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# Ruthenium-Catalyzed [2 + 2] Cycloadditions of 2-Substituted Norbornenes

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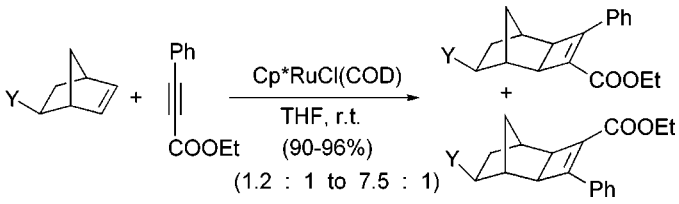
## ABSTRACT




**The studies of remote substituent effects in controlling regio- and stereoselectivities in chemical reactions provide important information in understanding long-range stereoelectronic effects. The effect of remote substituents on ruthenium-catalyzed [2 + 2] cycloadditions of 2-substituted norbornenes has been investigated. The cycloadditions occurred at room temperature in excellent yields, and regioselectivities of 1.2:1 to 7.5:1 were observed with various 2-substituted norbornenes.**

Cycloaddition reactions are among the most powerful methods for the construction of rings.[1] The [2 + 2] cycloaddition of alkenes and/or alkynes represents an important strategy for the synthesis of cyclobutane derivatives.[2] This process which is thermally forbidden by the Woodward−Hoffmann rules[3] can be achieved photochemically,[4] by thermal reactions via biradical intermediates,[5] by the use of Lewis acid catalysts,[6] and by the use of transition metal catalysts.[1c] To date, very few successful examples have been reported on transition metal catalyzed [2 + 2] cycloadditions of alkenes with alkynes.[7] No studies on the regioselectivity of transition metal catalyzed [2 + 2] cycloadditions of unsymmetrical alkenes with unsymmetrical alkynes have been reported in the literature.

While the study of long-range stereoelectronic effects of a remote substituent in controlling the regio- and stereoselectivities on nucleophilic and electrophilic additions to $\pi$-bonds are well documented,[8] less attention has been paid to cycloaddition reactions.[9] To the best of our knowledge, prior to this study, there were no reported examples on the remote substituent effect of the regioselectivity of any

(1) (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapters 1−9. (b) *Advances in Cycloaddition*; JAI Press: Greenwich, 1988−1999; Vols. 1−6. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(2) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 2.

(3) *The Conservation of Orbital Symmetry*; Woodword, R. B., Hoffmann, R., Eds.; Academic Press: New York, 1970.

(4) Crimmins, M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 123.

(5) Baldwin, J. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 63.

(6) (a) Narasaka, K.; Hayashi, Y.; Iwasawa, N.; Sakurai, H. *Chem. Lett.* **1989**, 1581. (b) Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068. (c) Mitani, M.; Sudoh, T.; Koyama, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1683. (d) Knolker, H. J.; Baum, E.; Schmitt, O. *Tetrahedron Lett.* **1998**, *39*, 7705.

(7) (a) Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294. (b) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580 and references therein.

(8) For recent reviews, see: (a) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265. (b) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337. (c) Mahta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437. See also: (d) Mayo, P.; Poirier, M.; Rainey, J.; Tam, W. *Tetrahedron Lett.* **1999**, *40*, 7727 and references therein.

(9) (a) Black, K. A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341. (b) Arjona, O.; Manzano, C.; Plumet, J. *Heterocycles* **1993**, *35*, 63. (c) Arjona, O.; Csáky, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 7338.

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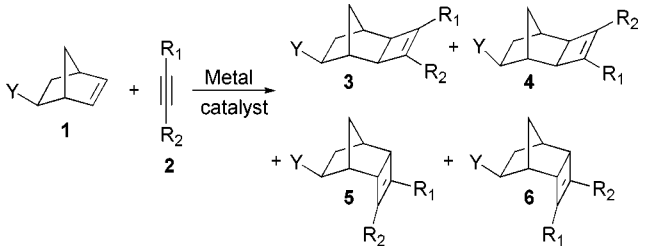
transition metal catalyzed [2 + 2] cycloaddition reactions. In this paper, we report our initial results of remote substituent effects on ruthenium-catalyzed [2 + 2] cycloadditions of 2-substituted norbornenes with an alkyne.

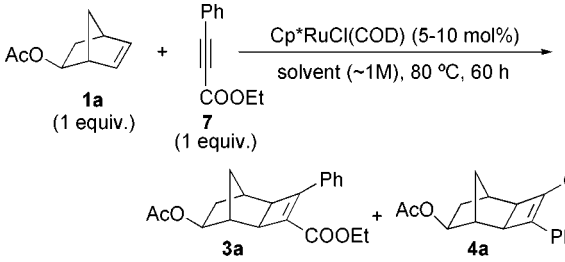
Four different [2 + 2] cycloadducts are theorectically possible in the cycloaddition between a 2-substituted norbornene and an unsymmetrical alkyne (Scheme 1). On the basis of the work by Mitsudo and co-workers,[7b] Cp*RuCl(COD)-catalyzed [2 + 2] cycloaddition of norbornene (**1**, Y = H) with alkynes produced only the *exo* cycloadducts. Thus, although four possible cycloadducts could be formed, we anticipated that only regioisomers of the *exo* cycloadducts, **3** and **4**, would be formed in the cycloadditions.

**Scheme 1.** Possible Cycloadducts




When an equimolar amount of norbonene **1a** (Y = OAc) and acetylene **7** were treated with 5 mol % of Cp*RuCl(COD) at 80 °C for 60 h, 11% of a mixture of *exo* regioisomers **3a** and **4a** was obtained in a ratio of 3.1:1 (measured by GC and $^1$H NMR) (Table 1, entry 1). No *endo* isomers, **5** or **6**, were detected. Using hexanes, toluene, DMF, or 1,2-dichloroethane as solvent, the yields of the cycloaddition were still low (11−38%, Table 1, entries 2−5). However, with $Et_3N$ or THF as solvents, the yields increased considerably to 65% and 89% (Table 1, entries 6 and 7). Very little changes on the regioselecivity were observed with the use of different solvent.

**Table 1.** Effect of Solvent

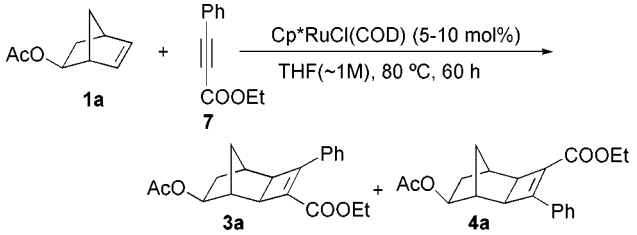



| entry | solvent | yield[a] | 3a : 4a[b] |
|---|---|---|---|
| 1 | neat | 11% | 3.1 : 1 |
| 2 | Hexanes | 13% | 2.9 : 1 |
| 3 | Toluene | 22% | 2.4 : 1 |
| 4 | DMF | 22% | 3.6 : 1 |
| 5 | 1,2-dichloroethane | 38% | 3.1 : 1 |
| 6 | $Et_3N$ | 65% | 3.3 : 1 |
| 7 | THF | 89% (68%) | 2.8 : 1 |

[a]GC yields using naphthalene as internal standard. Isolated yields are shown in parentheses. [b]Ratios measured by GC.

To optimize the yield and the regioselectivity of the cycloaddition, several different reaction conditions were varied. Altering the equivalence of alkyne **7** led to minimal changes in the regioselectivity. However, a dramatic reduction in the yield was observed as the equivalence of alkyne **7** was increased (Table 2, entries 1−4). Increasing the number of equivalents of norbornene **1a** led to higher yields and better regioselectivities (Table 2, entries 5−8). When we carried out the cycloaddition at different temperatures (Table 3), we noticed that the cycloaddition occurred even at *room temperature* with essentially the same yield and regioselectivity.

**Table 2.** Effect of Number of Equivalence of Norbornene **1a** and Alkyne **7**




| entry | equivalency: norbornene 1a | equivalency: alkyne 7 | yield[a] | 3a : 4a[b] |
|---|---|---|---|---|
| 1 | 1 | 1 | 89% (68%) | 2.8 : 1 |
| 2 | 1 | 2 | 29% | 3.6 : 1 |
| 3 | 1 | 5 | 9% | 3.4 : 1 |
| 4 | 1 | 10 | 4% | 3.0 : 1 |
| 5 | 1 | 1 | 89% (68%) | 2.8 : 1 |
| 6 | 2 | 1 | 90 | 4.3 : 1 |
| 7 | 5 | 1 | 99 (82%) | 4.2 : 1 |
| 8 | 10 | 1 | 100 (94%) | 3.9 : 1 |

[a]GC yields using naphthalene as internal standard. Isolated yields are shown in parentheses. [b]Ratios measured by GC and/or by $^1$H NMR.

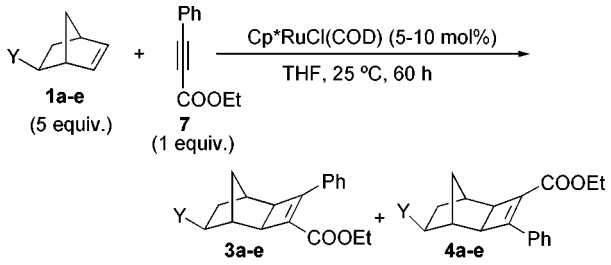
Thus, under the optimized cycloaddition conditions, when 1 equiv of alkyne **7** and 5 equiv of norbornene **1a** were

**Table 3.** Effect of Temperature

| entry[a] | temperature | yield[b] | 3a : 4a[c] |
|---|---|---|---|
| 1 | 25 °C | 100% | 4.1 : 1 |
| 2 | 40 °C | 100% | 4.1 : 1 |
| 3 | 80 °C | 99% | 4.2 : 1 |

[a]Reaction conditions: 5 equiv. of **1a**, 1 equiv. of **7**, 5-10 mol% of Cp*RuCl(COD), THF as solvent (~ 1M), 60 h. [b]GC yields using naphthalene as internal standard. [c]Ratios measured by GC.

**Table 4.** Ruthenium-Catalyzed [2 + 2] Cycloadditions of *exo* 2-Substituted Norbornenes



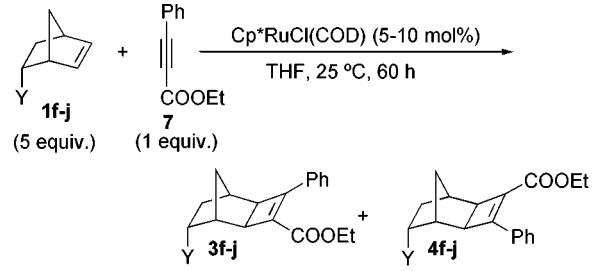

| entry | norbornene | Y | yield[a] | 3 : 4[b] |
|---|---|---|---|---|
| 1 | **1a** | OAc | 94% | 4.0 : 1 |
| 2 | **1b** | OBn | 93% | 3.0 : 1 |
| 3 | **1c** | OTBS | 92% | 1.5 : 1 |
| 4 | **1d** | OH | 91% | 2.0 : 1 |
| 5 | **1e** | COOMe | 96% | 2.4 : 1 |

[a]Isolated yields after column chromatography. [b]Ratios measured by GC and/or by $^1$H NMR.

treated with 5−10 mol % of Cp*RuCl(COD) in THF at *room temperature*, cycloadducts **3a** and **4a** were produced in 94% isolated yield in a ratio of 4.0:1.

To study the remote effect of the Y substituent of norbornene **1** on the cycloaddition, *exo* and *endo* 2-substituted norbornenes **1a**−**1j** (Y = COOMe, OH, OTBS, OBn, OAc) were prepared[8d] and their ruthenium-catalyzed [2 + 2] cycloadditions with alkyne **7** were studied (Tables 4 and 5). Under the optimized reaction conditions, both *exo* and *endo* norbornenes undergo ruthenium-catalyzed [2 + 2] cycloadditions with alkyne **7** smoothly, giving the corresponding cycloadducts in excellent yields. The regioselectivities were only modest, and generally *exo* norbornenes

**Table 5.** Ruthenium-Catalyzed [2 + 2] Cycloadditions of *endo* 2-Substituted Norbornenes

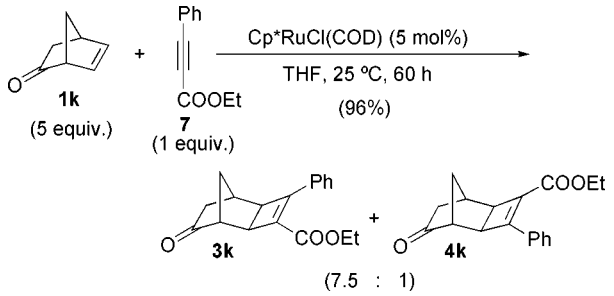



| entry | norbornene | Y | yield[a] | 3 : 4[b] |
|---|---|---|---|---|
| 1 | **1f** | OAc | 94% | 1.4 : 1 |
| 2 | **1g** | OBn | 92% | 1.2 : 1 |
| 3 | **1h** | OTBS | 93% | 2.0 : 1 |
| 4 | **1i** | OH | 90% | 1.4 : 1 |
| 5 | **1j** | COOMe | 91% | 2.0 : 1 |

[a]Isolated yields after column chromatography. [b]Ratios measured by GC and/or by $^1$H NMR.

gave higher regioselectivities than their corresponding *endo* isomers. For *exo* norbornenes **1a**−**e**, regioselectivities of 1.5:1 to 4.0:1 were observed, with **1a** (Y = OAc) giving the highest regioselectivity. In the case of *endo* norbornenes **1f**−**1j**, very small differences in the regioselectivities were observed with different Y substituents. When 2-norbornenone **1k** was subjected to the Ru-catalyzed cycloaddition conditions, an excellent yield (96%) and good regioselectivity (7.5:1) were observed (Scheme 2).

**Scheme 2**




The *exo* stereochemistry of the cycloadducts was proven by the coupling pattern of $H^b$ and $H^c$ in the $^1$H NMR spectra (Figure 1).[10] Since the dihedral angles between $H^b$ and $H^d$

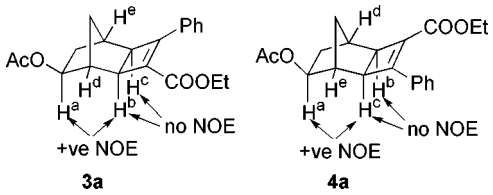



**Figure 1.** Determination of regiochemistry.

and $H^c$ and $H^e$ in the *exo* cycloadducts are close to 90°, their coupling constants should be very small ($J \sim 0-2$ Hz). For *endo* cycloadducts, the corresponding dihedral angles are approximately 42° and give coupling constants of ~5 Hz. In all of our cycloadducts, both $H^b$ and $H^c$ are doublets (coupled only with each other but not with $H^d$ or $H^e$); therefore all the cycloadducts must possess *exo* stereochemistry. The regiochemistries of the cycloadducts were determined by the use of NMR techniques. A mixture of cycloadducts **3a** and **4a** (Y = OAc) were separated by fractional recrystallization. $H^b$ and $H^c$ of the two regioisomers in the $^1$H NMR were identified by the NMR technique of heteronuclear multiple bond coherence (HMBC). In both regioisomers, $H^b$ is the allylic proton on the cyclobutene ring that is three bonds away from the carbonyl carbon of the COOEt group on the cyclobutene ring. For the major regioisomer **3a**, $H^a$ showed an NOE effect with $H^b$ but not

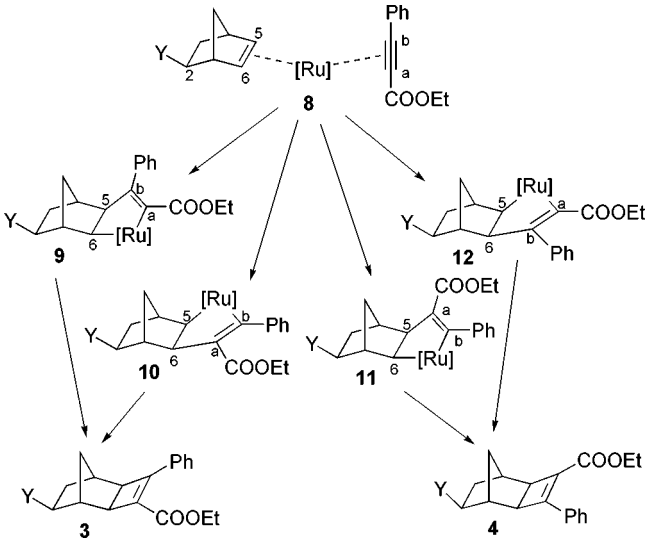
(10) Yip, C.; Handerson, S.; Jordan, R.; Tam, W. *Org. Lett.* **1999**, *1*, 791 and references therein.

with $H^c$, whereas for the minor isomer **4a**, $H^a$ showed an NOE effect with $H^c$ but not with $H^b$.

Similar NMR techniques were used to determine the regiochemistry of the *endo*-OAc cycloadducts **3f**/**4f** and the ketone cycloadducts **3k**/**4k**, as these regioisomers were separable by flash column chromatography. Other pairs of regioisomers were difficult to separate, and their regiochemistries were determined by conversion to the corresponding OAc derivatives (**3a**/**4a** or **3f**/**4f**) and comparison of their $^1$H NMR spectra. In all the cases, **3** were found to be the major regioisomers.

Upon complexation of an unsymmetrical norbornene **1** and alkyne **7** with the Ru catalyst to give **8** (Scheme 3), four

**Scheme 3.** Possible Cycloaddition Pathways




different metallacyclopentenes **9**−**12** could be formed. Carbon−carbon formation may first occur between the acetylenic carbon attached to the Ph group (C-b) with one of the olefinic carbons of norbornene **1** (C-5 or C-6) to give **9** or **12**. Alternatively, formation of the carbon−carbon bond between the acetylenic carbon attached to the COOEt group (C-a) with one of the olefinic carbons of norbornene **1** (C-5 or C-6) will give **10** or **11**. In **9** and **11**, the carbon−ruthenium bond is closer to the electron-withdrawing substituent Y whereas in **10** and **12** the carbon−ruthenium bond is farther away from the electron-withdrawing substituent Y. Reductive elimination of the metallacyclopentenes **9** and **10** would lead to the formation of the major regiosiomer **3** whereas reductive elimination of the metallacyclopentenes **11** and **12** would lead to the formation of the minor regiosiomer **4**. Because of the different electron-withdrawing power of different Y substituents, the energy difference of the metallacyclopentenes **9**−**12** could be quite different and this leads to different regioselectivities with different Y substituents. The exact nature of the stereoelectronic effect of the remote substituent is still not certain at this stage, and further investigations, including molecular modeling studies on the relative stability of different metallacyclopentenes **9**−**12**, are ongoing in our laboratory.[11]

In conclusion, we have demonstrated the first examples of the remote substituent effect on the regioselectivity of ruthenium-catalyzed [2 + 2] cycloadditions of 2-substituted norbornenes with an alkyne. The cycloadditions occurred at *room temperature*, giving the cycloadducts in excellent yields (90−96%). Regioselectivities of 1.2:1 to 7.5:1 were observed with various sustituents on the *C-2* position of norbornenes. Further investigation on the mechanism of the cycloaddition and the role of the remote substituent on the regioselectivity of the cycloaddition as well as an intramolecular variant of the cycloaddition 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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