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COMMUNICATIONS

Published on Web 07/17/2004

Tandem Cyclopropanation/Ring-Closing Metathesis of Dienynes

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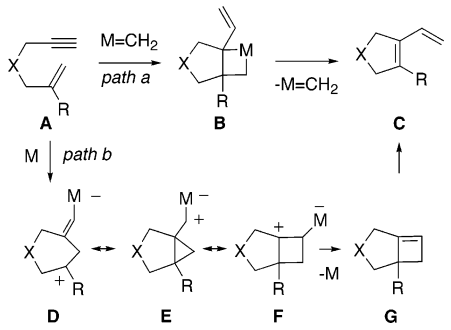
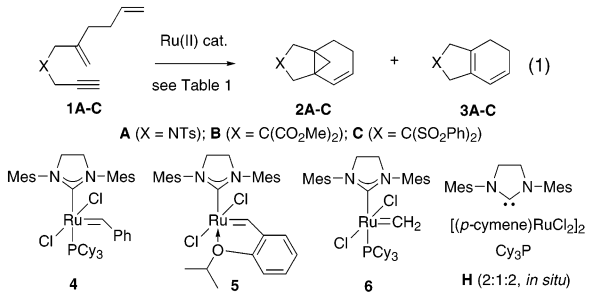
Enyne metathesis can be categorized into two mechanistic superfamilies, one mediated by metal carbenes (path a, Scheme 1), the other by metal activation of the alkyne (path b).[1] These catalytic processes are distinct: metal carbenes react via cycloaddition, while noncarbene metal complexes (e.g., $PtCl_2$) serve as π-Lewis acids.

Scheme 1. Enyne Metathesis Mechanisms



For reactions that can elude these pathways, new catalytic processes may be realized that will also enhance our understanding of the parent enyne metathesis. In this communication, we report a catalytic cyclopropanation/ring-closing metathesis that is initiated either by ruthenium carbenes **4** and **5** or by an in situ noncarbenic ruthenium(II) complex (from **H**, eq 1). These studies suggest an unexpected interplay between the two mechanisms of enyne metathesis.



Through ring-closing alkene metathesis (RCM), the side-chain alkene influences the course of enyne bond reorganization. This catalytic tandem process leading to **2** was not expected on the basis of previous metathesis work using ruthenium carbenes. The cyclopropanation part of the reaction is highly unusual for Grubbs' ruthenium carbenes and has not been observed as a catalytic process.[2] It is also surprising that the noncarbenic metal complex from **H** gives the same product, since enyne bond reorganization occurs by a mechanistically-distinct catalytic process. The pendant terminal alkene interrupts normal enyne metathesis leading to diene **3** (eq 1), ushering the product manifold toward cyclopropane **2**. This complexity-generating tandem transformation provides insight into the reactive nature of intermediate cyclopropyl ruthenium carbenes. In addition, the tandem alkene metathesis product **3** can be obtained by an appropriate choice of catalysts.

The dienynes of eq 1 were subjected to standard ring-closing enyne metathesis conditions, which triggered the tandem process as summarized in Table 1. The tosyl amide **1A** gave tandem ring-closing metathesis, accompanied by trace amounts of the cyclopropane **2A**,[3] but higher temperatures produced a greater proportion of **2A** (entries 1−4). In these runs, the percentage of cyclopropanes **2A** (7−21%) exceeded the catalyst loading, and complete conversions of **1A** were observed, suggesting that reductive elimination giving noncarbenic ruthenium(II) does not halt catalysis.[2b,c] With malonate **1B**, an even greater proportion of cyclopropane was formed, increasing with reaction temperature (entries 5, 6). Using carbene **4** or **5** as precatalyst, the bissulfone **1C** gave cyclopropane **2C** as the sole product (entries 7, 8).[4] If RCM could serve to trap intermediate **E** in the noncarbenic enyne metathesis manifold, then a $Ru{=}CH_2$ would be produced. We tested this hypothesis by preparing an in situ catalyst **H**, composed of a 1:2:2:4 molar ratio of $[(p\text{-cymene})RuCl_2]_2$, 1,3-bis(mesityl)-4,5-dihydroimidazolium chloride, tricyclohexylphosphine, and Cs_2CO_3. This is an adaptation of the formulation reported by Dixneuf,[5] with phosphine added.[5c] Complete conversions were obtained by addition of alkyne to the preheated catalyst mixture (entries 9, 10). Both carbene and noncarbene precatalysts trigger the tandem process.[6]

Table 1. Tandem Cyclopropanation/RCM[a]

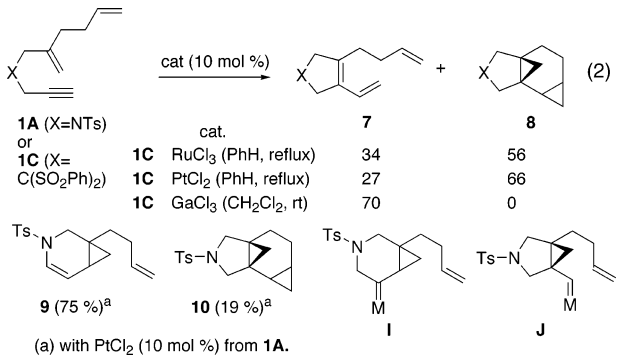
entry	enyne	cat	solv/temp	time/h	**2** (% yield)	**3** (% yield)
1	**1A**	**4**	CH_2Cl_2, rt	2.5	7	75
2	**1A**	**5**	CH_2Cl_2, rt	2.5	8	74
3	**1A**	**4**	CH_2Cl_2, reflux	0.8	8	76
4	**1A**	**4**	PhH, reflux	1	21	74
5	**1B**	**4**[b]	CH_2Cl_2, rt	24	31[c]	63[c]
6	**1B**	**4**	PhH, reflux	24	45[c]	21[c]
7	**1C**	**4**	PhH, reflux	24	83[d]	0
8	**1C**	**5**	PhH, reflux	24	74	0
9	**1C**	**H**[e]	tol, 80 °C	24	60	0
10	**1C**	**H**[b,e]	tol, 80 °C	24	69	0

[a] 5 mol % catalyst used in these runs. [b] 10 mol % catalyst used. [c] Yield determined by NMR vs mesityleneinternal standard. [d] 76% with purified **4** (chromatography). [e] 5 mol % Ru atom, catalyst **H** prepared in situ from 1:2:2:4 molar ratio of $[(p\text{-cymene})RuCl_2]_2$, 1,3-bis(mesityl)-4,5-dihydroimidazolium chloride, Cy_3P, and Cs_2CO_3, respectively.

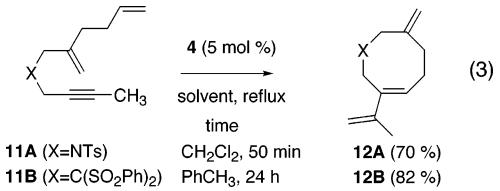
While the initial ring closure by cyclopropanation is influenced by the geometry of the enyne tether, the second trapping reaction is sensitive to the metal and its coordination environment. With catalysts **4** and **H**, **1C** gives efficient pendant alkene trapping by RCM (Table 1). The salt $RuCl_3$ produced a single ring-closing enyne metathesis product **7** (eq 2) and instead of RCM, gave trapping of the proposed carbenoid intermediate **E** by cyclopropanation. A similar result was observed with $PtCl_2$ (eq 2, which shows related tandem cyclopropanation).[7] Remarkably, $GaCl_3$[8] produces normal enyne bond reorganization without a tandem process (cyclopropanation or RCM). In contrast to the tandem RCM results of entries 1−4 (Table 1, above), tosylamide **1A** reacted with $PtCl_2$ to give initial cyclopropanation,[9] but this was followed by either endocyclic carbene formation (via **I**) to give **9** or exocyclic carbene formation (e.g., **J**), which led to biscyclopropane **10**.

Normal, carbene-mediated ring-closing enyne metathesis is observed when the alkyne is internal (eq 3). Less favorable alkyne bind-

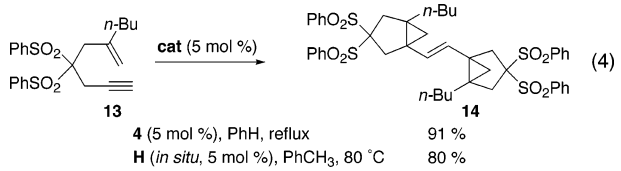
10.1021/ja049079o CCC: $27.50



ing leads to preferential reaction of the metal carbene with the 1-alkene of **11**. The resulting alkylidene produces **12** by ring-closing metathesis.

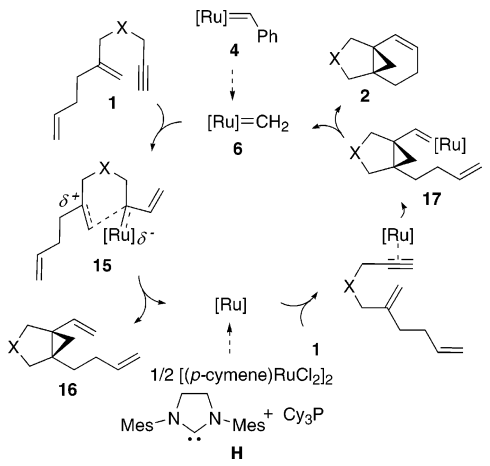


The intermediate cyclopropyl carbenes in eq 2 gave competing cyclopropanation and enyne metathesis. To test the predilection of bissulfone **1C** for initial cyclopropanation and to determine whether the exocyclic cyclopropyl carbene might interconvert into an endocyclic carbene, the pendant alkene was removed (**13** in eq 4). In this case, both the Grubbs' carbene **4** and the in situ complex **H** promoted cyclopropanation/cross metathesis to give **14** as a 1:1.5 mixture of *syn*- and *anti*-diastereomers. Most likely this occurs via intermediate cyclopropyl carbenes.

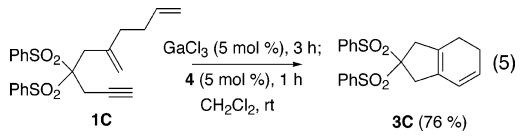


The above evidence points to a catalytic mechanism operating with interplay between the "dichotomous" reaction mechanisms of Scheme 1. Ring constraint in the dienyne and the consecutive RCM step are important features permitting this interaction. Ring constraint in **1C** (vs **1A**) encourages cyclopropanation via **15** (Scheme 2).[10] This would normally stop catalysis by metal carbenes. The ring-closing enyne metathesis step is especially critical to this catalytic process since it allows metal activation to result in metal carbene production (**17** to **2** and **6**).[11] Further mechanistic studies are needed, but it is clear that either noncarbenic metal complexes or metal carbenes may catalyze the tandem cyclopropanation/ring-closing metathesis.

Scheme 2. Proposed Mechanism



Last, the tendency of **1C** toward cyclopropanation can be overridden to obtain the tandem metathesis product **3C** by sequential addition of catalysts in a one-pot transformation. The bond reorganization was triggered by $GaCl_3$, and ring closure of the intermediate triene was accomplished with the Grubbs' carbene **4** (eq 5). Sequential, tandem catalysis in this case leads to tandem ring-closing enyne metathesis/ring-closing alkene metathesis.



In conclusion, a catalytic tandem cyclopropanation-RCM process has been discovered. For noncarbene precatalysts, the ring closure generates a carbene; for carbene precatalysts, a cyclopropanation process results in production of a noncarbene. Substrate geometry plays an important role in dictating the initial cyclopropanation, but this can be overcome for 1,3-cyclohexadiene synthesis by a sequential use of catalysts. Further mechanistic studies on this reaction are ongoing.

Acknowledgment. We thank Jordan Markham for preliminary data with **3B** and the NIH for generous support of this work through Grant R01CA090603.

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

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(1) Reviews: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (b) Schmidt, B. *Angew. Chem., Int. Ed.* **2003**, 42, 4996−4999. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (d) First report using Pd(II): Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636−1638.

(2) A notable exception is the coordinatively saturated Ru(II) carbene of Nishiyama that gives cyclopropanation: (a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223−2224. Reductive elimination of noncarbene Ru(II) from Ru(IV) ruthenacyclobutanes has been suggested as a competing process that *consumes* propagating metal carbenes. See: (b) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020−1022. (c) Kitamura, T.; Sato, Y.; Mori, M. *Chem. Commun.* **2001**, 1258−1259.

(3) Minor byproducts evident from crude ^{1}H NMR include <1% of the eight-membered ring (see **12A**, eq 3) and showed 1 to 2% aromatization of **3A**.

(4) Identical results were obtained with purified commercial and synthesized batches of **4**. In these runs there are no isolable byproducts. The crude ^{1}H NMR reveals ca. 2 to 3% unreacted **1C**, no styrene and 1 to 2% dimeric byproduct (see **14**).

(5) (a) Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Helv. Chim. Acta* **2001**, *84*, 3335−3341. (b) Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2002**, *344*, 585−595. (c) Cy_3P was added to approximate the ligand environment of the reductive elimination product. Without Cy_3P, the in situ catalyst (20 mol %) gave incomplete conversion: 40% **1C**, 5−10% **2C**.

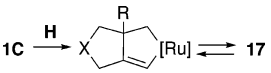
(6) Carbene generation by 1-alkyne to vinylidene carbene rearrangement is discounted since allenes were not detected and because regeneration of a carbene would consume 50 mol % of dienyne, restricting yields to 50%.

(7) Related carbenoid trapping for polycyclic ring synthesis: Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104−9105.

(8) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295.

(9) (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305−8314. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785−6786.

(10) (a) Diene **16** could also arise by reductive elimination from a ruthenacyclobutane. (b) A bidentate, cyclometallative pathway is also possible for the right side of Scheme 2.



(11) This is an important difference between the parallel studies of Dixneuf, where the metal carbene was regenerated with added diazoalkane. See: Monnier, F.; Castillo, D.; Derien, S.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5474−5477.

JA049079O