

# Lewis Acid Assisted Ring-Closing Metathesis of Chiral Diallylamines: An Efficient Approach to Enantiopure Pyrrolidine Derivatives

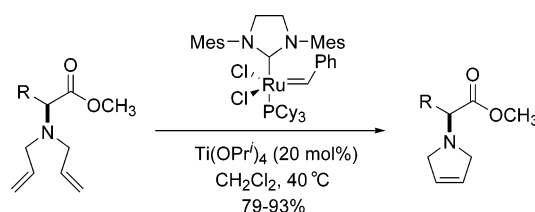
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## ABSTRACT



Lewis acid assisted ring-closing olefin metathesis (RCM) of chiral diallylamines, using the second generation RCM ruthenium-based catalyst, leads to enantiopure pyrrolidine derivatives in 79–93% yields under very mild conditions. The scope of the olefin metathesis has been expanded.

With the development of highly stable and active ruthenium alkylidenes bearing *N*-heterocyclic carbene ligands,<sup>1</sup> the ring-closing metathesis (RCM) reaction has become an important and powerful approach for the construction of many functionalized carbocycles and heterocycles from acyclic diene precursors.<sup>2</sup> Consequently, the RCM of olefinic ethers, esters, thioethers, allylic phosphanes, and allylphosphonamides has been well established using various catalytic systems.<sup>3</sup> To our knowledge, however, the metathesis of diallylamines possessing *basic* or *nucleophilic* nitrogen atoms has not been

carried out to afford pyrrolidines, even under harsh reaction conditions.<sup>4</sup> These substrates have to be deactivated by the conversion to amides, carbamates, or sulfonamides or by protonation for the ruthenium-catalyzed metathesis reaction.<sup>5</sup> The only exception is the RCM reaction of the less basic *N,N*-diallylanilines using the first generation Grubbs catalyst, with *ortho*-halo and *ortho*-vinyl anilines being the best substrates.<sup>6</sup>

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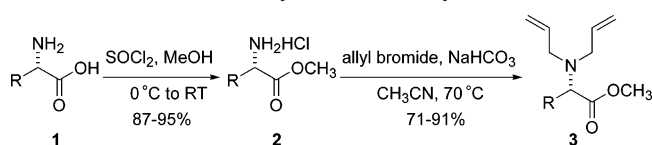
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In view of the wide range of biological activities, pyrrolidine derivatives and cyclic amino acids have received much attention. For example, pyrrolidine-3-carboxylate has been utilized as a  $\beta$ -turn motif in a GPIIb/IIIa antagonist.<sup>7</sup> Some of these derivatives have been proven to be enzyme inhibitors<sup>8</sup> or neurotransmitters.<sup>9</sup> They can also be incorporated as a 3,4-dehydro-isoproline peptidomimetic scaffold or be used as intermediates to construct alkaloid natural products and drug candidates.<sup>10</sup>

As part of our ongoing project on the synthesis of heterocyclic structures by RCM,<sup>11</sup> we report herein a straightforward method for the preparation of pyrrolidine derivatives by Lewis acid assisted RCM of diallylamine substrates.

The synthesis of chiral diallylamine precursors was based on the known procedure<sup>12</sup> from commercially available L- $\alpha$ -amino acids and shown in Scheme 1.

**Scheme 1.** Synthesis of Diallylamines



Initial studies were focused on examining the feasibility of the RCM and optimizing reaction conditions that could be applied to various diallylamines. The RCM reaction of methyl 2-diallylamino-3-phenyl-propanoate (**4**) was chosen as a model reaction and a series of Grubbs-type Ru catalysts (Figure 1) were tested.

The catalyst screening indicated that the model reaction (Table 1) did not work at all when **5**, **6a**, **7**, **11**, or **12** was

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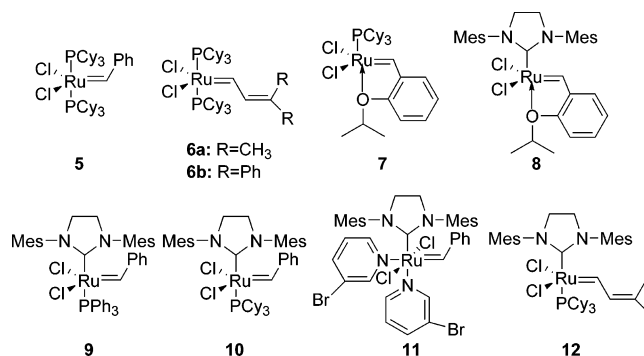
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**Figure 1.** Ruthenium catalysts investigated.

employed as the catalyst at 40 °C in CH<sub>2</sub>Cl<sub>2</sub>. The starting material, **4**, was recovered in 89–93% yield after 24 h, and the catalyst decomposed. The reaction only gave very poor results even with highly active catalysts such as **8**, **9**, or **10**. With catalyst **8**, we obtained the RCM product **13** only in 11% yield. When **9** or **10** was employed, the isolated yield of **13** was less than 25% in both cases. We ran the reaction in different solvents (1,2-dichloroethane and toluene) at higher temperature with a higher catalyst loading of **10** (15 mol % vs 5 mol %); however, the efficiency of the reaction did not improve.

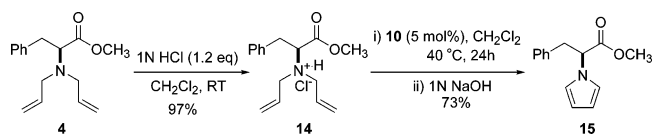
It was reported that catalyst **6b** could catalyze the RCM reaction of hydrochloride salts of amino dienes.<sup>5f</sup> To obtain compound **13** in a reasonable yield, this method was applied to the RCM reaction of the hydrochloride salt of methyl 2-diallylamino-3-phenyl-propanoate, **14** (Scheme 2). To our surprise, the reaction afforded the pyrrole **15** in 73% isolated yield, instead of the corresponding pyrrolidine **13**. This result, to some extent, is consistent with Stevens<sup>4a</sup> and Yang's observations.<sup>13</sup>

**Table 1.** Ru-Catalyzed RCM Reaction of **4**

catalyst	solvent	temp (°C)	time (h)	yield of <b>13</b> (%) <sup>a</sup>
<b>5</b> (5 mol %)	CH <sub>2</sub> Cl <sub>2</sub>	40	48	0
<b>6a</b> (5 mol %)	CH <sub>2</sub> Cl <sub>2</sub>	40	48	0
<b>7</b> (5 mol %)	CH <sub>2</sub> Cl <sub>2</sub>	40	48	0
<b>8</b> (5 mol %)	CH <sub>2</sub> Cl <sub>2</sub>	40	48	11
<b>9</b> (5 mol %)	CH <sub>2</sub> Cl <sub>2</sub>	40	48	17
<b>10</b> (5 mol %)	CH <sub>2</sub> Cl <sub>2</sub>	40	48	24
<b>11</b> (5 mol %)	CH <sub>2</sub> Cl <sub>2</sub>	40	48	0
<b>12</b> (5 mol %)	CH <sub>2</sub> Cl <sub>2</sub>	40	48	0
<b>10</b> (15 mol %)	DCE <sup>b</sup>	80	36	27
<b>10</b> (15 mol %)	toluene	110	12	19

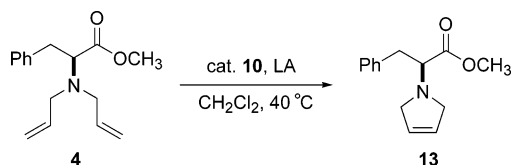
<sup>a</sup> Isolated yield. <sup>b</sup> 1,2-Dichloroethane.

**Scheme 2. RCM Reaction of 4**



According to the above as well as others' results, we believe that the basicity and nucleophilicity of the N-atom play a crucial role in the RCM reaction of diallylamines and the coordination between the N-atom and a ruthenium species may turn down the expected RCM reactions. Amines, indeed, are good ligands and have been widely used in transition metal and Lewis acid catalyzed synthetic reactions because of their good coordination to metals.<sup>14</sup> We envisioned that, in principle, if some metal complexes or Lewis acids were introduced to the reaction system to compete or prevent the coordination of the N-atom to the ruthenium carbene intermediate, the RCM reaction of diallylamines should occur. Furthermore, Furstner and co-worker have demonstrated that the RCM reaction of 4-pentenoic esters can reach a preparatively useful level when **5** and the Lewis acid are used as a binary catalyst system.<sup>15</sup> Therefore, we ran the model reaction in the presence of Lewis acids to examine the feasibility of this idea (Table 2).

**Table 2. RCM Reaction of 4 in the Presence of Lewis Acids<sup>a</sup>**



Lewis acid	amount (mol %)	time (h)	yield of <b>13</b> (%)
LiI	100	36	53
AlCl <sub>3</sub>	100	2	0 <sup>b</sup>
La(OTf) <sub>3</sub> <sup>c</sup>	100	2	0 <sup>b</sup>
Ti(O <sup>i</sup> Pr) <sub>4</sub>	100	2	91
Ti(O <sup>i</sup> Pr) <sub>4</sub>	50	5	82
Ti(O <sup>i</sup> Pr) <sub>4</sub>	20	6	93

<sup>a</sup> Reaction conditions: **4** (2 mmol), **10** (0.1 mmol), LA (20–100 mol %), 40 °C, CH<sub>2</sub>Cl<sub>2</sub> (20 mL). <sup>b</sup> Catalyst decomposed. <sup>c</sup> La(OTf)<sub>3</sub>: lanthanum(III) trifluoromethanesulfonate.

The preliminary study indicates that Ti(O<sup>i</sup>Pr)<sub>4</sub> is the best choice in this reaction. When the reaction was run in the presence of 1 equiv of Ti(O<sup>i</sup>Pr)<sub>4</sub>, the reaction gave the expected RCM product, **13**, in 91% isolated yield in 2 h. Decreasing the amount of Ti(O<sup>i</sup>Pr)<sub>4</sub> did not affect the reaction

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**Table 3. Lewis Acid Assisted RCM Reactions<sup>a</sup>**

Substrate	time (h)	Product	Yield (%) <sup>b</sup>
<b>4</b>	6	<b>13</b>	93
<b>16</b>	2	<b>17</b>	78 <sup>c</sup>
<b>18</b>	4	<b>19</b>	91
<b>20</b>	8	<b>21</b>	82
<b>22</b>	13	<b>23</b>	79
<b>24</b>	4	<b>25</b>	79

<sup>a</sup> Reaction conditions: diallylamines (2 mmol), **10** (0.1 mmol), Ti(O<sup>i</sup>Pr)<sub>4</sub> (20 mol %), 40 °C, CH<sub>2</sub>Cl<sub>2</sub> (20 mL), 2–13 h. <sup>b</sup> Isolated yield. <sup>c</sup> Isolated it by making its HCl salt.

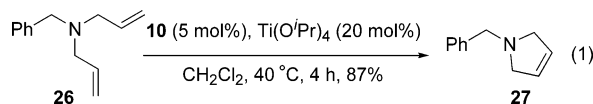
that much, if the reaction time was prolonged. Even with a catalytic amount of Ti(O<sup>i</sup>Pr)<sub>4</sub>, the reaction afforded **13** in 93% isolated yield after 6 h. AlCl<sub>3</sub> and La(OTf)<sub>3</sub> were too strong to use in this reaction, and they would decompose the catalyst in a short time. Some other Lewis acids, such as LiI, also work for RCM of **4**; however, the reactions needed more Lewis acid and more time to be completed, and then they were ruled out for further investigation.

This new protocol was then successfully used in the synthesis of enantiopure pyrrolidine derivatives from chiral diallylamines. The RCM reactions of a series of diallylamines were performed using 5–8 mol % Grubbs second generation catalyst **10** and 20 mol % Ti(O<sup>i</sup>Pr)<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (10 mL per 1 mmol of diallylamines) at 40 °C for 2–13 h; the results are summarized in Table 3.

As can be seen, the RCM reactions of all diallylamines worked very well under the optimized conditions. The

reaction afforded the corresponding pyrrolidine in good to excellent yields. HPLC analysis of compound **13** showed that there is no racemization in the course of the reaction.<sup>16</sup>

We have also briefly investigated if this process can be applied to the RCM of amino dienes. Thus, exposure of diallyl benzylamine (**26**) to our optimized RCM conditions led to a formation of 1-benzyl-2,5-dihydro-1*H*-pyrrole (**27**) in 87% yield (eq 1).<sup>17</sup>



In conclusion, we have shown that basic and nucleophilic diallylamines can participate in RCM reactions with the use

(16) See the HPLC analysis of **13** and its enantiomer in Supporting Information.

(17) Grubbs and co-workers have carried out the RCM reaction of the corresponding hydrochloride salt of **26** using **6b** as the catalyst, affording **27** in 79% isolated yield after the treatment of NaOH. Please see ref 5f.

of the second generation Grubbs ruthenium catalyst **10** in the presence of  $\text{Ti}(\text{O}^i\text{Pr})_4$ . This new procedure can be used to produce a diverse series of pyrrolidine derivatives in high yields. We are currently examining further variations of this methodology, as well as applications to the synthesis of other heterocyclic systems.

**Acknowledgment.** We are grateful to the Natural Science Foundation of China (20472021), the National Key Project for Basic Research of China (2004CCA00100), and the Hubei Province Science Fund for Distinguished Young Scholar (2004ABB011), for support of this research. We thank Drs. Richard Pederson, Choon Woo Lee, and Mike Giardello for fruitful discussions and Materia, Inc., Pasadena, CA for the generous gift of catalysts.

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

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