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Study on the Reactivity of Oxabicyclic Alkenes in Ruthenium-Catalyzed [2+2] Cycloadditions

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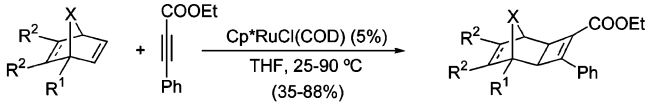

General trend of the relative rate of cycloaddition:

Oxanorbornadienes (X = O) > Norbornadiene (X = CH_2) > Azanorbornadienes (X = N-Boc) > Norbornene (X = CH_2)

The ruthenium-catalyzed [2+2] cycloadditions of various bicyclic alkenes with an alkyne have been investigated. The presence of the oxygen in the bridgehead of the bicyclic alkene significantly enhanced the rate of the ruthenium-catalyzed [2+2] cycloadditions. The presence of a C1-substutuent on the oxanorbornadiene decreased the rate of the cycloaddition and electron-withdrawing C1-substutuents were found to be more reactive than electron-donating C1-substutuents in the Ru-catalyzed [2+2] cycloaddition. The nature of the substituent on the benzene ring of oxabenzonorbornadienes showed little effect on the rate of the cycloaddition.

Typically cycloaddition reactions can be carried out by using heat, light, or Lewis acids.[1] However, these promoters usually require the presence of polar functional groups in the substrates, and extreme conditions (high temperature and high pressure) are usually required for unactivated substrates. Transition metal catalysts provide a new opportunity to promote cycloadditions of unactivated substrates and cycloadditions that are theoretically forbidden or difficult to achieve. We have studied various types of cycloaddition reactions of bicyclic alkenes, and are especially interested in those catalyzed by transition metals.[2−4] Unlike many other metal-catalyzed cycloadditions for the formation of 5- to 8-membered rings (via [2+2+1], [4+2], [5+2], [6+2], and [4+4] cycloadditions) that have been studied extensively,[5−9] there are relatively few studies on metal-catalyzed [2+2] cycloadditions for the formation of 4-membered rings. Various aspects of transition metal-catalyzed [2+2] cycloadditions of an alkene and an alkyne for the synthesis of cyclobutenes have been studied by us and others, including development of novel catalysts, study of the intramolecular variant of the reaction, investigation of the chemo- and regioselectivity of unsym-

(1) (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, Chapters 1−9. (b) *Advances in Cycloaddition*; JAI Press: Greenwich, CT, 1988−1999; Vols. 1−6.

(2) For our recent contibutions on non-metal-catalyzed cycloaddition reactions of bicyclic alkenes, see: (a) Yip, C.; Handerson, S.; Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 276. (b) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113. (c) Tranmer, G. K.; Tam, W. *Org. Lett.* **2002**, *4*, 4101.

(3) For our recent contibutions on metal-catalyzed cycloaddition reactions of bicyclic alkenes, see: (a) Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031. (b) Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367. (c) Jordan, R. W.; Tam, W. *Tetrahedron Lett.* **2002**, *43*, 6051. (d) Villeneuve, K.; Jordan, R. W.; Tam, W. *Synlett* **2003**, 2123. (e) Villeneuve, K.; Tam, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 610. (f) Jordan, R. W.; Khoury, P. K.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2004**, *69*, 8467. (g) Villeneuve, K.; Riddell, N.; Jordan, R. W.; Tsui, G. C.; Tam, W. *Org. Lett.* **2004**, *6*, 4543. (h) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681. (i) Burton, R. R.; Tam, W. *Tetrahedron Lett.* **2006**, *47*, 7185. (j) Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843. (k) Riddell, N.; Tam, W. *J. Org. Chem.* **2006**, *71*, 1934. (l) Liu, P.; Jordan, R. W.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2006**, *71*, 3793. (m) Jordan, R. W.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2006**, *71*, 5830.

(4) For reviews on transition metal-catalyzed cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129.

(5) For recent reviews on transition metal-catalyzed [2+2+1] cycloadditions, see: (a) Pericas, M. A.; Balsells, J.; Castro, J.; Marchueta, I.; Moyano, A.; Riera, A.; Vazquez, J.; Verdaguer, X. *Pure Appl. Chem.* **2002**, *74*, 167. (b) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589.

(6) (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (b) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. (c) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. (d) Murakami, M.; Ubukata, M.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2248. (e) Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045. (f) Hilt, G.; Smolko, K. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2795. (g) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624.

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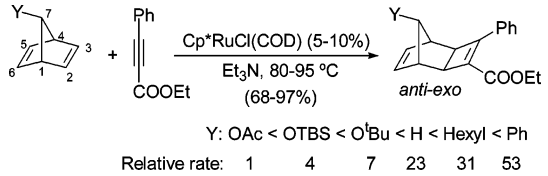
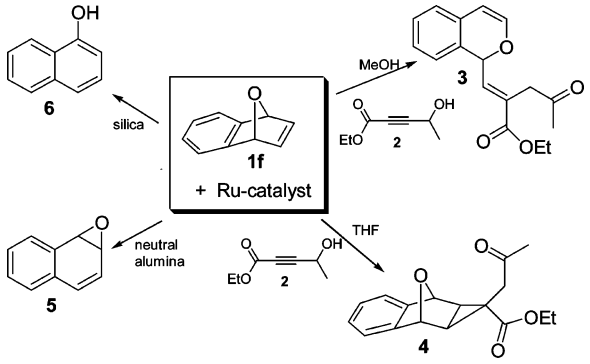
SCHEME 1. Reactivity of the Alkene Component



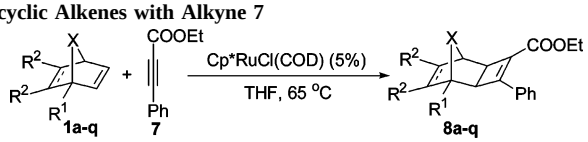
SCHEME 2. Ru-Catalyzed Reactions of Oxabenzonorbornadiene 1f

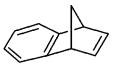
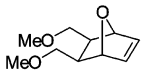
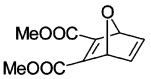
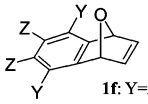
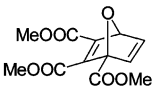
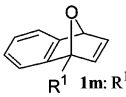
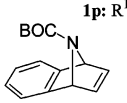


metrical substrates, and asymmetric induction studies with chiral auxiliaries on the alkyne component.[3,10−12] In order to understand the mechanism of the Ru-catalyzed [2+2] cycloadditions thoroughly so that one can design more active catalysts for the cycloadditions, studies on the reactivity of both the reaction partners are essential. Very little is known about 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 between a 7-substituted norbornadiene and an alkyne.[3f] Our results indicated that the reactivity of the alkene component decreases dramatically as the alkene becomes more electron deficient (Scheme 1). We have also examined different aspects of Ru-catalyzed reactions involving oxabenzonorbornadiene **1f**, and found that depending on the reaction conditions, different products (**3**−**6**) could be obtained (Scheme 2). For example, when oxabenzonorbornadiene **1f** is treated with the secondary propargylic alcohol **2** in the presence of the neutral Ru catalyst, Cp*Ru(COD)Cl, in MeOH or using a cationic Ru catalyst, isochromene **3** is formed.[13] On the other hand, if the same reaction between **1f** and **2** is carried out with Cp*Ru(COD)Cl in THF, cyclopropane **4** is produced.[14] In the absence of an alkyne, Cp*Ru(COD)Cl catalyzes the isomerization of **1f** to the corresponding naphthalene oxide **5** or naphthol **6**.[15] Since these types of Ru-catalyzed processes (Scheme 2) only occur on oxabicyclic alkenes but not on carbobicyclic alkenes (norbornadienes and norbornenes), we are interested in studying the effect of the oxygen at the bridgehead of bicyclic alkenes in Ru-catalyzed [2+2] cycloadditions. In this paper, we report our results of the reactivity of oxabicyclic alkenes in Ru-catalyzed [2+2] cycloadditions.

To investigate the reactivity of oxabicyclic alkenes in ruthenium-catalyzed [2+2] cycloadditions and compare their

TABLE 1. Ru-Catalyzed [2+2] Cycloadditions of a Variety of Bicyclic Alkenes with Alkyne 7



entry	bicyclic alkene	time (h)	yield (%)[a]
1	 **1a**	48	89
2	 **1b**	48	90
3	 **1c**	72	51
4	 **1d**	24	74
5	 **1e**	72	78
6	 **1f**: Y=Z=H	72	71
7	**1g:** Y=OMe, Z=H	24	63
8	**1h:** Y=Me, Z=H	48	79
9	**1i:** Y=H, Z=Br	20	68
10	**1j:** Y=H, Z=F	24	69
11	**1k:** Y=Z=F	72	45
12	 **1l**	120	57[b]
13	 **1m**: R[1]=C(O)Me	120	82[b]
14	**1n:** R[1]=COOMe	120	85[b]
15	**1o:** R[1]=Me	120	75[b]
16	**1p:** R[1]=CH$_2$OH	120	36[b,c]
17	 **1q**	48	88

[a] Yield of isolated cycloadducts after column chromatography. [b] Since alkenes **1***l*−**p** are unsymmetrical, two regioisomers were obtained in each case. In all cases, the major regioisomer is the one with the Ph group of the alkyne closer to the C1 substitutent. Different regioselectivity was observed for different C1-substituted alkenes: **1***l* (>99:1); **1m** (66:1); **1n** (76:1); **1o** (1:1); **1p** (8:1); see the Supporting Information for details. [c] Incompleted reaction, 60% of alkyne **7** was recovered.

(7) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976. (c) Trost, B. M.; Shen, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313. (d) Wender, P. A.; Williams, T. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4550.

(8) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815.

(9) (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrino, A.; Vagberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908.

(10) Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294.

(11) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580.

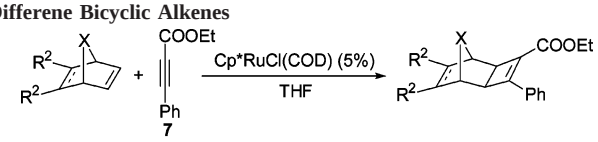
(12) (a) Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, *6*, 3706. (b) Chao, K. C.; Rayabarapu, D. K.; Wang, C.-C.; Cheng, C.-H. *J. Org. Chem.* **2001**, *66*, 8804.

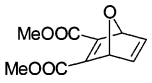
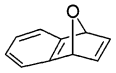
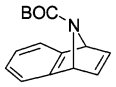
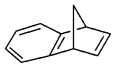
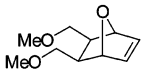
(13) Villeneuve, K.; Tam, W. *Eur. J. Org. Chem.* **2006**, 5499.

(14) Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843.

(15) Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, *128*, 3514.

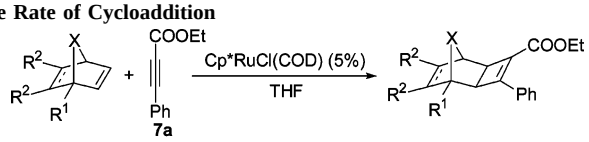
TABLE 2. Relative Rate of Ru-Catalyzed [2+2] Cycloadditions of Differene Bicyclic Alkenes

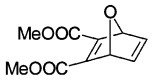
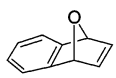
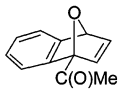
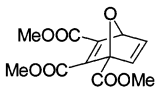
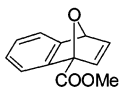
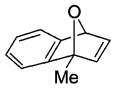
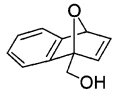


entry	bicyclic alkene		relative rate[a]
1		**1e**	162
2		**1f**	100
3		**1b**	13
4		**1q**	7.5
5		**1c**	7.2
6		**1d**	4
7		**1a**	1

[a] Measured from competition experiments, see text. The number indicated is the average number from 2−3 runs.

TABLE 3. Effect of a C1-Substitutent of Oxabicyclic Alkenes on the Rate of Cycloaddition



entry	bicyclic alkene		relative rate[a]
1		**1e**	135
2		**1f**	83
3		**1m**	48
4		**1l**	25
5		**1n**	17
6		**1o**	5
7		**1p**	1

[a] Measured from competition experiments, see text. The number indicated is the average number from 2−3 runs.

reactivities with those of other bicyclic alkenes, various [2+2] cycloadducts **8a**−**q** were synthesized by the ruthenium-catalyzed [2+2] cycloadditions (Table 1).

To our delight, ruthenium-catalyzed [2+2] cycloadditions of all the bicyclic alkenes occurred smoothly, giving the corresponding [2+2] cycloadducts as single stereoisomers (*exo* cycloadducts) in moderate to good yields.[16]

To study the reactivity of oxabicyclic alkenes in Ru-catalyzed [2+2] cycloadditions and compare their reactivities with other bicyclic alkenes, the relative rate of the ruthenium-catalyzed [2+2] cycloadditions of different bicyclic alkenes was measured by competition experiments. A typical competition experiment employed 4−5 equiv of equimolar amounts of two different bicyclic alkenes with 1 equiv of alkyne **7** in the presence of 5 mol % of Cp*RuCl(COD) in THF (large excesses of the alkynes were used in order to approach pseudo-first-order conditions).[17] The reactivity of each alkyne was assessed by evaluation of the product ratio by capillary gas chromatography.[18] The results of these reactivity studies are shown in Tables 2−4.

Several trends can be observed from the reactivity study of various symmetrical bicyclic alkenes (Table 2). First, norbornadiene derivatives (entries 1−5) are always more reactive than the norbornene derivatives (entries 6 and 7). One possible reason could be due to the fact that the strain energies of the bicyclic framework of norbornadiene derivatives are much higher than those of the norbornene derivatives,[19] and reacting with alkynes in the cycloaddition will relieve the ring strain of the highly strained norbornadiene framework. Second, the presence of an oxygen at the bridgehead of the bicyclic framework significantly increased the rate of the cycloadditions. For example, oxanorbornene **1d** reacts four times faster than norbornene **1a** (compare entries 6 and 7). This rate enhancement effect of the bridgehead oxygen is even more dramatic for norbornadiene derivatives (compare entries 1 and 2 with entries 3−5). One possible explanation is the oxygen at the bridgehead of the bicyclic framework is capable of coordinating with the Ru in some of the intermediates in the catalytic cycle, thus lowering the activation energy in some of the steps in the Ru-catalyzed cycloaddition. Finally, a diester-substituted oxanorbornadiene (**1e**) reacts faster that a benzo-substituted oxanorbornadiene (**1f**) (compare entries 1 and 2).

The relative rate of cycloaddition with various C1-substituted oxabicyclic alkenes is shown in Table 3. The addition of a C1 subtituent always lowers the reactivity of the bicyclic alkene regardless of the electronic nature of the C1 substituent (compare entries 1 and 2 with entries 3−7). This is likely due to the steric

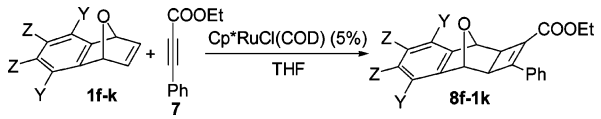
(16) For determination of *exo* and *endo* stereochemistry of [2+2] cycloadducts, see our previous work in ref 3.

(17) 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.

(18) 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.

(19) Khoury, P. K.; Goddard, J. D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103.

TABLE 4. Effect of Substituents on the Benzene Ring of Oxabenzonorbornadienes on the Rate of Cycloaddition



entry	bicyclic alkene	Y	Z	relative rate[a]
1	**1h**	Me	H	2.26
2	**1i**	H	Br	1.78
3	**1f**	H	H	1.15
4	**1k**	F	F	1.09
5	**1j**	H	F	1.01
6	**1g**	OMe	H	1.00

[a] Measured from competition experiments, see text. The number indicated is the average number from 2−3 runs.

effect of the C1 substituent as it is close to the reacting double bond and hinders the complexation of the double bond with the Ru catalyst. Increasing the electron-withdrawing power of the C1 substitutent of the oxabenzonorbornadiene increases the reactivity of the alkene component in the Ru-catalyzed [2+2] cycloadditions (compare entries 3, 5, and 6, reactivity of **1m**: C1 = C(O)Me > **1n**: C1 = COOMe > **1o**: C1 = Me). The exceptionally low reactivity of C1-substituted oxabenzonorbornadiene **1p** could be due to the fact that the bridgehead oxygen, the C1-primary alcohol, and the double bond of the bicyclic alkene could coordinate to the Ru at the same time. This would prevent coordination of the alkyne **7** to the Ru, which is required for the cycloaddition to occur. The last trend that can be observed in Table 3 is that a diester-substituted oxanorbornadiene is always more reactive than a benzo-substituted oxanorbornadiene (compare **1e** with **1f** and compare **1*l*** with **1n**).

The effect that the substituents on the benzene ring of oxabenzonorbornadienes have on the rate of Ru-catalyzed [2+2] cycloadditions with alkyne **7** is shown in Table 4. Unlike the dramatic rate difference observed in Tables 2 and 3, the addition of electronically different substitutents (electron-withdrawing or electron-donating groups) on the oxabenzonorbornadiene showed very little effect on the rate of the Ru-catalyzed [2+2] cycloadditions (Table 4). Oxabenzonorbornadiene **1h** (Y = Me, Z = H) is the most reactive oxabenzonorbornadiene and oxabenzonorbornadiene **1g** (Y = OMe, Z = H) is the least reactive one.

In conclusion, we have studied the reactivity of oxabicyclic alkenes in the ruthenium-catalyzed [2+2] cycloadditions. The presence of the oxygen in the bridgehead of the bicyclic alkene significantly enhanced the rate of the ruthenium-catalyzed [2+2] cycloadditions. The presence of a C1-substutuent on the oxanorbornadiene decreased the rate of the cycloaddition and electron-withdrawing C1-substutuents were found to be more reactive than electron-donating C1-substutuents in the ruthenium-catalyzed [2+2] cycloaddition. The nature of the substituent on the benzene ring of oxabenzonorbornadienes showed little effect on the rate of the cycloaddition. 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

General Procedure for the Ru-Catalyzed [2+2] Cycloadditions. A mixture of a bicyclic alkene (0.25 mmol, 1.25 equiv), alkyne **7** (0.20 mmol, 1 equiv), and dry THF (0.5 mL) 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 dry box, 5 mg, 0.013 mmol, 5 mol %) under nitrogen. The reaction mixture was stirred in the dark at 65 °C for various lengths of time (20−120 h). The crude product was purified by column chromatography (EtOAc−hexanes mixtures) to give the cycloadduct.

Cycloadduct 8d (Table 1, entry 4). 8d was obtained following the above general procedure, with oxabicyclic alkene **1d** (44 mg, 0.241 mmol), alkyne **7** (35.0 mg, 0.201mmol), THF (0.5 mL), and Cp*Ru(COD)Cl (4 mg, 0.011 mmol). The crude product was purified by column chromatography (EtOAc:hexanes = 2:8) to give cycloadduct **8d** (53.2 mg, 0.148 mmol, 74%) as a white solid. R_f 0.25 (EtOAc:hexanes = 3:7); mp 105−107 °C; GC (HP-1 column) retention time = 32.5 min; IR (CH_2Cl_2) ν_{max} (cm^{-1}) 2983 (m), 2079 (w), 1706 (s), 1630 (s), 1491 (w), 1450 (w), 1213 (m), 1185 (m), 1107 (m), 690 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (m, 2H), 7.37 (m, 3H), 4.29 (s, 1H), 4.28 (s, 1H), 4.25 (dq, 2H, J = 7.1, 0.9 Hz), 3.35 (m, 4H), 3.34 (s, 6H), 3.10 (d, 1H, J = 3.7 Hz), 2.98 (d, 1H, J = 3.7 Hz), 2.13 (m, 2H), 1.34 (t, 3H, J = 7.1 Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 162.5, 154.5, 132.0, 130.1, 128.9, 128.3, 127.6, 76.4, 76.2, 71.1, 70.8, 60.1, 58.84, 58.76, 46.3, 46.0, 45.3, 44.9, 14.4. Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found C, 70.11; H, 7.50.

General Procedure for Rate Study. A mixture of a standard oxabicyclic alkene (~250 μL of 1 M stock solution in THF, 4 equiv), the comparitive alkene (0.250 mmol, 4 equiv), alkyne **7** (0.0625 mmol, 1 equiv), and dry THF in an oven-dried vial was added via cannula to an oven-dried screw-cap vial containing Cp*RuCl(COD) (weighed out from a dry box, 0.003 mmol, 5 mol %) under nitrogen. The reaction mixture was stirred in the dark at 65 °C for 24 h. Each rate study was done with duplicate or triplicate samples. The crude mixtures were filtered through a plug of silica with an eluent of ethyl acetate and hexanes (8:2). The filtered crude mixture is then injected into a gas chromatograph (HP-5680 with HP-1 column, inject at 100 °C and hold for 2 min, increase temperature at 5 deg/min until 325 °C is reached). These parameters were used in all cases unless otherwise specified. The peak identification for the resultant cycloadducts was found by comparing the chromatogram to that of a 1:1 mixture of pure cycloadducts injected previously with the same GC parameters. The peak area values for the rate study samples are normalized based on the area/mmol ratio of the pure cycloadducts and are then compared to each other to obtain the relative rate of formation of the cycloadduct. If the difference in duplicate samples is greater than 5%, then a triplicate sample is made and run.

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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