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Published on Web 12/08/2005

Preparation of Alkenyl Cyclopropanes through a Ruthenium-Catalyzed Tandem Enyne Metathesis−Cyclopropanation Sequence

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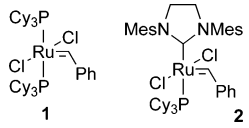
A significant advantage of tandem or concurrent transformations[1] is that valuable materials can be prepared more economically through shorter routes.[2] Along these lines, the ability of a catalyst to perform several mechanistically distinct transformations provides important opportunities for developing highly efficient, multi-bond-forming processes that are carried out in a single reaction vessel.[3] Accordingly, we, and others, have been exploring alternative transformations catalyzed by the popular olefin metathesis catalysts **1** and **2**.[4] Tandem transformations catalyzed by ruthenium alkylidenes **1** or **2** developed to date include olefin metatheses, followed by atom transfer reactions,[5] olefin hydrogenations,[6] and olefin isomerizations.[7]



The variety of reactions catalyzed by ruthenium suggests that numerous other tandem processes might also be possible.[8] In particular, the ability of ruthenium alkylidenes to cyclopropanate olefins,[9] combined with similarities between the olefin metathesis and cyclopropanation mechanisms (Figure 1), indicates that a tandem metathesis−cyclopropanation reaction sequence should be achievable.[10] We originally reasoned that ligand modifications to the olefin metathesis catalyst would be required to alter the prevailing mechanism; however, our findings reported herein do not support this assumption. We observed that alkylidene **1** can catalyze a ring-closing enyne metathesis followed by a selective cyclopropanation of the resulting diene after addition of diazoesters, generating vinyl cyclopropanes in a single operation without making deliberate changes to the ruthenium complex.

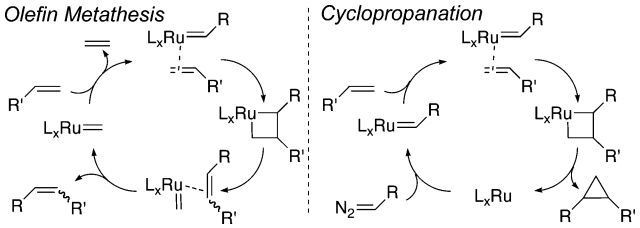
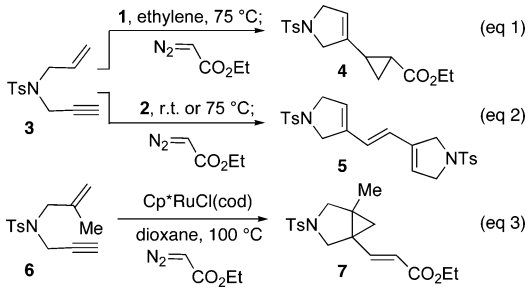


Figure 1. Mechanism of ruthenium alkylidene-catalyzed olefin metatheses and cyclopropanations.

After examining tandem ring-closing metathesis/cyclopropanations on isolated cyclic olefins without success, we were pleased to observe that 1,3-dienes formed in a ring-closing enyne metathesis with Grubbs' ruthenium catalyst **1** could be cyclopropanated when diazoacetate is added to the reaction at elevated temperatures (eq 1). The tandem process appears to be specific to catalyst **1**; alkylidene **2** provides only the triene dimer without any evidence of cyclopropanation (eq 2).[11] The cyclopropanation occurs almost exclusively on the less-hindered olefin with moderate *E*/*Z* stereoselectivity. The regioselectivity is noteworthy, especially considering that the related, ruthenium-catalyzed multi-bond-forming process disclosed by Dixneuf and co-workers provides the opposite regioselectivity (eq 3).[12] The subtle mechanistic differences between these ruthenium-catalyzed processes provide highly complementary means of generating regioisomeric vinyl cyclopropane systems from the corresponding enynes.

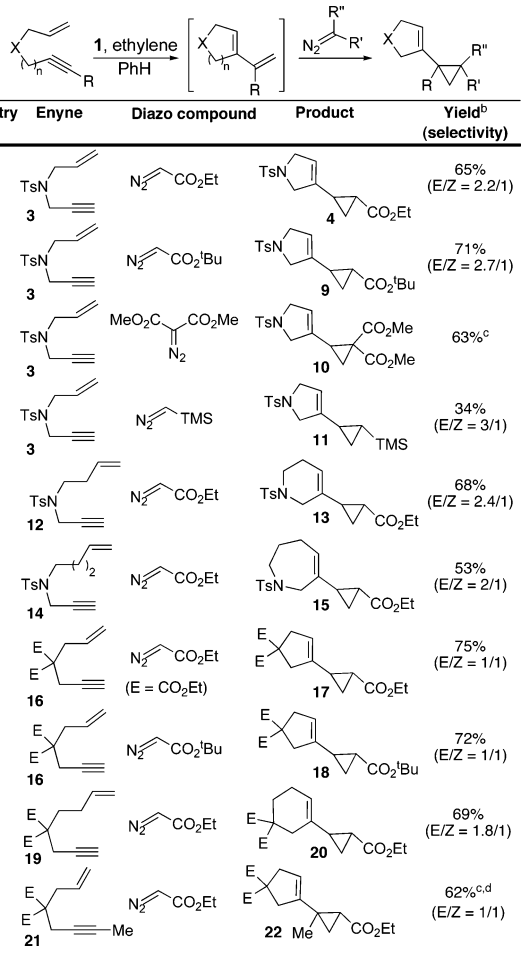


Enynes with a variety of substituents were subjected to ring-closing metathesis and then warmed with a diazo compound to effect a ruthenium-catalyzed cyclopropanation of the resulting 1,3-diene. Table 1 summarizes a series of vinyl cyclopropanes prepared in a single reaction vessel from the readily prepared enynes. Entries 1−10 indicate that five-, six-, and seven-membered cycloalkenyl cyclopropanes can be generated through this ruthenium-catalyzed tandem process accompanied by only trace amounts of the regioisomeric cyclopropane (i.e., <5%).[13] Entries 2 and 8 demonstrate that an increase of the bulkiness of the diazoester group from ethyl to *t*-butyl does not influence significantly the *cis*/*trans* isomeric ratio observed in the cyclopropanation. Entry 3 shows that a highly stabilized diazodiester is also transferred effectively to the 1,3-diene in good yield, but higher temperature and increased amount of catalyst (20 mol %) is required for complete conversion (→**10**). Entry 4 reveals that unstabilized trimethylsilyl diazomethane is also suitable for cyclopropanation, but the reaction is less efficient than other diazo transfer reactions, leading to lower yields of the tandem product **11**. Entry 10 indicates that high temperature, as well as increased amount of catalyst (20 mol %), is required for the cyclopropanation of more substituted 1,3-diene.

Overall, these results suggest that, even though the ruthenium carbene complex is generally electrophilic,[14] the steric hindrance of the diene appears to override any electronic bias in determining the regioselectivity of the cyclopropanation reaction.[15] The stereoselectivity of the cyclopropanation with Grubbs' catalyst is moderate at best with *E*/*Z* ratios ranging from 1/1 to 3/1. These isomers were assigned through nOe experiments, as well as examining the carbonyl ^{13}C NMR signal of the *E*-isomer, which is consistently

10.1021/ja055993l CCC: $33.50

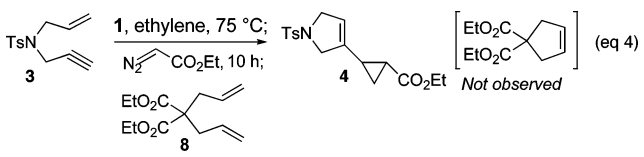
Table 1. Tandem Enyne Metathesis/Cyclopropanation



[a] Conditions: 10 mol % of **1** at 75 °C [0.05−0.10 M in C_6H_6]; enyne RCM was conducted under CH_2CH_2 atm; cyclopropanation was conducted under N_2 atm. [b] Isolated yield based on starting enyne. [c] With 20 mol % of catalyst **1** at 100 °C [0.05−0.10 M in toluene]. [d] 1,3-Diene isolated in 21% yield.

observed at lower field compared to the *Z*-isomer as a consequence of the γ-effect.[16]

^{31}P NMR studies to identify the specific ruthenium catalyst responsible for the cyclopropanation were not conclusive; the NMR after tandem reaction revealed new ^{31}P NMR signals at 34.7 and 48.8 ppm. Both signals are different from the ^{31}P NMR signal observed after the enyne ring-closing metathesis (31.2, 35.5, and 47.9 ppm).[17] In addition, when diene **8** was added after the cyclopropanation step to see whether the ruthenium catalyst responsible for the cyclopropanation was still olefin metathesis active, no new metathesis products were observed (eq 4). This evidence suggests that ruthenium complex **1** is modified in situ by the diazo compound to form a cyclopropanation active catalyst.[18]



Overall, a tandem ring-closing enyne metathesis/cyclopropanation reaction has been developed. A variety of diazo compounds participate successfully in a regioselective cyclopropanation of 1,3-dienes,[19] prepared in situ from various enynes, using Grubbs' ruthenium catalyst **1**. Further mechanistic studies are required to help identify the ruthenium species responsible for the cyclopropanation activity, as well as to expand the scope of the tandem process.

Acknowledgment. We thank Boston College, the National Science Foundation, and CMDS-KOSEF at KAIST for financial support. Ryan Murrelli is gratefully acknowledged for some experimental support. We are also grateful to Schering-Plough for X-ray facility support, and Materia for the gift of metathesis catalyst.

Supporting Information Available: Experimental procedures and data on new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) The terms tandem, domino, cascade, concurrent, and sequential catalysis are used interchangeably without bias for the mechanistic implications of their emerging definitions. For further discussion, see: (a) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (d) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.

(2) (a) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.

(3) For recent review of tandem catalyst, see: Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.

(4) For recent reviews of nonmetathetic processes involving Grubbs' catalysts, see: (a) Alcaide, B.; Almendros, P. *Chem.—Eur. J.* **2003**, *9*, 1258. (b) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880.

(5) (a) Louie, J. Bielawski, C. W. Grubbs, R. H. *J. Am. Chem. Soc*. **2001**, *123*, 11312. (b) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 12872. (c) Simal, F.; Demonceau, A.; Noels, A. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3196.

(6) (a) Drouin, S. D.; Zamanian, F.; Fogg, D. E. *Organometallics* **2001**, *20*, 5495. (b) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 3196.

(7) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc*. **2002**, *124*, 13390. (b) Schmidt, B. *Eur. J. Org. Chem.* **2003**, *5*, 816.

(8) For an overview of ruthenium-catalyzed reactions, see: (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599−2660. (b) Trost, B. M.; Toste, D. F.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096.

(9) For recent reviews of cyclopropanation reaction with ruthenium, see: (a) Nishiyama, H. *Top. Organomet. Chem*. **2004**, *11*, 81. (b) Mass, G. *Chem. Soc. Rev*. **2004**, *33*, 183.

(10) For a related example of this process, see: (a) Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc*. **2004**, *126*, 9524. Also see: (b) Casey, C. P.; Hornung, N. L.; Kosar, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4908 and references therein. For computational studies addressing cyclopropane formation from **1**, see: (c) Bernardi, F.; Bottoni, A.; Miscione, G. P. *Organometallics* **2003**, *22*, 940. (d) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, Megan M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332−14333.

(11) This is in contrast to the cyclopropanations catalyzed by alkylidene **2** that were observed by Diver and co-workers (ref 10a). In any event, while cyclopropanation products were not observed, fumarate and maleate diazo decomposition products were present.

(12) (a) Monnier, F.; Castillo, D.; Dérien, S.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed*. **2003**, *42*, 5474. (b) Eckert, M.; Monnier, F.; Shchetnikov, G. T.; Titanyuk, I. D.; Osipov, S. N.; Toupet, L.; Dérien, S.; Dixneuf, P. H. *Org. Lett.* **2005**, *7*, 3741. Also see: (c) Demonceau, A.; Abreu Dias, E.; Lemoine, C. A.; Stumpf, A. W.; Noels, A. F.; Pietraszuk, C.; Gulinski, J.; Marciniec, B. *Tetrahedron Lett.* **1995**, *36*, 3519.

(13) The fumarates and maleates were major byproducts in this reaction.

(14) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (b) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12.

(15) For an example of similar cyclopropanation regioselectivity, see; Sen, S. E.; Prestwich, G. D. *J. Med. Chem*. **1989**, *32*, 2152.

(16) Mass, G.; Werle, T.; Alt, M.; Mayer, D. *Tetrahedron* **1993**, *49*, 881 and references therein.

(17) For ^{31}P NMR studies on modified olefin metathesis catalysts, see: Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672 and references therein.

(18) The loss of metathesis activity upon treatment with diazoester suggests that metathesis active enoic ruthenium complexes are not being generated. For examples of these complexes, see: (a) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689. (b) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417.

(19) The requirement of a 1,3-diene in a cyclopropanation has been observed previously and may provide insight into the mechanistic course of this reaction. For example, see: Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 8916.

JA055993L