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Efficient and *Z*-Selective Cross-Metathesis of Conjugated Enynes

Eric C. Hansen and Daesung Lee*

Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706

dlee@chem.wisc.edu

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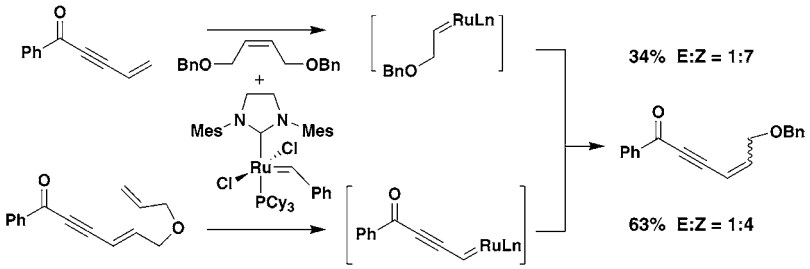
ABSTRACT



The generation of a conjugated alkynyl alkylidene has been achieved using an allyl ether moiety as an intramolecular catalyst delivery vehicle. The reaction of this intermediate with alkenes and alkynes yields conjugated enynes with *Z*-selectivity.

Olefin metathesis has become a powerful carbon−carbon bond-forming method which has had a profound impact in synthetic chemistry.[1] The extensive research involving olefin metathesis is driven by the development of well-defined reactive ruthenium[2] and molybdenum-based catalysts[3] showing broad functional group compatibility. From the standpoint of new applications of metathesis chemistry, the synthesis of enediynes via the metathesis process is an attractive yet challenging goal (eq 1). The enediyne substructure constitutes the unique architecture of the enediyne family of natural products that are characterized by their potent antitumor and antibiotic activities.[4] Typically, the enediyne functionality is embedded in either a nine-membered ring **1** (bicyclo[7.3.0]-dodecadiynene) or a 10-membered ring **2** (bicyclo[7.3.1]-tridecadiynene) as a stable precursor, which upon activation leads to benzene-1,4-diyl. It has been shown that the diyl generated by the Bergman-[5] or Myers-type cycloaromatization[6] of enediyne warheads induces single and double strand DNA cleavage, which is presumed to be the basis for the potent in vitro and in vivo biological activity. Both the novel structural and biological characteristics of the enediynes have invited intense synthetic as well as clinical studies.[7]

Numerous synthetic methods have been developed to construct the enediyne substructures, and many total syntheses of complex natural enediynes have been reported.[4]

(1) For reviews on olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (f) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. For recent reviews of enyne metathesis, see: (g) Giessert, A. J.; Diver, S. T. *Chem. Rev.* **2004**, *104*, 1317. (h) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (i) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133.

(2) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, 28, 446. (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (e) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (f) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

(3) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; O'Reagan, M.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

(4) For reviews on enediynes, see: (a) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (b) Maier, M. E. *Synlett* **1995**, 13. (c) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed.* **1991**, *30*, 1387.

(5) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.

(6) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493.

(7) For overview of recent clinical findings, see: (a) Schor, N. F. In *Cancer Therapeutics: Experimental and Clinical Agents*; Teicher, B., Ed.; Humana Press: Totowa, NJ, 1996; p 229. (b) Maeda, H.; Edo, K.; Ishida, N. Eds., *Neocarzinostatin: The Past, Present, and Future of an Anticancer Drug*; Springer-Verlag: New York, 1997.

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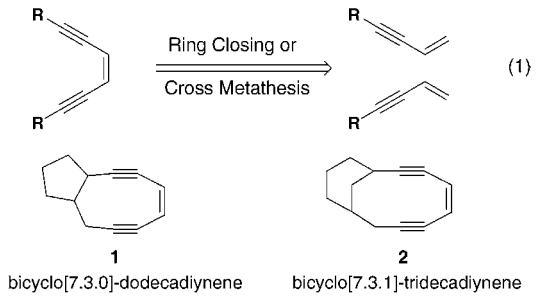


However, to the best of our knowledge, no attempt to synthesize enediynes and related structures using metathesis chemistry has been reported.

We were intrigued by the possibility of constructing the enediyne substructure directly from conjugated enyne precursors via cross-metathesis (CM).[1e] For this plan to be viable, the efficient generation of conjugated alkynyl alkylidene **4** is crucial and its reactivity toward both alkene and alkyne substrates needs to be understood.[8] There are several reports that describe the use of conjugated and unconjugated enynes as CM counterparts either in the presence of catalyst **6** or a more active version **7**,[9] yet the CM reaction involving the

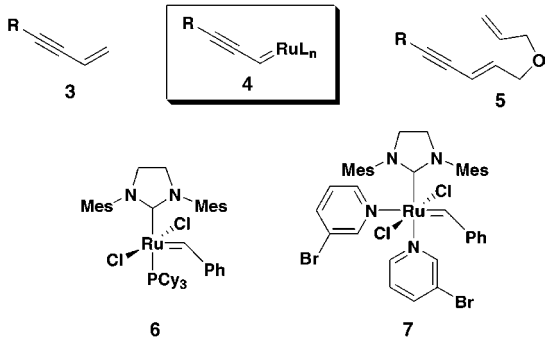
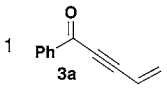
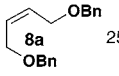
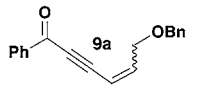
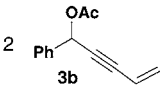
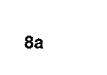
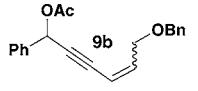
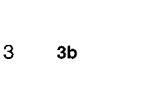
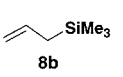
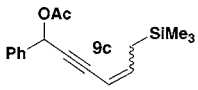


Figure 1.

conjugated alkynyl alkylidene of type **4** as a propagating species has not been reported.[10] We developed an efficient way of generating alkylidene **4** from precursor **5** that carries a more active terminal alkene appendage as a catalyst delivery vehicle. Herein we wish to report the first successful generation of conjugated alkynyl alkylidene **4** and its use in the context of CM reaction.

To calibrate the reactivity of simple conjugated enynes toward the CM reaction similar to those reported by Chang and co-workers,[9] the CM reaction of enynes **3a**,**b** and several alkene counterparts were examined (Table 1). Quite unexpectedly, enynes **3a**,**b** are reasonably good substrates for CM

Table 1. Diene CM Reaction of Terminal Conjugated Enynes[a]

entry	enyne	alkene	temp (°C)/ time (h)	CM product	yield (%)[c] E / Z[b]
1			25 / 18		1:7 34
2			25 / 8		1:20 37
3			25 / 8		1:5 40

[a] Catalyst **6** (5−10 mol %) was added to a solution of the enyne and the alkene in CH_2Cl_2. [b] Determined by ^1H NMR. [c] Isolated yield.

reaction with catalyst **6**. First, substrate **3a** containing a terminal enyne conjugated to a carbonyl group was reacted with symmetric disubstituted *cis*-alkene **8a** affording a moderate yield (34%) of the cross-coupled product **9a** as 1:7 mixture of *E*/*Z* isomers (entry 1). The related enyne **3b** possessing an acetate instead of the carbonyl group at the propargylic site reacted with **8a** to afford the expected CM product **9b** in 37% yield with a significantly increased *E*/*Z* ratio of 1:20 (entry 2).[9,11,12] The CM reaction between **3b** and trimethylallylsilane **8b** yielded the cross-coupled product in 40% yield with a 1:5 ratio of *E*/*Z* isomers (entry 3). In terms of overall reactivity, the electron-deficient substrate **3a** seems to be less reactive compared to **3b**, taking much longer reaction time to reach similar conversion (18 h vs 8 h).

The successful examples of CM reactions in Table 1 are in sharp contrast to those reported by Chang in which the CM reactions of conjugated enynes failed by using **6**, requiring the use of more active catalyst **7**. Thus, the catalyst deactivation by the putative complexation between catalyst and simple conjugated enynes suggested by these authors is not the major encumbrance for the metathesis of conjugated enynes **3a**,**b**, which is probably the consequence of different stereoelectronic environments caused by dissimilar substituents on the alkyne. The CM with more active catalyst **7** afforded **9a** in slightly improved yield (45% vs 34%) but overall performance of **7** was quite similar to that of **6**.

Mechanistically, we believe that the catalytic cycle of this enyne−alkene CM reaction starts from the reaction between alkenes **8a**−**c** and catalyst **6** (the top half of Scheme 1). The resultant propagating alkylidene species **10** then reacts with conjugated alkyne **3a**,**b**, generating metalacyclobutane **11**, the [2 +2] cycloreversion of which gives a CM product **9a**−**c** and methylidene, which initiates another round of the catalytic cycle. The moderate yields obtained in Table 1 are probably the consequence of the low reactivity of conjugated enynes **3a**,**b** toward the propagating alkylidene **10**.

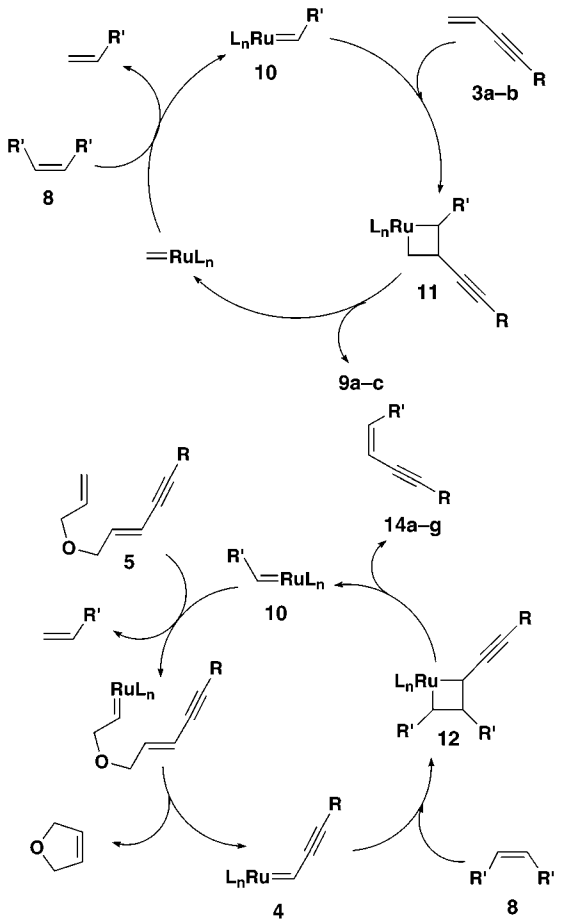
Due to the lack of flexibility in modulating the reactivity of simple enynes **3a**,**b**, we considered the development of a new type of enyne substrate **5** that would participate in metathesis reactions with completely different reaction

(8) (a) Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Organometallics* **2001**, *20*, 3845. (b) von Otterlo, W. A. L.; Ngidi, E. L.; de Knoing, C. B.; Fernandes, M. A. *Tetrahedron Lett.* **2004**, *45*, 659.

(9) (a) Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041. (b) Ratnayake, A. S.; Hemscheidt, T. *Org. Lett.* **2002**, *4*, 4667.

(10) Mechanistically, conjugated alkenyl alkylidenes are involved in all enyne methathesis processes. For recent examples of ring closing metathesis reactions employing conjugated dienes as starting materials to generate the putative conjugated alkenyl alkylidenes as intermediates, see: (a) Frederique, R.; Claire, V.; Laurent, E.; Laurence, G. *Org. Lett.* **2003**, *5*, 2007. (b) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (c) Evano, G.; Schaus, J. V.; Panek, J. S. *Org. Lett.* **2004**, *6*, 525.

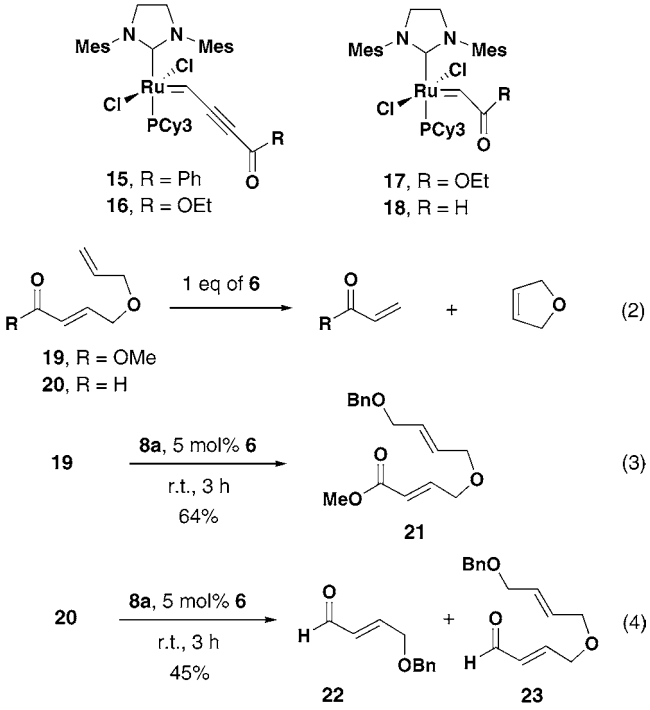
Scheme 1. Two Different Catalytic Cycles for the CM Reaction



manifold (the bottom half of Scheme 2). For substrate **5**, with the allyl ether appendage acting as a catalyst delivery vehicle, the CM reaction will selectively initiate at the terminal olefin of the allyl group, generating the conjugated alkynyl alkylidene **4** after the extrusion of dihydrofuran.[13] Subsequent reaction of the alkylidene **4** with alkene **8** to form the metalacyclobutane intermediate **12** followed by its cycloreversion would provide CM products **14**. Overall, the biggest difference between these two catalytic cycles is the step forming **11** and **12**. We believe that the reaction of alkylidene **10** and conjugated enyne **3a**,**b** is slower than that of conjugated alkylidene **4** and alkene **8**, thereby providing lower overall CM efficiency.[14]

On the basis of this mechanistic hypothesis, we prepared substrates **5a**−**e** that contain the allyl ether moiety and carried out their CM reactions.[15] With the more active conjugated enyne equivalent **5a**−**e**, the CM product **9a** and **14a**−**e** were obtained in significantly improved chemical yields yet with somewhat decreased *E*/*Z* selectivity for certain substrates (Table 2). The CM reaction of **5a** with alkene **8a** afforded

Scheme 2



improved yield of **9a** within shorter reaction time (entry 1 in Table 2; 6 h, 63% yield) compared to that of **3a** (entry 1 in Table 1; 18 h, 34% yield). Notably, the stereoselectivity (1:4 vs 1:7) is somewhat different between the two reactions, which may indicate different reaction mechanisms involving different alkylidene intermediates (**10** vs **4**) from enyne substrates **5a** and **3a**, respectively. The protecting group change in alkene counterpart from **8a** to **8c** in the CM reaction with **5a** did not significantly change the yield and stereoselectivity, affording acetate **14a** in 59% yield with an *E*/*Z* ratio of 1:5 (entry 2). The highest yield was obtained from the CM of the TBS-protected enyne **5b** with alkene **8c**, affording CM product **14b** in 80% yield and an *E*/*Z* ratio of 1:10 (entry 3). The CM reaction of electron deficient substrate **5c** with alkene **8c** provided the conjugated ethyl alkynoate **14c** in 66% yield with excellent *Z*-selectivity (entry 4). The significantly different reaction rate between **5b** and **5c** at the same temperature (0.7 h vs 10 h) implies that the generation of alkylidene species such as **15** becomes slower if the resultant alkylidene is electron deficient. Unexpectedly, the CM of **5d**, which does not carry electron-withdrawing

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

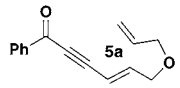
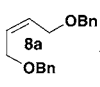
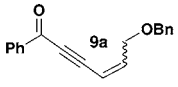
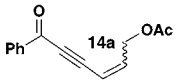
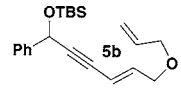
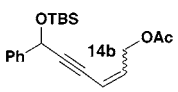
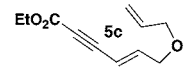
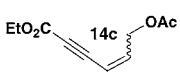
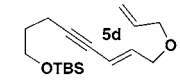
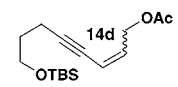
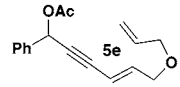
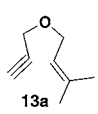
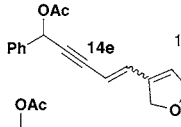
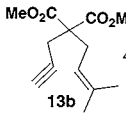
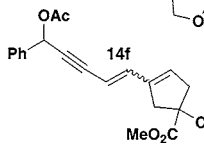
(12) The *Z*-selective cross metathesis of acrylonitrile, see: (a) Crowe, W. E.; Goldberg D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162. (b) Randle, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430.

(13) A similar strategy to generate alkylidene at a less reactive site by the initiation from the remote site followed by intramolecular delivery of the catalyst has been pursued by Hoye and co-workers and termed "Relay Metathesis". See: Zhao, H. Ph.D. Thesis, University of Minnesota, 2001. Lange, B. S. *Abstracts of Papers*, 227th National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, 2004; CHED 899. See also ref 12b and Robinson, J.; Piscopio, A. D. *Abstracts of Papers*, 226th National Meeting of the American Chemical Society, New York, NY; American Chemical Society: Washington, DC, September, 2003.

(14) The involvement of a slow initiating methylidene in the former could also result in inefficient turn over.

(15) For the preparation of **5**, see the Supporting Information.

Table 2. CM Reaction of Enynes Containing an Allyl Ether Moiety for Catalyst Delivery[a]

entry	enyne	alkene	temp (°C)/ time (h)	CM product	E / Z[b]	yield (%)[c]
1			25 / 6		1:4	63
2			25 / 5		1:5	59
3		8c	40 / 0.7		1:10	80
4		8c	40 / 10		1:20	66
5		8c	40 / 14		1:7	60
6			40 / 2		1.5:1	55
7	5e		40 / 2		3:1	25

[a] Typical reaction conditions: Catalyst **6** was added to a solution of the enyne **5** and the alkene **8** or alkyne **13** in CH_2Cl_2. [b] Determined by ^1H NMR. [c] Isolated yield.

substituents (entry 5), is similar to that of **5c**, providing a 60% yield of **14d** in 14 h but with reduced *Z*-selectivity (1:20 vs 1:7).

We next used enyne **13a**,**b** as the CM partner where the ene moiety is deactivated by steric hindrance of three substituents, leaving the alkyne moiety as the initially reacting functional group with alkylidene **4**. The CM reaction between **5e** and enyne **13a** provided the conjugated dienyne **14e** in 55% yield and a 1.5:1 ratio of *E*/*Z* isomers (entry 6). A similar result was obtained from the CM with a slightly different enyne **13b**, affording **14f** in 25% yield with *E*/*Z* selectivity favoring the *E*-isomer in a 3:1 ratio.[16] The sudden change in *E*/*Z* selectivity in the reaction of **13a** and **13b** is not clear at this point.

The formation of products **14e**,**f** has important mechanistic implication for these CM reactions which supports our mechanistic hypothesis depicted in Scheme 1 because the cross-coupling between **5e** and **13a**,**b** is possible only if the reaction occurs via the intermediacy of alkylidene **4**. Another salient feature of the CM reaction with enyne **5** is the facile formation of the electron-deficient conjugated alkylidenes **15** and **16** in the presence of normal alkenes. Additionally, the alkene initiation can be deduced from the formation of **14e**,**f** in the CM reaction with the sterically and stereoelectronically unbiased allyl and propargyl group in **5e** and **13a**,**b**, which provides an insight into one of the most controversial mechanistic question in enyne metathesis; whether the initiation occurs at the alkene or the alkyne.

The favorable involvement of putative alkylidene species **15** and **16** in CM reaction suggests that other electron deficient, thus very reactive,[17] conjugated alkylidene species **17** and **18** might also be generated similarly using the catalyst delivery vehicle strategy such as in the reaction of **19** and **21** (Scheme 2). To test the feasibility of this reasoning, **19** and **20** were treated with stoichiometric amount of **6** and the progress was monitored by ^1H NMR (Scheme 2, eq 2). The formation of dihydrofuran in both reactions strongly suggests initiation at the terminal alkene followed by catalyst delivery to the α-carbon of the carbonyl group to generate **17** and **18**. These electron-deficient alkylidenes were not directly observed by NMR due to rapid catalytic turnover by **17** and **18** to form methyl acrylate and acrolein, respectively.[18] However, the CM reaction of **19** in the presence of alkene **8a** and catalytic amount of **6** provided only the terminal allyl group cross-coupled product **21**, which indicates the formation of enoate alkylidene intermediate **17** is prohibited in the presence of external alkene. Interestingly, the CM reaction of aldehyde **20** afforded 2:1 mixture of **22** and **23** (Scheme 2, eq 4). We believe enal **22** is derived from a propagating alkylidene **18**.

In summary, we achieved the efficient cross metathesis reaction between conjugated enynes and alkenes by designing a novel substrate containing a catalyst delivery vehicle. By using this device a conjugated alkynyl alkylidene of type **4** could be generated and utilized for CM reaction, which should find useful application in other types of metathesis processes. Further study toward the formation of cyclic and acyclic enediynes using this strategy is underway.

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Note Added after ASAP. Footnote 13 of the version posted ASAP on May 19, 2004 has been corrected; the corrected version was posted May 21, 2004.

Supporting Information Available: Experimental details and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The formation of cross-coupled products **14e**,**f** is a strong indication of the preferential initiation of the metathesis at the alkene moiety over the alkyne.

(17) (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.

(18) Although a stoichiometric amount of catalyst was used, only a small fraction underwent initiation to catalyze the reaction of **19** and **20**. Therefore, only a small amount of styrene was observed by NMR.