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# **Ring Size-Selective Ring-Closing Olefin Metathesis: Taking Advantage of the Deleterious Effect of Ethylene Gas**

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**Abstract:** The deleterious effect of ethylene gas on the ring-closing olefin metathesis (RCM) for the formation of 5- to 8-membered rings was investigated. Significant rate differences caused by ethylene gas were observed among the different ring-size formation reactions. Nevertheless, the rate differences can be advantageously utilized for chemoselective RCM.

**Keywords:** homogeneous catalysis; metathesis; ring closure; ring size-selective reaction; ruthenium

The utilization of ring-closing olefin metathesis (RCM) has seen an explosive growth in organic chemistry over the past two decades.<sup>[1]</sup> This outstanding reaction, however, is still hampered by some difficult problems. The chemoselective RCM of substrates with more than two multiple bonds available for the metathesis is one of the problems.<sup>[2,3]</sup>

During the course of our study, which is aimed at the development of new methods for the synthesis of aromatic compounds,<sup>[4]</sup> we recently tried to synthesize fused bicyclic benzenes 4 and 5 by applying the ringclosing envne metathesis (RCEM)/RCM sequence to a mixture of trienyne 1 and its isomer  $2^{[5]}$  (1:2=10:1) Grubbs' second-generation catalyst **3**<sup>[6]</sup> using (Scheme 1). As expected, under nitrogen gas, the reaction proceeded to produce 4 and 5 with double ring closing. However, under ethylene gas,<sup>[4c,7]</sup> the products detectable by <sup>1</sup>H NMR were only 4 and 6. Our surprise came not from the formation of 6 that should be formed from 2 by RCEM only, but from the absence of the corresponding RCEM product from 1, indicating that ring-size selectivity was observed between the six- and seven-membered ring formation reactions under ethylene gas.<sup>[8,9]</sup>

On these grounds, we have come to the conclusion that the generality of this type of selectivity is worthy of study. Here we report the results of our investigation in which rate differences caused by ethylene gas among 5- to 8-membered ring formation reactions were observed and the deleterious effect of ethylene gas could be used to improve selectivity in RCM synthesis of favorable ring sizes by limiting the formation of less-favorable ring sizes.

The easily prepared nitrogen-containing dienes  $7a-d^{[10]}$  were adopted as model substrates for this investigation (Scheme 2). While holding the pressure constant at 1 atm, we first compared the yields of RCM products **8a-d** under nitrogen gas with those under ethylene gas in the range of 0 to 80 °C using 1 mol%



**Scheme 1.** Incidentally observed ring size-selective RCM in which ethylene gas hindered only the RCM for 7-membered ring formation.

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<sup>[a]</sup> Ring-closing olefin metathesis was carried out with **7** and ruthenium catalyst (**3**, 1 mol%) in toluene (0.01 M) for 2 h under nitrogen or ethylene atmosphere (1 - 3 atm) at various temperatures (from 0 to 80 °C). The reaction was quenched by adding di(ethylene glycol)vinyl ether,<sup>[18]</sup> a deactivating reagent for the catalyst, to the reaction mixture. The yield was determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,4-bis(trimethylsilyl)benzene as the internal standard.

<sup>[b]</sup> Dimers and 8c (isomerization/RCM product) were formed as by-products.

Scheme 2. Investigation of deleterious effect of ethylene gas on RCM of 7a-d.<sup>[a]</sup>

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[d]

19

<35<sup>[e]</sup>

55

67<sup>[f]</sup>

Table 1. Ring size-selective RCM between 5- and 6-membered rings.<sup>[a]</sup>



6  $C_2H_4$  (3 atm) 60 7 93 [a] The reaction was carried out with 9 and ruthenium catalyst (3, 5 mol%) in toluene (0.01 M) for 2 h under a nitrogen or

44

 $30^{\left[f
ight]}$ 

ethylene atmosphere. The reaction was quenched by the addition of di(ethylene glycol)vinyl ether. [b]

20

20

The yield was determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,4-bis(trimethylsilyl)benzene as the internal standard.

[c] The reaction was carried out for 7 h.

[d] The product was not detected by <sup>1</sup>H NMR analysis.

 $C_2H_4$  (1 atm)

 $C_2H_4$  (3 atm)

[e] The yield could not be determined precisely due to the formation of significant amount of oligomer products whose <sup>1</sup>H NMR signals overlap those of **10** and **11**, and the oligomers could not be separated from **10** and **11** by silica gel chromatography.

<sup>[f]</sup> 3% of **9** was recovered.

Entry

1<sup>[c]</sup>

2

3

4

5

of catalyst 3 (Graphs 1-4 in Scheme 2). As predicted, ethylene hindered the progress of the reaction for all the substrates.<sup>[11,12]</sup> However, the degree of the hindrance varied with each ring formation and seemed to have the following order: 8-membered ring ≥7-membered ring > 5-membered ring  $\ge$  6-membered ring.<sup>[13,14]</sup> We were particularly interested in the contrast between the nearly complete hindrance of the 8-membered ring formation and the only slight hindrance of the 6-membered ring formation by ethylene.

While holding the temperature constant for each ring-size formation, the effect of ethylene pressure (1-3 atm)<sup>[15]</sup> was examined next (Graphs 5-8 in Scheme 2). As predicted, the deleterious effect of ethylene increased gradually as the pressure increased, and the trend of the relationship between the ring size and the degree of the hindrance by ethylene was similar to that observed in Graphs 1–4 (Scheme 2). Thus, the degree of the hindrance seemed to have the following order: 8-membered ring ≥7-membered ring > 5-membered ring  $\ge$  6-membered ring. The robustness of the 6-membered ring formation to the hindrance by even a pressure of 3 atm of ethylene to give 8b is noteworthy, whereas the formation reactions of other ring sizes were completely inhibited by 2–3 atm of ethylene.

We next investigated the RCM of triene 9 for the direct observation of ring size selectivity (Table 1). The RCM of 9 is expected to produce two cyclic compounds, cyclopentene 10 as a 5-membered ring product, and cyclohexene 11 as a 6-membered ring product. When the reaction was carried out at 0°C under nitrogen gas, only 10 was formed as a product detectable by <sup>1</sup>H NMR (entry 1). Increasing the temperature to 20°C gave 10 in 81% yield and 11 in 19% yield, indicating that 10 and 11 are kinetically favored and thermodynamically favored products, respectively (entry 2). Although a further increase in temperature to 60°C favored the formation of **11** to that of **10**, side reactions that yielded non-negligible amounts of by-products, most of which were assigned to oligomers arising from the cross metathesis, complicated the crude reaction mixture (entry 3). On the other hand, when the reaction was carried out at 20°C under 1 atm of ethylene gas, cyclohexene 11 was formed as the major product (entry 2 vs. 4). The reaction conducted under 3 atm of ethylene gas promoted the formation of 11 further (entry 5), and it was found that the reaction at 60 °C under 3 atm of ethylene gas furnished 11 as the predominant product (entry 6).<sup>[16]</sup> Under the conditions using ethylene gas, side reactions to give oligomers were not observed. This result implies that ethylene hindered the progress not only of the 5-membered ring formation reaction, but also of oligomerization (entry 3 vs. 6).<sup>[17]</sup>

Finally, we attempted the selective synthesis of 5 and 6 using 2 as the sole substrate (Table 2). Under nitrogen gas for 2 h, RCEM/RCM product 5 was formed as the major product, but it was found that RCEM product 6 was also formed as the minor product (entry 1). Prolonging the reaction time to 4 h completed the formation of 5, and 6 was not detected at

Table 2. Application of the ethylene effect to the selective synthesis of fused bicyclic benzene 5 and single-ring benzene 6.<sup>[a]</sup>



Entry	Atmosphere	<i>t</i> [h]	Yield of <b>5</b> [%] <sup>[b]</sup>	Yield of <b>6</b> [%] <sup>[b]</sup>
1	$N_2$ (1 atm)	2	79	21
2	$N_2$ (1 atm)	4	>95	_[c]
3	$C_2H_4$ (1 atm)	2	11	89
4	$C_2H_4$ (2 atm)	2	_[c]	>95

<sup>[a]</sup> The reaction was carried out with **2** and ruthenium catalyst (**3**, 7.5 mol%) in toluene (0.01 M) under a nitrogen or ethylene atmosphere at 80°C. The reaction mixture was treated with *p*-toluenesulfonic acid (10 mol%) at room temperature for 1 h.

<sup>[b]</sup> The yield was determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,4-bis(trimethylsilyl)benzene as the internal standard.

<sup>[c]</sup> The product was not detected by <sup>1</sup>H NMR analysis.

all by <sup>1</sup>H NMR (entry 2). Under 1 atm of ethylene gas, the proportion of **5** and **6** was changed dramatically, and the formation of **6** was predominant (entry 3). Increasing ethylene pressure to 2 atm was sufficient to obstruct the 7-membered ring formation completely to give **6** as the only detectable product (entry 4).

When equilibrium is considered, the strategy of performing RCM under ethylene gas seems to be an unconventional one. However, in the case in which competitive side reactions (e.g., another RCM or oligomerization) exist, performing the reaction under ethylene gas offers great benefits to control the chemoselectivity due to the rate differences caused by ethylene. Needless to say, selectivity can be effectively controlled by changing the reaction temperature, catalyst structure, solvent, and so on. It seems, however, that the effect of ethylene or inhibitors of equal ability is also of value for controlling selectivity. Our ongoing study is focused on the examination of the effect with other catalysts, the effect on substrates having other substituent patterns, and the mechanistic interpretations of the selectivity.

## **Experimental Section**

### General Procedure for the Synthesis of Cyclic Compounds 8, 10, 11, 5, and 6 [under Nitrogen or Ethylene Atmosphere (1 atm)]

To a solution of **7**, **9**, or **2** (0.102 mmol) in toluene (10.2 mL) was added a solution of catalyst **3** (1–7.5 mol%, 0.01 M, 1.02–7.65  $\mu$ mol) under nitrogen or ethylene at 0–80 °C. The

reaction mixture was stirred for 2–7 h at the same temperature. The reaction was quenched by adding di(ethylene glycol)vinyl ether (53.9 mg, 0.408 mmol, 400 mol%) and the yield was determined by <sup>1</sup>H NMR analysis of crude mixture using 1,4-bis(trimethylsilyl)benzene as the internal standard.

### General Procedure for the Synthesis of Cyclic Compounds 8, 10, 11, 5, and 6 [under Ethy-lene Atmosphere (2–3 atm)]

The reaction was conducted in a Fischer–Porter vessel. To a solution of **7**, **9**, or **2** (0.102 mmol) in toluene (10.2 mL) was added a solution of catalyst **3** (1–7.5 mol%, 0.01 M, 1.02–7.65 mmol) under nitrogen at 0°C. Then, the system was evacuated carefully and filled with ethylene gas (2–3 atm) in three cycles. The reaction vessel was placed in a bath maintained at 0–80 °C and the pressure was immediately readjusted to 2 or 3 atm by leaking excess gas. The reaction mixture was stirred for 2 h and quenched by adding di(ethylene glycol)vinyl ether (53.9 mg, 0.408 mmol, 400 mol%). The yield was determined by <sup>1</sup>H NMR analysis of crude mixture using 1,4-bis(trimethylsilyl)benzene as the internal standard.

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