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Selective Domino Ring-Closing Metathesis–Cross-Metathesis Reactions between Enynes and Electron-Deficient Alkenes

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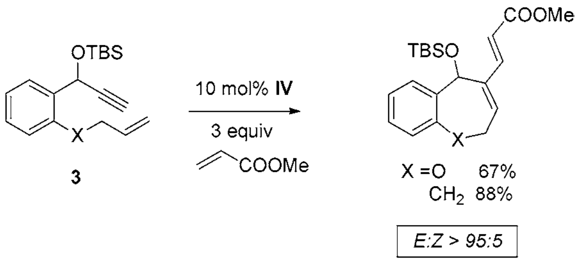
ABSTRACT



A selective domino ring-closing metathesis (RCM)–cross-metathesis (CM) process between enynes and electron-deficient alkenes is reported. The conditions have been optimized for enynes 3 and methyl acrylate with catalyst IV. The scope and limitations of this reaction are described, and a possible mechanism is discussed.

Over the past decade, olefin metathesis has emerged as a powerful tool in organic synthesis.[1] The development of ruthenium carbene complexes **I**,[2] **II**,[3] **III**,[4] and **IV**[5] by Grubbs' and other groups is particularly notable because of their availability, operational simplicity, and remarkable functional group tolerance (Figure 1).

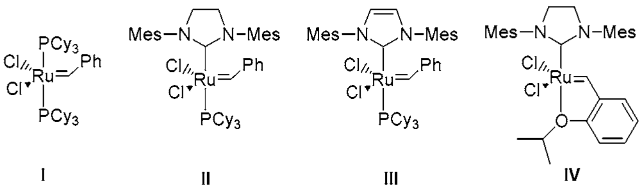


Figure 1.

Enyne metathesis is a very interesting and useful way to synthesize 1,3-dienes.[6] In an intramolecular version, the alkylidene part of the alkene moiety migrates onto the alkyne carbon. We were interested in using such a reaction to obtain compound **2** from the conjugated alkene **1** (Scheme 1).

Unfortunately, this reaction failed even with highly active catalysts such as **II**, **III**, or **IV**, probably due to the

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(1) For recent reviews, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2067. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (d) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (e) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (g) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(2) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

(3) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(4) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

(5) (a) Kingbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(6) For recent reviews, see: (a) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133. (b) Storm Poulsen, C.; Madsen, R. *Synthesis* **2003**, *1*, 18.

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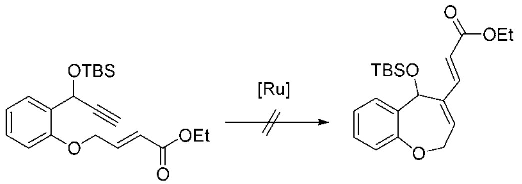
Scheme 1

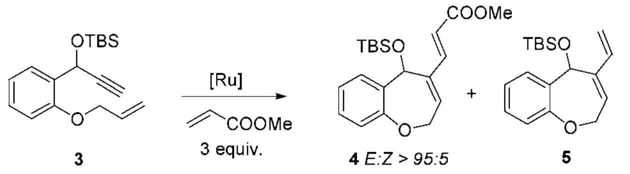


1 **2**

deactivation of the alkene moiety. To obtain compound **2**, we envisioned another strategy. Herein, we wish to report a tandem ring-closing metathesis (RCM)−cross-metathesis (CM) reaction between an enyne and a conjugated alkene.[7]

The metathesis reactions were effected with 3 equiv of the CM partner as classically required,[8] and different solvents and catalysts were used (Table 1). With catalyst **II** or **III**, we only obtained unsubstituted diene **5**. No trace of CM product **4** was detected. The use of catalyst **IV** (10 mol %) in dichloromethane at 40 °C for 12 h leads to the best results.

Table 1



3 **4** *E:Z* > 95:5 **5**

catalyst	solvent	temp	time	ratio **4*E***:**5** (isolated yield of **4*E***)
II or **III** (5 mol %)	CH_2Cl_2	rt	5 days	0:100
	CH_2Cl_2	40 °C	48 h	0:100
	toluene	80 °C	48 h	0:100
IV (5 mol %)	CH_2Cl_2	rt	5 days	80:20 (50%)
	CH_2Cl_2	40 °C	48 h	80:20 (50%)
IV (10 mol %)	CH_2Cl_2	40 °C	12 h	100:0 (67%)

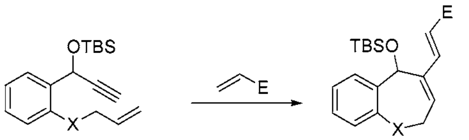
If less than 10 mol % catalyst is used, some diene **5** was obtained, but it can be resubmitted to the same conditions to furnish the desired product **4*E***.

Such an amount of catalyst might be necessary because of a possible chelation by the diene moiety, decreasing ruthenium turnover. This reaction is very selective: only the (*E*)-isomer was detected by ^{1}H NMR.

Several enynes and unsaturated alkenes were screened for this tandem reaction (Scheme 2).

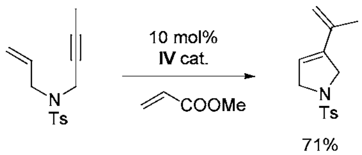
In all cases, except for acrylonitrile, the conjugated (*E*)-dienes were obtained in moderate to good yields with only traces of the homocoupling product. In the case of electron-rich alkenes such as styrene, allyltrimethylsilane, or *tert*-butyldimethylsilyloxyallyl ether, only enyne RCM products were formed, contaminated by alkene homocoupling compounds. In the case of a substituted alkyne, we only observed the RCM product even after 3 days at reflux in dichloromethane (Scheme 3).

Scheme 2



E= CO_2Me; X = O 67%
E= CO_2Me; X = CH_2 88%
E= CHO; X = O 65%
E= CHO; X = CH_2 61%
E= COMe; X = O 68%
E= COMe; X = CH_2 73%
E= CN; X = O 0%

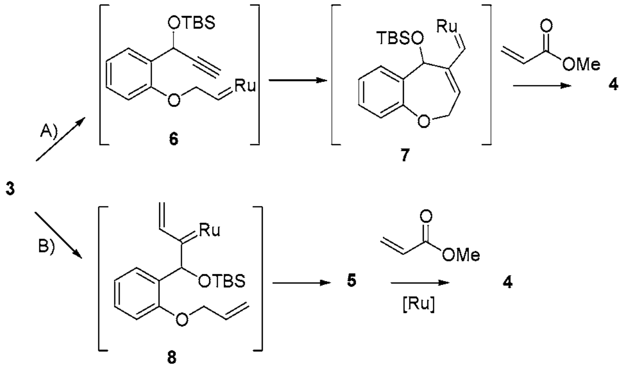
Scheme 3



To our knowledge, this reaction is among the first example of a CM between a diene and an alkene.[9]

Regarding the deactivation of the conjugated alkene toward metathesis, a mechanism starting with a CM process between the acrylate and the alkyne is mostly improbable. In the case of electron-rich olefins such as styrene, the dimerization observed could result from such a mechanism. But in the case of electron-deficient olefins, two distinct mechanisms can be invoked to explain the formation of **4**: (A) initial metathesis occurs at the alkene giving rise to carbene **7** (via carbene **6)**, which in turn undergoes CM with the electron-poor alkene, and (B) the initial reaction site is the alkyne, leading to the more substituted vinyl alkylidene **8**,[10] and an intramolecular process gives compound **5**, which is engaged further in a CM reaction with the conjugated alkene (Scheme 4).

Scheme 4



The formation of diene **5** observed all along the process seems to confirm pathway B.[11] Furthermore, we have

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(7) For a previous example of a tandem CM/RO/RCM, see: Randl, S.; Lucas, N.; Connon, S. J.; Blechert, S. *Adv. Synth. Catal.* **2002**, *344*, 631.

demonstrated that diene **5** could be re-engaged in a CM reaction simply by treating it with 3 equiv of methyl acrylate in the presence of catalyst **IV**.

In conclusion, we have developed a very selective domino RCM−CM process between enynes and conjugated alkenes. We have also demonstrated that the butadiene moiety is a good partner for CM reactions. This method provides an efficient one-step formation of conjugated (*E*)-1,3-dienes under mild conditions.

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Supporting Information Available: Synthetic procedures for the one-pot RCM−CM procedure as well as analytical and spectral data for dienes **4*E***. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.

(9) A previous example of a CM between a diene and an alkene was reported by Blechert et al. (in ref 7, see footnote 7).

(10) More substituted vinyl alkylidene is the more stable one according to: Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484.

(11) If this is the case, the process is a *pseudo*-domino one as described in: Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456−9459.