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Remarkable Effect of Ethylene Gas in the Intramolecular Enyne Metathesis of Terminal Alkynes

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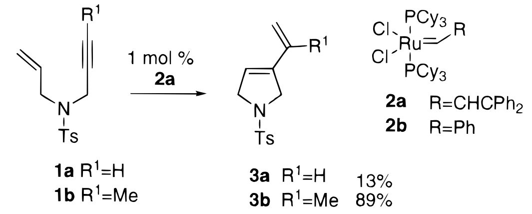
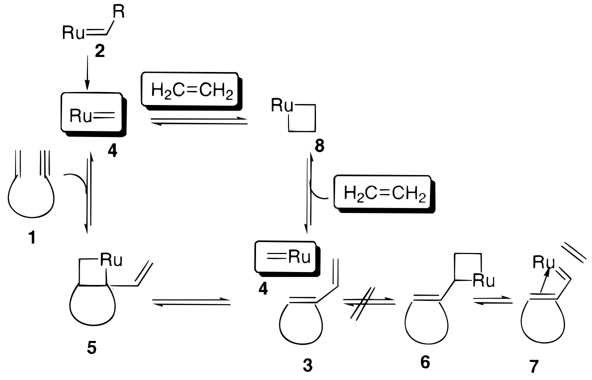
Metathesis reaction using molybdenum[1] and ruthenium carbene complexes[2] is a very attractive method for the synthesis of cyclized products.[3] It provides a new methodology for the synthesis of natural products, especially macrocyclic compounds. Enyne metathesis is also very interesting and useful, and it is also applicable for the synthesis of cyclized products.[4,5] In intramolecular enyne metathesis, the cyclized product having a diene moiety was obtained, and in this reaction, the alkylidene part of alkene in enyne migrates on the alkyne carbon. We have already reported ruthenium-catalyzed enyne metathesis.[6] In this reaction, a substituent on the alkyne was required. When enyne **1a** having no substituent on alkyne was treated with **2a** at rt, only 13% yield of **3a** was obtained, while enyne **1b** having a methyl group on the alkyne gave 89% yield of the desired cyclized product **3b** (Scheme 1).

Scheme 1



We reinvestigated ruthenium-catalyzed metathesis of enyne having no substituent on the alkyne. When enyne **1a** was treated with **2a**, diene **3a** was formed. In this reaction, no increase in the product was seen on TLC after several hours. It seems likely that the catalytic activity of the ruthenium catalyst decreased, although the color of the solution did not change. It was thought that the ruthenium catalyst would further react with the vinyl group of diene **3** to produce ruthenacyclobutane **6**. The retrocycloaddition of **6** produced alkylidene carbene complex **7**, which was coordinated by the olefin of diene (Scheme 2).

Scheme 2



In this reaction, methylidene ruthenium complex **4** reacts with enyne **1** to give ruthenacyclobutane **5**, which converts into diene **3** and methylidene ruthenium complex **4**. If this reaction is carried out under ethylene gas,[6] the generated methylideneruthenium complex **4** reacts with ethylene to produce ruthenacyclobutane **8**, which is in a state of equilibrium with methylidene ruthenium complex **4** and ethylene gas (a so-called nonproductive process). Thus, methylidene ruthenium complex **4** does not react with **3**, and it should react with **1** again.[7]

Table 1. Reaction of 1 with 2a or 2b under Various Conditions[a]

run	solvent	Ru	mol %	time (h)	under	yield (%)
1	benzene	**2a**	1	22	Ar	13
2	benzene	**2b**	1	22	Ar	15
3	CH_2Cl_2	**2b**	1	22	Ar	21
4	CH_2Cl_2	**2b**	1	22	$H_2C{=}CH_2$	90
5	CH_2Cl_2	**2b**	3	2.5	$H_2C{=}CH_2$	99

[a] All reactions were carried out at room temperature.

At first, we examined the catalytic activity of benzylidene ruthenium complex **2b** compared with **2a**. When a benzene solution of **1a** and 1 mol % of **2b** was stirred at rt for 22 h, the yield of **3a** was almost the same (Table 1, run 2). When the solvent was changed from benzene to CH_2Cl_2, the yield of **3a** was slightly improved. Surprisingly, when the reaction was carried out under an atmosphere of ethylene gas for 22

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(5) (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020; (b) *J. Org. Chem.* **1996**, *61*, 8356; (c) *Heterocycles*, **1997**, *46*, 287.

(6) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388.

(7) We have already reported that in the enyne metathesis ruthenium carbene complex **2a** should react at first with the alkyne part, not the alkene part.[5a] However, the reaction rates of diene metathesis and enyne metathesis were almost same. Even if methylidene ruthenium complex **4** reacts at first with the alkene part of **1**, the same ruthenium carbene compelx **7** would be formed via ruthenacyclobutane **9**, ruthenium carbene complex **10**, and ruthenacyclobutene **11**. In this case, ethylene gas should be also effective because **7** reacts with ethylene to produce **6**, which produces cyclized product **3** and methylidene carbene complex **4**.

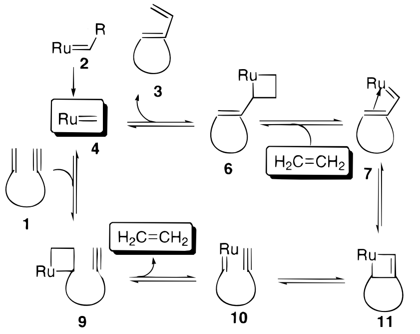

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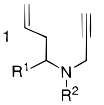
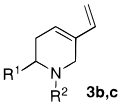
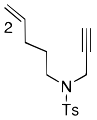
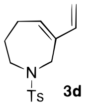
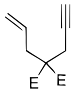
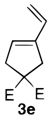
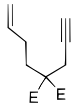
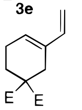
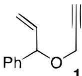
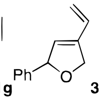
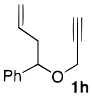
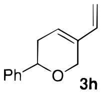
Table 2. Enyne Metathesis under an Ethylene Atmosphere[a]

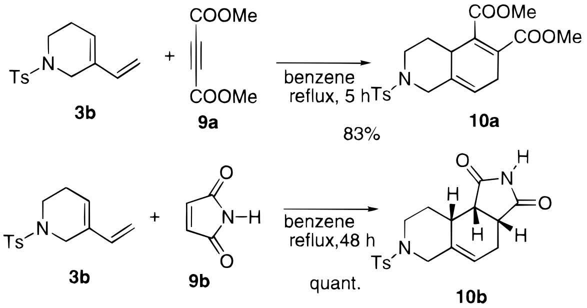
Run	Substrate	Product		Atmosphere	Time (h)	Yield (%)
1	 **1b**; R^1=H, R^2=Ts **1c**; R=COOEt, R^2=COCF$_3$	 **3b,c**	**1b**	Ar	14	19 (74)[b]
			1b	$H_2C{=}CH_2$	2	99
			1c[c)]	$H_2C{=}CH_2$	0.5	92
2	 **1d**	 **3d**		Ar	22	49 (30)
				$H_2C{=}CH_2$	22	65 (18)
3	 1e	 **3e** E=COOEt		Ar	22	15 (76)
				$H_2C{=}CH_2$	22	99
4	 **1f**	 **3f** E=COOEt		Ar	5	76 (8)
				$H_2C{=}CH_2$	5	99
5	 **1g**	 **3g**		Ar	22	6 (74)
				$H_2C{=}CH_2$	22	96
6	 **1h**	 **3h**		Ar	22	42 (52)
				$H_2C{=}CH_2$	14	99

[a] All reactions were carried out using 1 mol % of ruthenium catalyst **2b** in CH_2Cl_2. [b] Yield in parentheses is that of recovered material. [c] 3 mol % of **2b** was used.

h, the yield of **3a** increased to 90% (run 4). The use of 3 mol % of **2b** gave **3a** in quantitative yield only after 2.5 h (run 5).

The reactions of various enynes **1** having no substituent on the alkyne with ruthenium carbene complex **2b** were carried out, and the results are shown in Table 2. When only 1 mol % of ruthenium carbene complex **2b** was used for this reaction at rt under an atmosphere of ethylene gas, the desired cyclized diene **3** was obtained in an almost quantitative yield. Ethylene gas was quite effective for the formation of nitrogen heterocycles, carbocycles, and oxygen heterocycles and for the formation of 6- and 7-membered cyclic compounds. In the absence of ethylene gas, the desired product was obtained in low yield, although the conversion yield was good.

Scheme 3



Since these products have a diene moiety, we tried to synthesize isoquinoline derivative **10**, which is a useful heterocycle for the synthesis of biologically active substances, from piperidine derivative **3b** by the Diels–Alder reaction.

When a benzene solution of piperidine derivative **3b** and dimethyl acetylenedicarboxylate **9a** was refluxed for 5 h, isoquinoline derivative **10a** was obtained in 83% yield. In a similar manner, tricyclic compound **10b** was obtained in quantitative yield from **3b** and **10b** as a single product. The stereochemistry of **10b** was determined by an NOE experiment (Scheme 3).

Supporting Information Available: Experimental procedures and spectral data (^1H, ^{13}C, and MS) for **1**, **3**, and **13a**,**b** (6 pages).

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