

Conjugated Enynes as a New Type of
Substrates for Olefin Metathesis

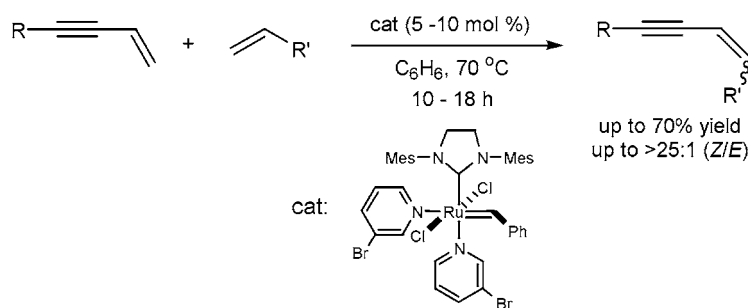
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ABSTRACT

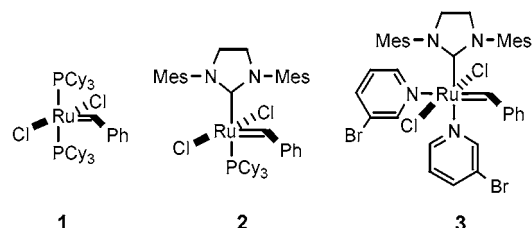
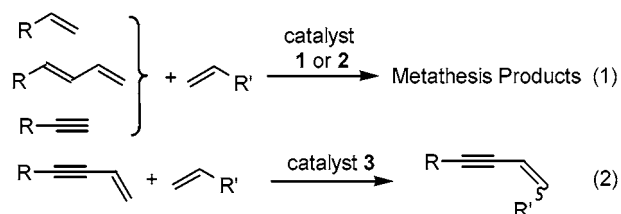


It has been demonstrated for the first time that conjugated enynes can be employed as a facile substrate in olefin metathesis with the use of a bispyridine-substituted ruthenium benzylidene catalyst. Cross-metathesis of the enynes with alkenes turns out to proceed with preferential formation of (*Z*)-isomers over (*E*)-isomers up to >25:1 in moderate to good yields. The intramolecular version of conjugated enynes affords novel butadienyl cycloalkenes, which are a highly useful synthetic building blocks, in acceptable yields.

Olefin metathesis is one of the most useful tools for the C–C bond formation in a diverse area of chemistry, including natural product synthesis, polymerization, peptide chemistry, and material science.¹ Mainly due to the advent of new carbene catalysts with advanced properties, the scope of the metathesis has been gradually expanded. Various substrates such as alkenes,² conjugated dienes,³ and alkynes⁴ are readily reacted with olefins (Scheme 1, eq 1). However, metathesis

of conjugated enynes has not been reported yet. Due to the fact that conjugated enynes have been extensively used for

Scheme 1. Substrate Types in Ru–Benzylidene-Catalyzed Metathesis



(1) For recent reviews of olefin metathesis, see: (a) Schuster, M.; Bleichert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2037. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (e) Connon, S. J.; Bleichert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1903.

(2) For selected examples, see: (a) Ashe, A. J., III; Fang, X. *Org. Lett.* **2000**, *2*, 2089. (b) Williams, D. R.; Cortez, G. S.; Bogen, S. L.; Rojas, C. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4612. (c) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903.

(3) Cabrejas, L. M. M.; Rohrbach, S.; Wagner, D.; Kallen, J.; Zenke, G.; Wagner, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2443.

(4) (a) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801. (b) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388.

molecular assembly,⁵ synthesis of bioactive compounds,⁶ and preparation of novel macrocycles,⁷ the facile synthesis of conjugated enynes would be highly desirable. Herein, we wish to report our recent results that conjugate enynes readily participate in metathesis to react with alkenes under both inter- and intramolecular conditions (Scheme 1, eq 2).

At the outset of our studies, a conjugated enyne, 4-phenyl-1-buten-3-yne (**4**), was subjected to metathesis conditions with ruthenium catalysts **1** and **2**. No change was observed even after long reaction times (72 h) at temperatures above 70 °C in various solvents, and enyne **4** was quantitatively recovered intact. In addition, the ruthenium carbenes **1** and **2** did not show any activity for the metathesis of alkenes in the presence of enynes. For example, when allyltrimethylsilane (**5**) was added to a solution of catalyst **1** or **2** (0.2 equiv) containing enyne **4** (1.0 equiv), no cross-metathesis compounds from the added olefin were detected under a variety of conditions examined. The significantly reduced activity of **1** and **2** could be explained by a strong prior binding of the triple bond to the ruthenium center. Our assumption was confirmed by tracing IR peaks of enyne **4** in the presence of complex **2** (Figure 1). The stretching

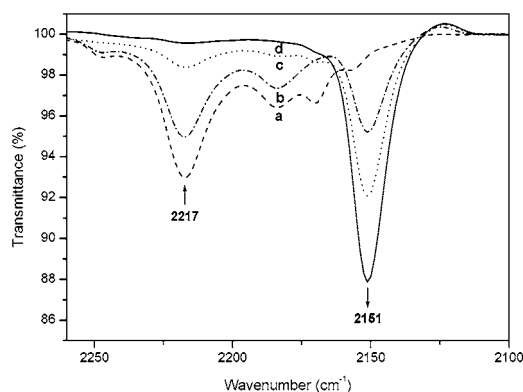


Figure 1. Change in a triple-bond stretching frequency of 4-phenyl-1-buten-3-yne (**4**) upon addition of Ru-benzylidene complex **2** in CH_2Cl_2 at 25 °C: (a) **4** only (0.5 M); (b) **4** (1.0 equiv, 0.5 M) and **2** (0.05 equiv, 7.5 h); (c) **4** (1.0 equiv) and **2** (0.2 equiv, 7.5 h); (d) **4** (1.0 equiv) and **2** (0.5 equiv, 7.5 h).

frequency of the triple bond in **4** was gradually shifted from 2217 to 2151 cm^{-1} upon the addition of complex **2**, which is consistent with weakening of a triple-bond character upon binding to a metal.⁸ In addition, ^1H NMR spectra showed that a new and stable carbene peak appeared by the addition of enyne **4** to a solution of **2**.⁹

(5) (a) Dosa, P. I.; Erben, C.; Iyer, V. S.; Wasser, I. M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1999**, *121*, 10430. (b) Moonen, N. N. P.; Boudon, C.; Gisselbrecht, J. P.; Seiler, P.; Gross, M.; Diederich, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 3044.

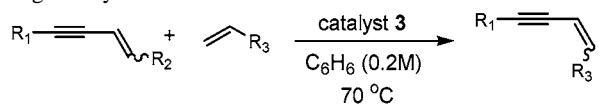
(6) (a) Schaus, S. E.; Cavalieri, D.; Myers, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 11075. (b) Dziegielewski, J.; Beerman, T. A. *J. Biol. Chem.* **2002**, *277*, 20549.

(7) Campbell, K.; Kuehl, C. J.; Ferguson, M. J.; Stang, P. J.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 7266.

(8) Observation that the original triple-bond stretching frequency of **4** disappeared almost completely upon addition of 0.5 equiv of **2** might indicate that two alkynes coordinate to the ruthenium center.

Grubbs et al. recently reported the preparation and the use of bispyridine ruthenium benzylidene catalyst **3**, which exhibited much faster initiation rates of metathesis than the parent complexes **1** and **2**.¹⁰ Surprisingly, when the catalyst **3** was employed in the reaction of conjugated enynes with alkenes, we observed that the metathesis did proceed to afford substituted enynes (Table 1).¹¹ Acceptable yields of

Table 1. Cross-Metathesis of Conjugated Enynes with Olefins Using Catalyst **3**^a



entry	enyne	alkene	yield (%), Z/E ^b
1	Ph-C≡C-CH=CH- 4	CH2=CH-TMS 5	60 (3.1:1)
2	<i>n</i> -Oc-C≡C-CH=CH- 4	5	47 (6.0:1)
3	MOMO-C≡C-CH=CH- 6	5	60 (4.5:1)
4	6	CH2=CH-Ph	56 (1.4:1)
5	6	CH2=CH-CH2-CH2- 7	59 (2.4:1)
6 ^c	4	TMSO-CH=CH-OTMS	30 (1.6:1) ^d
7	Ph-C≡C-CH=CH- 4	5	51 (1.1:1)
8	Ph-C≡C-CH=CH- 4	5	47 (1.2:1)
9	AcO-CH2-CH2-C≡C-CH=CH- 4	5	44 (6.5:1)
10 ^e	N-Ts-C≡C-CH=CH- 8	5	50 (>25:1)
11 ^e	8	7	70 (14:1)

^a Enyne (1.0 equiv), alkene (3.0 equiv), and **3** (10 mol %) in benzene (0.2 M) at 70 °C for 18 h (except entries 6, 10, and 11). ^b Isolated yields and ratios of Z/E determined by ^1H NMR of the crude reaction mixture. ^c Performed with 2.0 equiv of olefin. ^d Yield of desilylated alcohol. ^e Reaction was carried out with 5 mol % catalyst for 10 h under otherwise identical conditions.

new enynes could be obtained with the use of 5–10 mol % catalyst **3** in benzene at 70 °C (10–18 h). It was found that the new double bond was generated with (Z)-selectivity and that the extent of that selectivity varied depending on the substrate type used. It should be noted that the (Z)-selectivity observed in this study is highly unusual considering the fact that, in general, (E)-alkenes are favorably formed from the cross-metathesis between alkenes.¹²

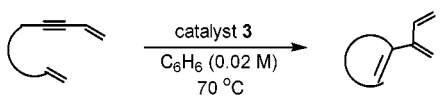
Steric hindrance around the triple bond of the alkynyl moiety did not affect the efficiency of the reaction (entries

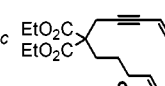
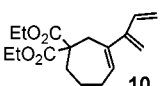
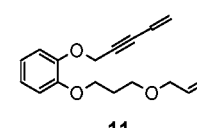
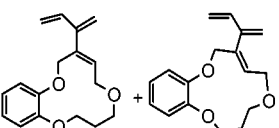
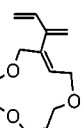
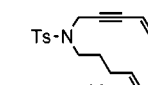
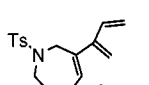
(9) Upon addition of enyne **4** (1.0 equiv) to a solution of catalyst **2** in CD_2Cl_2 , the original carbene peak (18.99 ppm) disappeared gradually on NMR and only a new peak (18.29 ppm, singlet) was observed after 2 h at 40 °C.

(10) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035.

(11) Bispyridine-substituted ruthenium carbene complex **3** was prepared according to a literature procedure (ref 10) with 80–85% yields.

Table 2. Ring-Closing Metathesis of Alkenyl Enynes Using Catalyst **3**^a



entry	substrate	products	yield (%) ^b
1 ^c			51
2		 	14a : 28 14b : 10
3			52
4 ^d	13	14	62

^a Catalyst (15 mol %) at 70 °C for 46 h under N₂. ^b Yield of isolated product. ^c Catalyst (10 mol %) at 70 °C for 18 h under N₂. ^d Catalyst (10 mol %) at 70 °C for 18 h under an ethylene atmosphere (1 atm).

3–5). Internal alkenes were also reacted with conjugated enynes under the same conditions to afford the corresponding enynyl adducts (entries 5, 6, and 11). When internal conjugated enynes bearing an alkyl substituent either in (*Z*)- or (*E*)-form were subjected to the reaction conditions, almost no difference was observed between the isomers judged from yields, selectivity, and reaction rates (entries 7 and 8).¹³ It is especially noteworthy that significantly high (*Z*)-selectivity was observed from the reaction of an amido enyne (**8**) with olefins (entries 10 and 11).¹⁴

With the results of cross-metathesis of conjugated enynes with alkenes, we turned our attention to an intramolecular version with the expectation of obtaining cyclic conjugated enynes.¹⁵ A malonate derivative **9** bearing both alkenyl and enynyl groups was cyclized upon treatment with **3** to afford a cycloheptene adduct **10** as a single product in a moderate yield (entry 1). It turned out that catalyst **2** was also effective for the ring closure, albeit with lower efficiency (35% yield of **10** under otherwise identical conditions) compared to **3**. It should be noted that the generated trienyl ring system is not easily assessed using conventional organic synthetic procedures. Substrate **11**, having a longer linker to the alkene, was also closed to provide the corresponding macrocyclic as a mixture of two stereoisomers, favoring the (*Z*)-isomers

(12) Recently, kinetically controlled cross-metathesis of alkenes with high (*E*)-selectivity has been reported, see: Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209.

(13) Lee and Grubbs have described the effects of positioning an auxiliary group onto the terminal olefinic site on the stereochemistry of ring formation; see: Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145.

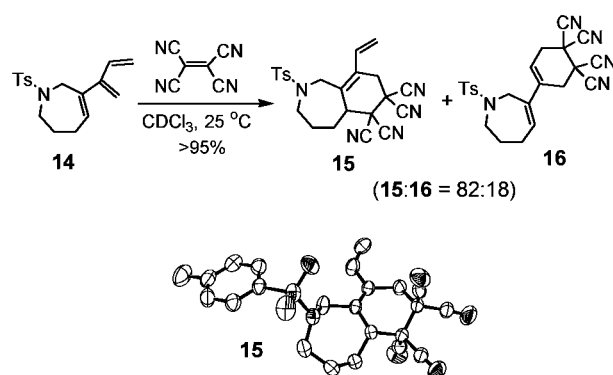
(14) Previously, acrylonitrile was found to undergo cross-metathesis with high *cis*-selectivity; see: Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162.

(15) Conjugated enynes were prepared in high yields from alkynes with vinyl bromides using Sonogashira conditions. See Supporting Information.

(entry 2). The efficiency of the cyclization was improved to some extent when the reaction was carried out in the presence of 1 atm of ethylene gas (entries 3 and 4).¹⁶

The synthetic utility of the conjugated triene products is evident.¹⁷ For example, triene **14** smoothly reacted with the dienophile, tetracyanoethylene, within a few minutes at 25 °C to afford Diels–Alder adducts with good selectivity (Scheme 2).¹⁸ The structure of the major bicyclic product

Scheme 2. Diels–Alder Reaction of **14** with Tetracyanoethylene and the Crystal Structure of Major Cycloadduct **15**



15 was confirmed by a single-crystal X-ray diffraction analysis.¹⁹

In conclusion, the first example of cross-metathesis of conjugated enynes with alkenes has been presented with the use of a bispyridine-substituted ruthenium catalyst, in which preferential formation of (*Z*)-isomers (with selectivities ranging from 1.1:1 to >25:1) was observed. The intramolecular version of the conjugated enynes gave a novel butadiene-substituted cycloalkene system that is otherwise difficult to attain with known synthetic procedures. Although the chemical yields obtained were moderate with the use of the present catalytic system, it is believed that useful and more efficient applications should soon arise as a result of our findings.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds obtained in this study. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) For previous studies of ethylene effects on enyne metathesis, see: (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (b) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788.

(17) (a) Couturier, M.; Brassard, P. *Synthesis* **1994**, 703. (b) Jenneskens, L. W.; de Wolf, W. H.; Bickelhaupt, F. *Chem. Ber.* **1986**, *119*, 754.

(18) Cycloaddition reactions proceeded smoothly and quantitatively also for other cyclic trienes prepared in this study.

(19) Detailed X-ray analysis data of compound **15** are described in Supporting Information.