + 2] cycloadducts in good yields. On the other hand, alkynes without an electron-withdrawing group are less reactive, and the reactions were incomplete even after prolong heating at a higher temperature (entries 7−9). Increase in the steric bulk of the substituent attached to the alkyne also decreases the reactivity of the alkyne in the ruthenium-catalyzed [2 + 2] cycloadditions (entries 10−12). The primary alkyl-substituted alkyne **2j** was completely consumed within 70 h when reacted with norbornadiene in the presence of the catalyst at 60 °C, whereas the secondary alkyl-substituted alkyne **2k** required a higher temperature (95 °C) and a longer reaction time to go to completion (entries 10 and 11). The most sterically hindered tertiary alkyl-substituted alkyne **2l** was completely inactive in the ruthenium-catalyzed [2 + 2] cycloaddition with norbornadiene (entry 12). Another interesting observation was found when comparing alkyl-substituted alkynes **2j**−**2l** with propargylic alcohols **2m**−**2o**. The propargylic alcohols seem to be more reactive than the alkyl-substituted alkynes with similar steric environment. For example, the cycloaddition of the primary propargylic alcohol **2m** was completed in 48 h, whereas the primary alkyl-substituted alkyne **2j** required a longer reaction time. The tertiary alkyl-substituted alkyne **2l** was completely inactive, but the tertiary propargylic alcohol **2o** produced the cycloadduct in good yield in 48 h.

To confirm these qualitative observations and to estimate the order of reactivity of different alkynes in the ruthenium-catalyzed [2 + 2] cycloadditions, the relative rate of the ruthenium-catalyzed [2 + 2] cycloadditions of different alkynes with norbornadiene was measured by competition experiments between different alkynes.[14] A typical competition experiment employed 4−5 equiv of equimolar amounts of two different alkynes with 1 equiv of norbornadiene **1** in the presence of 5 mol % of Cp*RuCl(COD) in THF (large excesses of the alkynes was used in order to approach pseudo-first-order conditions).[14] The reactivity of each alkyne was assessed by evaluation of the product ratio by capillary gas chromatography.[15] The results of these reactivity studies are shown in Tables 2−4.

(14) For an example of estimating the reactivity of reaction partners in metal-catalyzed cycloaddition reactions by competition experiments, see: Lautens, M.; Tam, W.; Edwards, L. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2143. See also ref 3f.

(15) 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.

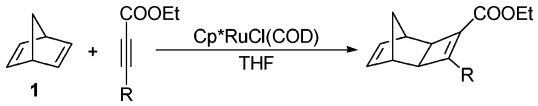
TABLE 3. Relative Rate of Cycloaddition with Electron-Deficient Alkynes



entry	alkyne	X	relative rate[a]
1	**2a**	COOH	1
2	**2b**	COMe	1.6
3	**2c**	COOEt	1.8
4	**2d**	SO_2Ph	2.2
5	**2e**	Br	3.6
6	**2f**	Cl	16.2

[a] Measured from competition experiments; see text. The number indicated is the average number from 3 to 5 runs.

TABLE 4. Steric and Chelation Effect



entry	alkyne	R	relative rate[a]
1	**2c**	Ph	30.5
2	**2j**	^{n}Bu	7.2
3	**2k**	Cy	1
4	**2l**	^{t}Bu	n/a[b]
5	**2m**	CH_2OH	397
6	**2n**	CHMeOH	171
7	**2o**	CMe_2OH	6.2

[a] Measured from competition experiments; see text. The number indicated is the average number from 3 to 5 runs. [b] No reaction was observed with alkyne **2l**.

Electron-deficient alkynes, such as those attached to halides, a sulfone, an ester, a ketone, and a carboxylic acid (Table 2, entry 4), are much more reactive than unactivated alkynes (entries 1−3). Comparing the reactivity of alkynyl bromide **2e** with that of alkyne **2g** (Br and Me have almost identical van der Waal radii), it is clear that, under similar steric environment, electron-deficient alkynes are much more reactive. It is also interesting to note that propargylic alcohol **2i** reacts 4 times faster than the propargylic silyl ether **2h** and reacts 25 times faster than alkyne **2g**. It is possibly due to the chelation of the propargylic OH group with the Ru that stabilizes some of the intermediates along the catalytic pathway (vide infra, see Table 4 for further investigation of this chelation effect).

The relative rate of cycloaddition with various electron-deficient alkynes is shown in Table 3. Among all the electron-deficient alkynes tested, alkyne **2a** (X = COOH) has the lowest reactivity. The reactivity increases slightly with alkynyl ketone **2b**, then with alkynyl ester **2c** and alkynyl sulfone **2d**. Alkynyl halides were found to be the most reactive, with alkynyl bromide **2e** reacting 3.6 times faster than alkyne **2a** and alkynyl chloride **2f** reacting 16.2 times faster than alkyne **2a**.

To investigate the steric effect of the alkyne component, the relative rates of cycloaddition of alkynes **2c**,**2j**−**2l** were compared (Table 4, entries 1−4). In general, the greater the steric hindrance around the alkyne component, the lower the reactivity of the alkyne. For example, an alkyne with a tertiary alkyl group (^{t}Bu, entry 4) was inactive in the cycloaddition, and a secondary alkyl group (cyclohexyl, entry 3) reacts 7.2 times slower than a primary alkyl group (^{n}Bu, entry 2). Alkyne with an aromatic group (Ph, entry 1) is more reactive than aliphatic alkyl groups (entries 2−4). Similar trend is observed with propargylic alcohols (entries 5−7). The primary propargylic alcohol **2m** reacts the fastest, then the secondary propargylic alcohol **2n**, and the tertiary propargylic alcohol **2o** reacts the slowest. It is interesting to compare the reactivity of the alkynes containing alkyl groups with those containing propargylic alcohol groups. For example, alkyne with a primary alkyl group **2j** reacts 55 times slower than the corresponding primary propargylic alcohol **2m** (compare entry 2 with entry 5). Similarly, alkyne with a secondary alkyl group **2k** reacts 171 times slower than the corresponding secondary propargylic alcohol **2n** (compare entry 3 with entry 6). This rate enhancement of propargylic alcohols is possibly due to the chelation of the propargylic OH group with the Ru that stabilizes some of the intermediates along the catalytic pathway.

In conclusion, we have studied the reactivity of the alkyne component in ruthenium-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne. We have greatly expanded the variety of alkynes in the Ru-catalyzed [2 + 2] cycloadditions and shown that alkynes attached to various functional groups, such as carboxylic acid, ketone, sulfone, halides, and propargylic alcohols, are all compatible with the Ru catalyst, giving the corresponding [2 + 2] cycloadducts as single stereoisomers (*exo* cycloadducts) in moderate to good yields. The results of our study on the relative rate of various alkynes in Ru-catalyzed [2 + 2] cycloadditions with norbornadiene indicated that reactivity of the alkyne component increases dramatically as the alkyne becomes more electron deficient. We have also shown that increase in steric bulk of the alkyne decreases the reactivity of the alkyne component in the Ru-catalyzed [2 + 2] cycloaddition, and that addition of a propargylic alcohol group greatly increases the reactivity of the alkyne component. Further investigations on the use of the cycloadducts for the synthesis of more complex polycyclic natural products are currently in progress in our laboratory.

Experimental Section[16]

General Procedure for the Ru-Catalyzed [2 + 2] Cycloadditions. A mixture of norbornadiene **1** (2.5−5 equiv), alkyne (1 equiv), and THF 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, 5−10 mol %) under nitrogen. The reaction mixture was stirred in the dark at 25−95 °C for 48−90 h. The crude product was purified by column chromatography (hexanes or ethyl acetate/hexanes mixture) to give the cycloadduct.

4-Phenyltricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3-carboxylic acid (3a, Table 1, entry 1). Following the above general procedure, with norbornadiene **1** (75.6 mg, 0.820 mmol), acetylene **2a** (29.1 mg, 0.199 mmol), THF (0.35 mL), and Cp*RuCl(COD) (4.5 mg, 0.012 mmol). The reaction mixture was stirred in the dark at 60 °C for 80 h. The crude product was purified by column chromatography (EtOAc:hexanes = 1:4, 2:3) to provide cycloadduct **3a** (40.7 mg, 0.171 mmol, 86%) as a white solid: R_f 0.56 (EtOAc:hexanes = 2:3); mp 178.5−179.5 °C; GC (HP-1 column) retention time = 15.7 min; IR (neat) ν 2305−3100 (br s), 3058 (s), 2987 (s), 2941 (s), 1673 (s), 1610 (s), 1570 (w), 1491 (m), 1448 (w), 1423 (w), 1404 (m), 1317 (m), 1296 (m), 1266 (s) 1235 (m), 1046 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.19 (w br s, 1H), 8.09

(16) General methods were described in previous publications. See refs 2d and 3f.

(m, 2H), 7.44 (m, 3H), 6.25 (m_{ABX}, 2H), 2.82 (br s, 1H), 2.75 (br s, 1H), 2.74 (d, 1H, $J = 3.7$ Hz), 2.65 (d, 1H, $J = 3.7$ Hz), 1.40 (q_{AB}, 2H, $^2J = 9.4$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 160.7, 136.8, 135.4, 132.2, 130.5, 129.8, 129.2, 128.5, 43.4, 42.6, 39.8, 39.2, 38.9. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.29; H, 6.12.

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and ^{1}H and ^{13}C 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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