

Synthesis of Cyclic Dienamide Using Ruthenium-Catalyzed Ring-Closing Metathesis of Ene-Ynamide

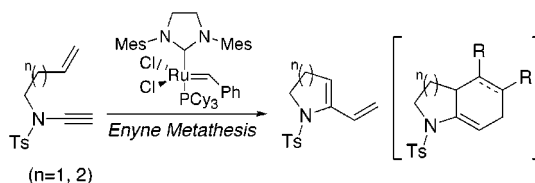
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ABSTRACT



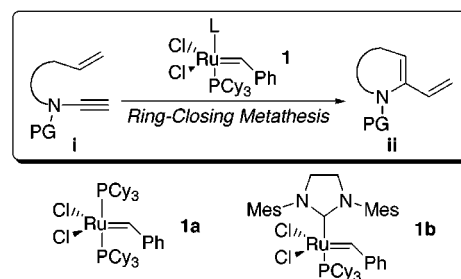
Ring-closing metathesis of ene-ynamide using the second-generation Grubbs' catalyst produced nitrogen-containing heterocycles, which have dienamide moieties, in high yields. Diels–Alder reaction of the cyclized product and dienophile proceeded smoothly to afford a bi- or tricyclic compound.

A transition metal catalyzed metathesis reaction is recognized as one of the most powerful and useful methodologies in synthetic organic chemistry.¹ Ring-closing metathesis (RCM) is widely used for the synthesis of complex cyclic compounds, including natural products. An intramolecular enyne metathesis is a particularly interesting reaction, because the double bond of the enyne is cleaved and the alkylidene part of the olefin migrates to the alkyne carbon to afford a cyclized product that has a diene moiety.² We have recently developed enyne metathesis using a Grubbs' ruthenium catalyst **1** and have reported some applications, including natural product synthesis, using this reaction.³

(1) For recent reviews on metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) *Topics in Organometallic Chemistry*; Fürstner, A., Ed.; Springer-Verlag: Berlin, Heidelberg, 1998; Vol. 1. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (f) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (g) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (h) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (i) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (j) Shrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (k) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945. (l) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490. (m) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (n) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787.

Herein we report the synthesis of cyclic dienamide using ruthenium-catalyzed RCM. As shown in Scheme 1, enyne

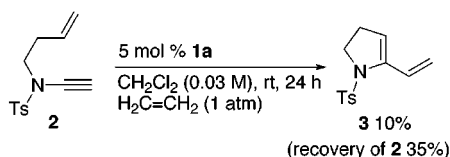
Scheme 1



metathesis of the substrate **i** having an ynamide moiety⁴ would give the cyclized product **ii**, which has an electron-donating group on the diene part (i.e., dienamide part). It is expected that the dienamide moiety could be used for a further carbon–carbon bond-forming reaction, such as the Diels–Alder reaction.⁵

To examine the feasibility of this approach, RCM of ene-ynamide **2** was attempted (Scheme 2). When a solution of **2**

Scheme 2



and 5 mol % of **1a**^{6a} in CH₂Cl₂ (0.03 M) was stirred at room temperature for 24 h under ethylene gas^{3e,h,i} (1 atm), the desired pyrrolidine derivative **3**, which has a dienamide moiety, was produced in 10% yield along with the starting material **2** in 35% yield.

Encouraged by this result, RCM of **2** was investigated under various conditions (Table 1). A solution of **2** and **1a**

Table 1. Ring-Closing Metathesis of **2** Using **1a** or **1b**

run	catalyst	conditions	time	yield (%)
1	1a	CH ₂ Cl ₂ /reflux	24 h	7 (36) ^a
2	1b	CH ₂ Cl ₂ /reflux	4 h	66
3	1b	toluene/80 °C	15 min	83
4 ^b	1b	toluene/80 °C	30 min	76

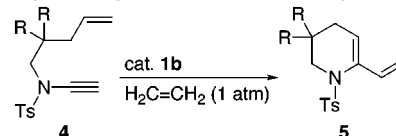
^a The yield in parentheses is that of recovered **2**. ^b The reaction was carried out under Ar.

in CH₂Cl₂ was refluxed for 4 h to give **3** in only 7% yield (run 1). However, we were surprised to find that the use of the second-generation Grubbs' catalyst **1b**^{6b} accelerated the reaction rate and improved the yield of **3**. Thus, when a solution of **2** and **1b** in CH₂Cl₂ was refluxed for 4 h, **3** was obtained in 66% yield (run 2). Furthermore, the reaction of **2** in the presence of **1b** in toluene was completed within 15 min at 80 °C to give **3** in 83% yield (run 3). It is noteworthy that this ene-ynamide cyclization using **1b** proceeded smoothly under argon to afford **3** in 76% yield (run 4).⁷

On the basis of the above results, the synthesis of a piperidine derivative was investigated under various condi-

(2) For reviews on enyne metathesis, see: (a) Mori, M. *Topics in Organometallic Chemistry*; Fürstner, A., Ed.; Springer-Verlag: Berlin, Heidelberg, 1998; Vol. 1, p 133. (b) Mori, M. *J. Synth. Org. Chem. Jpn.* **1998**, 56, 115. For recent applications, see: (c) Hoye, T. R.; Donaldson, S. M.; Vos, T. *J. Org. Lett.* **1999**, 1, 277. (d) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, 39, 372. (e) Renaud, J.; Graf, C.-D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, 39, 3101. (f) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, 122, 6785. (g) Stragies, R.; Voigtmann, U.; Blechert, S. *Tetrahedron Lett.* **2000**, 41, 5465. (h) Bentz, D.; Laschat, S. *Synthesis* **2000**, 1766. (i) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, 7, 3236. (j) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, 40, 4274. (k) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; Van der Mare, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **2001**, 42, 8231.

(3) (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020. (b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, 61, 8356. (c) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, 46, 287. (d) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, 119, 12388. (e) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, 63, 6082. (f) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, 55, 8155. (g) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, 2, 543. (h) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, 3, 1161. (i) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654. (j) Kitamura, T.; Sato, Y.; Mori, M. *Chem. Commun.* **2001**, 1258.

Table 2. Ring-Closing Metathesis of **4** Using Catalyst **1b**

run	substrate	1b (mol %)	conditions	time (h)	yield ^a (%)
1	4a (R = H)	5	toluene/80 °C	20	22
2		5	toluene/60 °C	20	19 (20)
3		5	CH ₂ Cl ₂ /reflux	27	36 (38)
4		10	CH ₂ Cl ₂ /reflux	6	85
5 ^b		10	CH ₂ Cl ₂ /reflux	5	82
6	4b (R = Me)	10	CH ₂ Cl ₂ /reflux	6	61

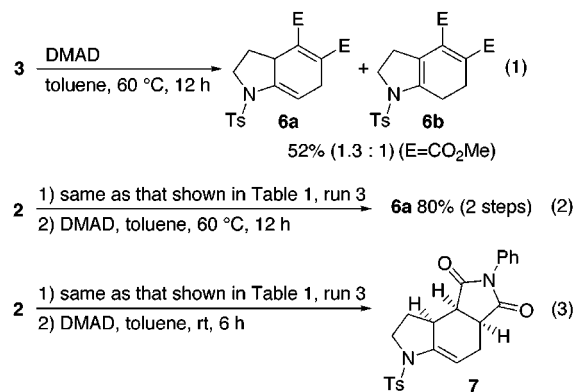
^a The yield in parentheses is that of the recovered **4**. ^b The reaction was carried out under Ar.

tions (Table 2). The reactions of **4a** and 5 mol % of **1b** gave poor results (runs 1–3). However, when reaction of **4a** and 10 mol % of **1b** in CH₂Cl₂ was carried out under reflux condition for 6 h, the yield of **5a** increased to 85% (run 4).⁸ The RCM of **4a** also proceeded under argon (1 atm) to give **5a** in 82% yield (run 5). Moreover, enyne metathesis of **4b** under the same conditions produced **5b** in 61% yield (run 6).

Next, we turned our attention to the synthesis of polycyclic compounds using Diels–Alder reaction of the cyclized product.

When a solution of **3** and dimethyl acetylenedicarboxylate (DMAD) was stirred at 60 °C, indole derivatives **6a** and **6b** were obtained in a total 53% yield in a ratio of 1.3 to 1 as an inseparable mixture (Scheme 3, eq 1). It was thought that

Scheme 3

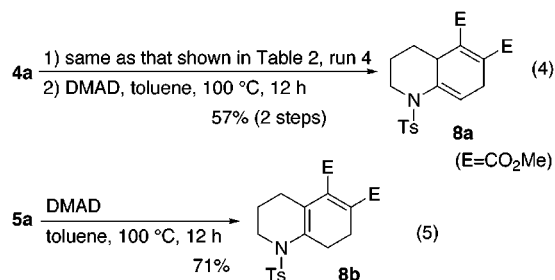


6b was formed via isomerization from **6a** under the reaction conditions. RCM of **2** was carried out under the same conditions as those shown in Table 1 (run 3), and then a solution of the crude product and DMAD in toluene was heated at 60 °C without purification to give **6a** as a sole product in 80% yield (2 steps, from **2**) (eq 2).⁹ Next, the

reaction of the crude product, which was obtained from RCM of **2**, and *N*-phenylmaleimide was attempted (eq 3). The reaction proceeded smoothly in toluene at room temperature, and the tricyclic compound **7** was produced in 68% yield (2 steps, from **2**).

In a manner similar to that of indole derivative synthesis, preparation of quinoline derivative was examined (Scheme 4). When a toluene solution of the crude product, which was

Scheme 4



obtained from the RCM of **5a**, and DMAD was heated at 100 °C for 12 h, the quinoline derivative **8a** was obtained in 57% yield (2 steps, from **4a**) (eq 4). However, the reaction

(4) For a recent review on the chemistry of ynamines and ynamides, see: (a) Zifcsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, 57, 7575 and references therein. For recent examples of nitrogen-heterocycles synthesis by cyclization of ynamide using transition metals, see: (b) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, 37, 489. (c) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 2426. (d) Witulski, B.; Gössmann, M. *Chem. Commun.* **1999**, 1879. (e) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, 1, 2037. (f) Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, 65, 7272. (g) Witulski, B.; Stengel, T. Fernández-Hernández, J. M. *Chem. Commun.* **2000**, 1965.

(5) For reviews on Diels–Alder reaction of dienamide, see: (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753 and references therein. (b) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421 and references therein. For recent examples of preparation and reaction of dienamides, see: (c) Gauvry, N.; Huet, F. *J. Org. Chem.* **2001**, 66, 583 and references therein.

of isolated **5a** and DMAD in toluene gave only **8b**, which would have been isomerized from **8a**, in 71% yield as a sole product (eq 5).¹⁰

These results indicate that nitrogen-heterocycles having dienamide moieties (i.e., cyclic dienamides) can easily be synthesized by using ruthenium-catalyzed ring-closing metathesis of ene-ynamide. It was also demonstrated that the dienamides are suitable substrates to prepare indole and quinoline derivatives via Diels–Alder reaction. Further studies along these lines are in progress.

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Supporting Information Available: Experimental procedures and spectral data for the synthesis of substrates **2** and **4**; spectral data of cyclized products **3** and **5** and Diels–Alder products **6–8**; typical procedures for RCM. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(6) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2039. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, 1, 953.

(7) When ene-ynamide was used as the substrate, the enyne metathesis of terminal alkyne proceeded smoothly under argon for the first time (cf. ref 3e). Recently, RCM of electron-rich terminal alkynes using **1** without ethylene gas has been reported (refs 2d and 2k). We continued to examine the reaction under ethylene gas, since the yield of the cyclized product that was obtained from the reaction under ethylene gas is greater than that of the cyclized product obtained from the reaction under argon.

(8) For precedence of solvent effect on the reactivity of the second-generation Ru-carbene complex, see: Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, 65, 2204.

(9) **Synthesis of 6a (Scheme 3, eq 2).** A solution of **2** (55 mg, 0.22 mmol) and **1b** (10 mg, 0.012 mmol) in degassed toluene (7 mL) was refluxed for 30 min under ethylene gas (1 atm). After the reaction mixture cooled to room temperature, the atmosphere of ethylene gas was replaced by argon gas. To this solution was added DMAD (0.14 mL, 1.2 mmol), and the resulting mixture was stirred at 60 °C for 12 h. After evaporation of the solvent, the residue was purified by silica gel flash column chromatography (hexane/AcOEt 3:1) to give **6a** (69 mg, 80%, 2 steps) as a colorless oil.

(10) The reason the reaction of the isolated product **3** or **5a** gave isomerization products of the double bond **6b** or **8b** is not clear.