

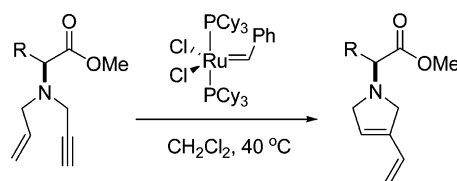
Efficient Method for the Synthesis of Chiral Pyrrolidine Derivatives via Ring-Closing Enyne Metathesis Reaction

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ABSTRACT



A series of new pyrrolidine derivatives were prepared directly in very good yields, from the substrates containing a basic or nucleophilic N atom via ring-closing enyne metathesis reaction under mild reaction conditions. Moreover, the reaction occurs smoothly without the presence of ethylene gas.

With the development of air-stable, functionally compatible, and highly active ruthenium catalysts, such as **1** (first-generation Grubbs catalyst)¹ and **2** (second-generation Grubbs catalyst)² (Figure 1), the ring-closing metathesis (RCM)

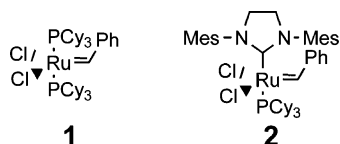


Figure 1. First- and second-generation Grubbs catalysts.

reaction has become one of the most powerful methods to synthesize many kinds of cyclized products from acyclic diene or enyne precursors.³

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The ruthenium-catalyzed ring-closing enyne metathesis (RCEM) reaction has also become a very useful process⁴ because it produces conjugated dienes which can be used, for example, in Diels–Alder⁵ and cyclopropanation⁶ reactions to form polycyclic products. In addition, it is a totally atom-economical process.⁷

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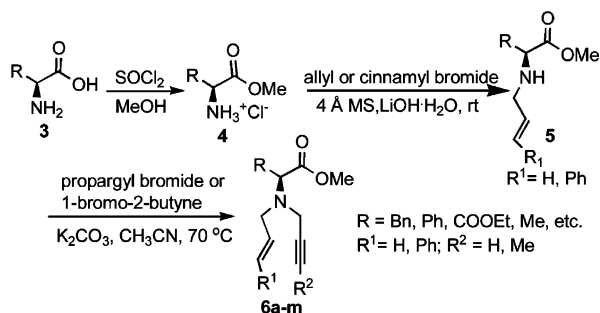
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Although there are a number of reports on the synthesis of various nitrogen heterocyclic compounds via the RCEM reaction,⁸ to the best of our knowledge, no publications have appeared concerning the use of enyne substrates containing a basic or nucleophilic N atom.⁹ It is also noteworthy that with terminal alkynes ethylene was usually required to increase the reaction rate and the yield of the reaction.¹⁰

Herein, we report a simple method for the preparation of a series of new pyrrolidine derivatives by RCM reaction of enynes containing a basic or nucleophilic N atom in the absence of ethylene gas.

We first synthesized several enyne substrates in fine yields from commercially available chiral amino acids, following literature procedures (Scheme 1).^{11,12} Enyne **6a** was used to

Scheme 1. Synthesis of Enyne Substrates



determine the optimum reaction conditions, and the results are presented in Table 1.

The RCEM reaction occurred successfully, with or without $\text{Ti}(\text{O}^i\text{Pr})_4$, and the desired product was obtained in almost the same yields (Table 1, entries 1 and 2). The result indicates that the Lewis acid does not play any substantive role in this enyne RCM reaction. We previously reported that with the assistance of the Lewis acid $\text{Ti}(\text{O}^i\text{Pr})_4$, diallyl amines containing a basic or nucleophilic N atom can successfully undergo the RCM reaction.¹³ Otherwise, the RCM reaction of such dienes is very difficult.¹⁴ When we subjected **6a** to the less active and cheaper catalyst **1** in the absence of the Lewis acid, almost the same result was obtained except that a longer reaction time was needed (Table 1, entry 3). If the

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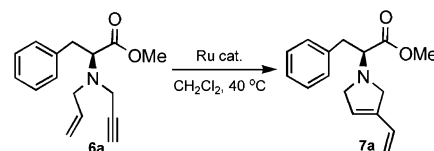
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Table 1. RCEM Reaction of **6a**^a



entry	catalyst (mol %)	$\text{Ti}(\text{O}^i\text{Pr})_4$ (mol %)	time (h)	yield (%) ^b
1	2 (5.0)	20	3	90
2	2 (5.0)	—	3	91
3	1 (5.0)	—	15	84
4 ^c	1 (3.0)	—	15	52

^a Reaction conditions: **6a** (1 mmol), CH_2Cl_2 (20 mL). ^b Isolated yield. ^c 31% starting material was recovered.

catalyst loading was reduced to 3 mol %, the yield decreased significantly and the starting material was not completely consumed (Table 1, entry 4).

Considering that catalyst **2** is more expensive than catalyst **1**, the latter was employed to assess the scope of the RCEM reaction. The results are presented in Table 2. Enynes containing ester, indole, etc. afforded the pyrrolidines, nearly always, in good yields.

To further extend the scope of this reaction, we tried some other substrates with substituents on the alkene or alkyne bond (Table 3, entries 1–3). With enynes **6i** and **6j**, the reactions went smoothly and good yields were obtained. However, when substrate **6k** was subjected to the same reaction conditions, a large amount of starting material was recovered because of the steric effect. Substrate **6l**, which contains a sulfur atom, gave no reaction under the same conditions. This may be due to the fact that the sulfur atom is a stronger electron donor, therefore causing the alkylidene ruthenium carbene to coordinate with the sulfur atom. This results in the deactivation of the catalyst.¹⁴ However, when 40 mol % of $\text{Ti}(\text{O}^i\text{Pr})_4$ was added to the reaction system, the reaction occurred successfully in 68% yield (Table 3, entry 4).¹³ Also, we tried an enyne with a less basic N atom, and the same good result was obtained (Table 3, entry 5).

There are at least two possible pathways for the RCEM reaction.¹⁵ In some cases, it was proven that the alkylidene ruthenium carbene reacts with the alkene first,^{15a,e,g,h} whereas in others, the ruthenium carbene first coordinates with the alkyne.^{15b,f,i} It can be seen from the literature that the RCM reaction of dienes containing a basic or nucleophilic N atom is difficult to achieve.¹⁶

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Table 2. RCEM Reaction of Enyne Containing a Basic or Nucleophilic N Atom^a

entry	substrate	product	yield (%) ^b
1			84
2			81
3			76
4			73
5			89
6			86
7			81
8			78

^a Reaction conditions: substrate (1 mmol), catalyst **1** (0.05 mmol), CH₂Cl₂ (20 mL), 40 °C, 15 h. ^b Isolated yield.

However, when one of the double bonds is replaced with a triple bond, the reaction occurs successfully with the less active catalyst **1**. This result may be due to the fact that a triple bond is more electron donating than a double bond, so when we subjected the enynes to the first-generation Grubbs catalyst, the ruthenium carbene coordinated with the triple bond instead of with the nitrogen atom. Thus, this reaction usually proceeds well under mild conditions.

Table 3. RCEM Reaction of Some Other Substrates^a

entry	substrate	product	yield (%) ^b
1			81
2			84
3 ^c			31
4 ^d			68
5			80

^a Reaction conditions: substrate (1 mmol), catalyst **1** (0.05 mmol), CH₂Cl₂ (20 mL), 40 °C, 15 h. ^b Isolated yield. ^c 48% starting material was recovered. ^d 40 mol % of Ti(OⁱPr)₄ was added. Without Ti(OⁱPr)₄, no reaction occurred.

In conclusion, the RCEM reaction of enynes containing a basic or nucleophilic N atom using a first-generation Grubbs catalyst occurs under mild conditions in the absence of ethylene to give the cyclized products in good yields. Additionally, it is believed that the RCEM reaction proceeds via coordination of the metal carbene with the alkyne moiety first. Alternative possibilities will also be considered as part of a broader investigation.

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Supporting Information Available: General procedures for the RCEM reaction and analytical and spectral data for the RCEM products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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