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Terminal Enyne Ring-Closing Metathesis Catalyzed by Ruthenium Carbene Catalysts†

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Enyne ring-closing metathesis (RCM) has recently emerged as a powerful tool for the formation of 1,3-conjugated dienes.[1-4] Under the influence of its efficacy and reliability, the enyne RCM reaction with ruthenium (Ru)-based catalysts has been elegantly applied toward the total synthesis of bioactive compounds or natural products.[5-7] In spite of its usefulness, the enyne RCM has yet a problem which remains to be solved: *endo*/*exo* mode selectivity.

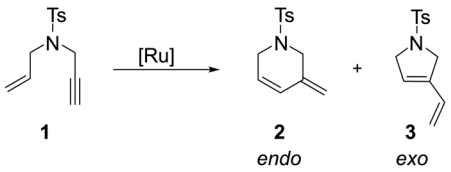
The *exo*/*endo*-selectivity in the enyne RCM has been studied and the reported results have varied. Mori reported that RCM of enyne having an mono- or di-substituted alkene and a terminal alkyne gave only the *exo* product, while that of enyne having a disubstituted alkene and an internal alkyne gave a mixture of both *endo* and *exo* products.[8] Lee reported that a competitive cross metathesis (CM) of the alkyne moiety in enyne substrate with ethylene led to a triene, which then underwent ring closure offering selectively *endo* product in 9-11 membered macrocycles.[9] In the investigation on the reactivity profile of catalysts, Grela observed that the use of Grubbs' first-generation complexes containing PCy_3 ligand such as A and C led to only an *exo* product, while the use of second-generation complexes containing *N*-heterocyclic carbene (NHC) ligand led to a mixture of *endo* and *exo* products in the RCM of enyne having a disubstituted alkene and a terminal alkyne.[10] Schrock and Hoveyda reported their elegant results on *endo*-selective enyne RCM reactions promoted by use of *in situ* generated molybdenum (Mo)-based complexes containing pyrrole ligand[11] and later by both tungsten (W)- and Mo-based mono-aryloxide pyrrolide (MAP) imido alkylidene complexes.[12]

Therefore, we envisioned that the *endo*/*exo* selectivity of terminal enyne RCM with Ru carbene catalysts could lead us to the selective synthesis of medium-sized *N*-containing heterocycles as shown in Scheme 1.

We examined the well-known Ru-based complexes **A**-**D** as well as pyridine-chelating Ru complex **E**[13] (Fig. 1). It was expected that the NHC ligand along with pyridine moiety in complex **E** would have an effect on the *endo*/*exo* selectivity in enyne RCM reactions.

Our study started from a simple representative substrate **1** bearing a terminal alkyne at one end and a terminal olefin at the other. Each of five catalysts (**A**-**E**, 5 mol %) was added to the solution of **1** in benzene and the solution was refluxed for 2 h under an atmosphere of Ar. RCM of enyne **1** mediated by catalysts **A**-**D** gave only the 5-membered *exo*-cyclized compound **3** (Entry 1-4, Table 1). On the other hand, pyridine chelating catalyst **E** produced a small but significant amount of 6-membered *endo*-cyclized product **2** with the *endo: exo* ratio of 27:73 (45% conversion, 6% isolated yield of combined *exo*/*endo*) (Entry 5, Table 1). It is the first example of the *endo*-cyclized product being formed in the terminal enyne RCM using Ru-based catalyst. Since we were interested in the determination of *endo*/*exo* selectivity in terminal enyne RCM with Ru carbene catalysts under various reaction conditions, the task of improving isolated yield in each reaction was beyond the scope of the work described in this paper.

Subsequently, we tested enyne RCM of **1** using the catalyst **E** in several representative solvents (Table 2). Among suitable organic solvents, toluene, benzene, tetrahydrofuran (THF), 1,2-dimethoxyethane (DME) and 1,2-dichloroethane (DCE) were carefully selected and examined because catalyst **E** showed the activating



Scheme 1. Terminal enyne RCM with ruthenium carbene catalysts.

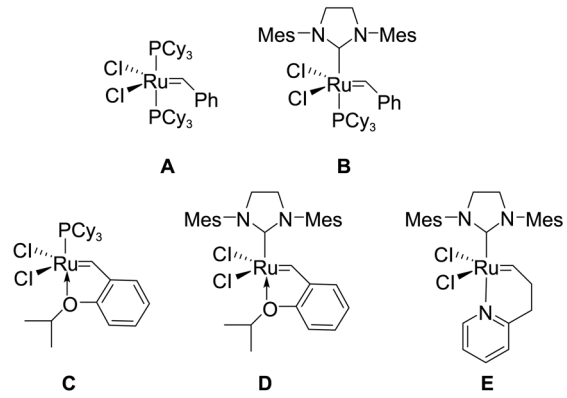


Figure 1. Ruthenium carbene catalysts.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

Table 1. Terminal enyne RCM with catalysts **A-E**[a]

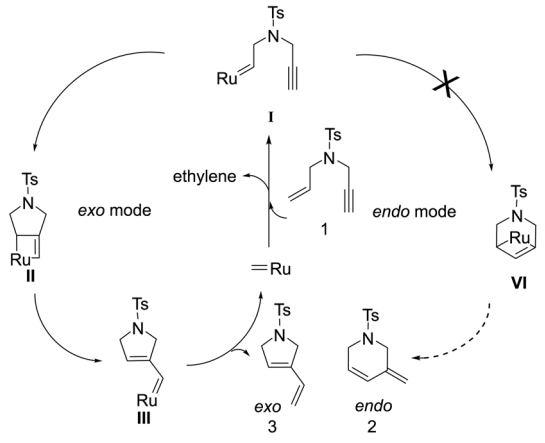
Entry	Catalyst	Conv. (%)[b]	Product ratio (%) *endo*:*exo*[c]	Yield (%)
1	**A**	>98	0:100	66
2	**B**	95	0:100	37
3	**C**	85	0:100	13
4	**D**	85	0:100	27
5	**E**	45	27:73	6[d]

[a]Procedure: To a benzene (0.02 M) of **1** (1.0 equiv) was added catalysts (**A-E**, 5 mol %) at rt, and the resulting mixture was refluxed for 2 h under Ar atmosphere.
[b]Conv. was based on consumption of substrate **1**.
[c]Ratios were determined by analysis of ^{1}H NMR spectra of unpurified reaction mixtures.
[d]Yield was confirmed after purification of column chromatography.

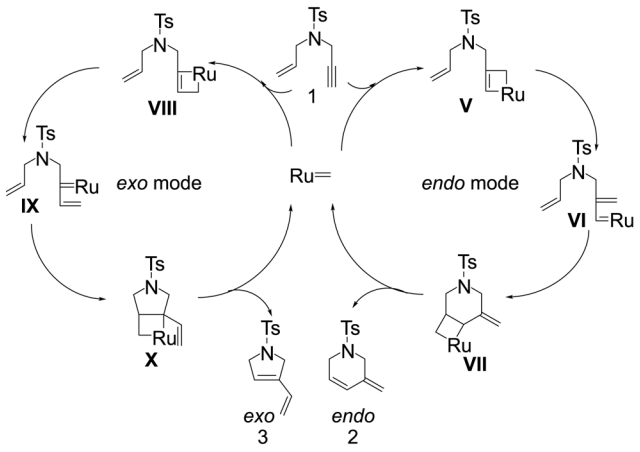
Table 2. Solvents screening in terminal enyne RCM with catalyst E[a]

Entry	Solvents	Conv. (%)[b]	Product ratio (%) *endo*:*exo*[c]	Yield (%)
1	Toluene	70	0:100	< 1
2	Benzene	45	27:73	6
3	THF	50	20:80	12
4	DME	30	40:60	4
5	DCE	35	47:53	<4

[a]Procedure: To a benzene (0.02 M) of **1** (1.0 equiv) was added catalysts (**A-E**, 5 mol %) at rt, and the resulting mixture was refluxed for 2 h under Ar atmosphere.
[b]Conv. was based on consumption of substrate **1**.
[c]Ratios were determined by analysis of ^{1}H NMR spectra of unpurified reaction mixtures.



Scheme 2. Postulated "Ene-then-yne" pathway of terminal enyne **1** during RCM.



Scheme 3. Postulated "Yne-then-ene" pathway of terminal enyne **1** during RCM.

temperature at higher than 60 °C. While the reaction in toluene produced only *exo* product, both product isomers were observed with the *endo*: *exo* ratio of 27:73 and 20:80 in benzene and THF, respectively (Entry 2 & 3, Table 2). In DME, the ratio of *endo* product to *exo* product was increased up to 40:60 (Entry 4, Table 2). The *endo* product was also observed in DCE with the ratio of nearly 1:1, though the yield was lower than in DME. Therefore, we are certain that the solvent plays a major role in *endo*/*exo* product selectivity of terminal enyne RCM promoted by Ru-based catalysts.

Even though the terminal enyne RCM mechanism with catalyst **E** has not yet been fully investigated, the effect of *N*-heteroaromatic ring on *endo*/*exo* selectivity can readily be predicted such as pyrrole ligand in the literature previously reported by Hoveyda.[11,12]

There are two possible reaction mechanisms for the terminal enyne RCM, namely "ene-then-yne" pathway (Scheme 2) and "yne-then-ene" pathway (Scheme 3). In "ene-then-yne" pathway, the Ru catalyst reacts first with the double bond of the terminal enyne to produce the intermediate **I**. This intermediate is then expected to proceed to the *exo* mode but not to the *endo*, because the formation of highly-strained bicylic intermediate **VI** is strongly disfavored as shown in Scheme 2. In contrast, the "yne-then-ene" pathway of enyne RCM involves intermediates further proceeding to both *endo* and *exo* modes. This can be easily predicted because the Ru catalyst in "yne-then-ene" pathway reacts first with the triple bond of the enyne to form the two

Table 3. Comparison of ethylene atmosphere vs. argon in terminal enyne RCM[a]

Entry	Solvents	Condition	Conv. (%)[b]	Product ratio (%) *endo*:*exo*[c]	Yield (%)[d]
1	DME	Ethylene	75	10:90	21
2	DME	Ar	89	40:60	18
3	DCE	Ethylene	60	0:100	16
4	DCE	Ar	90	44:56	11

[a]Procedure: To a solvent (0.02 M) of **1** (1.0 equiv) was added catalyst **E** (30 mol %) at rt, and the resulting mixture was refluxed for 2 h. [b]Conv. was based on consumption of substrate **1**. [c]Ratios were determined by analysis of ^{1}H NMR spectra of unpurified reaction mixtures. [d]Yields were confirmed after purification of column chromatography.

metal alkylidenes (**V** and **VIII**). The resulting intermediates are then separately subjected to a series of reactions to afford corresponding *endo* and *exo* products as shown in Scheme 3. Thus, the "yne-then-ene" pathway can be considered as a plausible reaction mechanism for the formation of *endo* product in terminal enyne RCM with Ru-based catalyst.

In order to study the role of ethylene gas in *endo*/*exo* product distribution, we carried out the RCM under an atmosphere of ethylene and compared the result with that of Ar (Table 3). As the quantity of catalyst **E** was increased from 5 mol % to 30 mol %, conversion yields were increased to 85-90% and isolated yields to 20%. Under Ar atmosphere, both isomers were obtained with *endo: exo* ratio 40:60 in DME and 44:56 in DCE (Entry 2 & 4, Table 3). On the other hand, the *endo* product was notably decreased under an ethylene atmosphere compared to the result of Ar (Entry 1 & 3, Table 3). It seems that the *exo* product is formed mostly by the activated Ru carbene species (Ru=) proceeding to the *exo* pathway (Scheme 2), while the *endo* product was produced compatibly by Ru complex **E** under Ar. From these results, we conclude that the effect of pyridine-chelating ligand on the formation of the *endo* product was not observed under the ethylene gas. It is predicted that the heteroatom-chelating pyridine ligand effects on the *endo*/*exo* selectivity, according to the "yne-then-ene" pathway of the terminal enyne **1**.

In conclusion, this study shows the first example of *endo*-cyclic product obtained from RCM reaction with terminal enynes in the presence of pyridine-chelating Ru carbene complex **E**. In spite of the great importance of generally accepted *exo* selectivity in terminal enyne RCM reactions with Ru-based catalysts, the *endo*-selective enyne RCM demonstrated here will make a marked impact on the area of catalysis and synthesis. As a result, the *endo*/*exo* selectivity of terminal enyne RCM reactions promoted by the ruthenium carbene catalyst discovered in this study will clearly render the elaboration of a variety of *N*-containing heterocycles easily by metathesis in the future. Further RCM studies with a series of hetero-atom containing enynes are under investigation in our laboratories.

Experimental Section

General Procedure. To a solution of **1** (10 mg, 0.04 mmol) in solvent (0.02 M) was added the pyridine-chelating Ru complex, **E** (5 mol % or 30 mol %) at rt. The mixture was refluxed for 2 h under the atmosphere of Ar or ethylene gas. The resulting mixture was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel. Products were characterized by ^{1}H and ^{13}C NMR.

NMR Spectral Data for the Products. (a) 3-Methylene-1-tosyl-1,2,3,6-tetrahydro pyridine (**2**, *endo* product) : ^{1}H NMR (300 MHz, $CDCl_3$,) δ 7.72 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 6.17 (dt, J = 10.2, 2.1 Hz, 1H), 5.75-5.69 (m, 1H), 4.94 (d, J = 4.2 Hz, 2H), 3.84 (t, J = 1.2 Hz, 2H), 3.74 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 136.8, 134.1, 129.6, 127.8, 127.5, 124.7, 113.1, 48.2, 44.8, 21.5. (b) 2,5-Dihydro-1-(4-toluene sulfonyl)-3-vinyl-1*H*-pyrrole (**3**, *exo* product): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 6.37 (dd, J = 17.7, 10.9 Hz, 1H), 5.61 (s, 1H), 5.18 (d, J = 10.8 Hz, 1H), 5.03 (d, J = 17.7 Hz, 1H), 4.22 (d, J = 2.4 Hz, 4H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.5, 134.1, 129.9, 129.8, 127.4, 123.3, 116.8, 55.1, 53.5, 21.6.

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