Intramolecular Cyclizations of Enynes Using $RuClH(CO)(PPh_3)_3$

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Transition metal-catalyzed coupling reaction between alkyne and alkene is a useful synthetic protocol for synthesis of 1,3-diene.[1] Not only are 1,3-dienes themselves important but they have also wide applicability in the Diels−Alder reaction. Recently, Mitsudo[2] and Trost[3] reported ruthenium-catalyzed intermolecular addition of alkynes to alkenes. In both reactions, formation of ruthenacyclopentene was proposed as an intermediate. We now report two types of intramolecular cyclizations of enynes using $RuClH(CO)(PPh_3)_3$ as a catalyst via the following three steps: hydrometalation, carbometalation, and then β-hydride elimination,[4] which provide cyclized compounds **I**[5] and **II**, respectively (Scheme 1). Among the many reports on hydroruthenation of $RuClH(CO)(PPh_3)_3$ toward multiple bonds,[6] this is the first example of a stereoselective carbon−carbon bond-forming reaction using $RuClH(CO)(PPh_3)_3$.

First, we examined ruthenium-catalyzed cyclizations using **1a** as a substrate (n = 3, Table 1, run 1). A solution of **1a** (0. 32 mmol) and $RuClH(CO)(PPh_3)_3$ (5 mol %) in toluene (1.5 mL) was refluxed for 9 h to afford the cyclized product **2a** in 62% yield. A strong NOE between two olefinic protons of **2a** clarified the structure of the product. The cyclization of **1b** also succeeded in providing **2b** in 57% yield (run 2). It is notable that both substrates, having an aromatic group or an alkyl group on the alkyne, can be used in this reaction.[7]

To examine the substituent effects on the aromatic ring, the cyclization of **1c**, having a methoxy group on the aromatic ring, was carried out to provide **2c** in 82% yield (run 3). Similarly, the reaction of **1d**, having a methyl group, proceeded to give **2d** in 67% yield (run 4). However, in the case of **1e**, having a trifluoromethyl group, the cyclized product **2e** was obtained in 53% yield along with recovered starting material **1e** (34% yield) (run 5). These results clearly indicated that the electron-withdrawing group on the alkyne reduced the yield of the product.

Surprisingly, when cyclization of **3a**, having a two-carbon tether between the alkyne and olefin, was carried out, the reaction was accomplished within 1 h to afford the cyclized product in 81% yield (Scheme 2). However, ^{1}H NMR and ^{13}C NMR spectra could not clarify the ring size of the product (**4** or **5a**). To confirm the structure of **5a**, hydrogenation was carried out to give **6** as a mixture of two isomers. The COSY data of one isomer confirmed that a five-membered ring was formed in this reaction.[8]

The effects of substituents on the aromatic ring were studied again (Table 2). Cyclization of **3b** afforded **5b** in 75% yield (run 2), and cyclization of **3c** provided **5c** in 67% yield (run 3). However, the reaction of **3d** was not completed to provide **5d** in only 48% yield along with **3d** (run 4). Accordingly, a tendency similar to that shown in the previous cyclization was also observed in this reaction.[9]

The reaction mechanism can be envisioned as shown in Scheme 3. The reaction starts with a hydroruthenation of the alkyne to give the vinylruthenium complex **III** or **IV**, which is in a state of equilibrium with **1** or **3**. In the reaction of **1** and $RuClH(CO)(PPh_3)_3$, intramolecular olefin insertion

Scheme 1

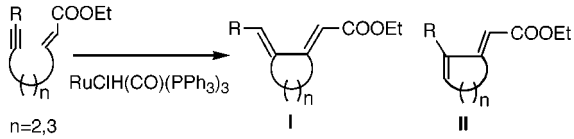
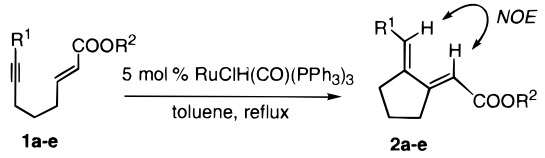


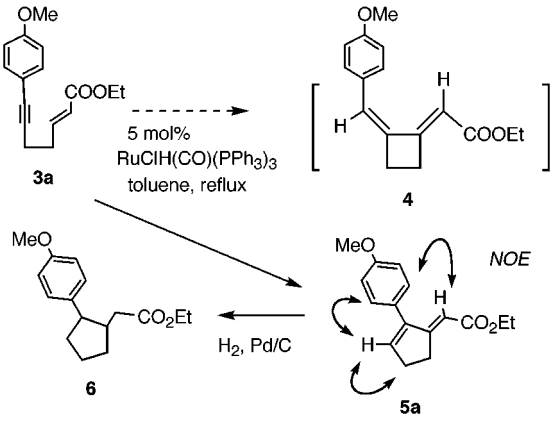
Table 1. Cyclization of 1 Using $RuClH(CO)(PPh_3)_3$



run	substrate	R_1	R_2	h	**2a−e** (%)
1	**1a**	Me	$(CH_2)_3Ph$	9	62
2	**1b**	Ph	Et	18	57
3	**1c**	4-MeO-Ph	Et	18	82
4	**1d**	4-Me-Ph	Et	18	67
5	**1e**	4-CF_3-Ph	Et	18	53[a]

[a] The recovery of **1e** was 34%.

Scheme 2



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(5) Trost reported that the same type of compound as **I** was obtained in the Pd-catalyzed enyne cyclization. Trost, B. M.; Romero, D. L.; Rise, L. *J. Am. Chem. Soc.* **1994**, *116*, 4268.

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(7) Cyclizations were examined using **1f** (R^1 = H, R^2 = $(CH_2)_3Ph$), **1g** (R^1 = TMS, R^2 = $(CH_2)_3Ph$), and **1h** (R^1 = COOMe, R^2 = COOEt) as substrates. In the case of **1f** and **1g**, double-bond isomerization took place to provide deconjugated compounds. In the reaction of **1h**, the starting material was recovered. Unfortunately, a six-membered ring compound was not formed in the reaction of (*E*)-9-(4-methoxyphenyl)-2-nonen-7-ynote.

(8) HMBC data of **5a** indicated that the aromatic group was connected to the tertially vinyllic carbon.

(9) Cyclizations were examined using **3e** (R^1 = Me, R^2 = 4-NO_2-C_6H_4-CH_2), **3f** (R^1 = Et, R^2 = 4-NO_2-$C_6H_4CH_2$), and **3g** (R^1 = *i*-Pr, R^2 = Et) as the substrates. In the reaction of **3e**, the starting material was recovered. In the case of **3g**, double-bond isomerization took place to provide deconjugated compounds. However, in the reaction of **3f**, a cyclized product was obtained in 22% yield along with 15% of **3f**.

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Scheme 3

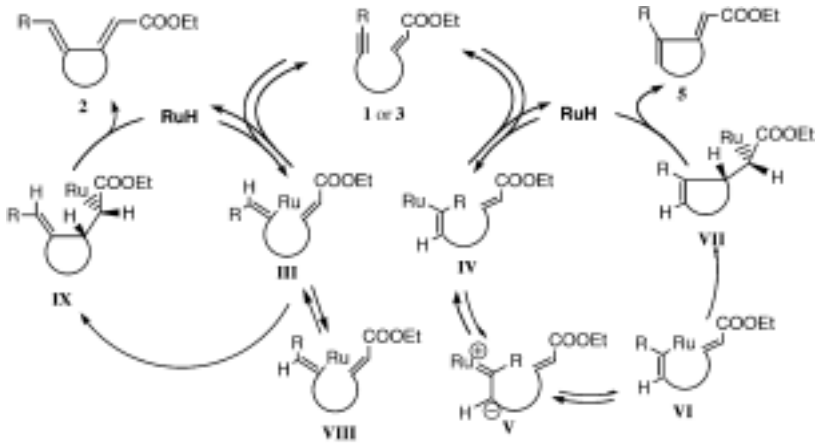
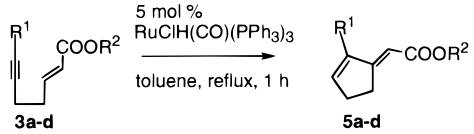


Table 2. Cyclization of 3 Using $RuClH(CO)(PPh_3)_3$



run	substrate	R^1	R^2	**5a−d** (%)
1	**3a**	4-MeO-Ph	Et	81
2	**3b**	4-Me-Ph	Et	75
3	**3c**	Ph	Et	67
4	**3d**	4-CF_3-Ph	Et	48[a]

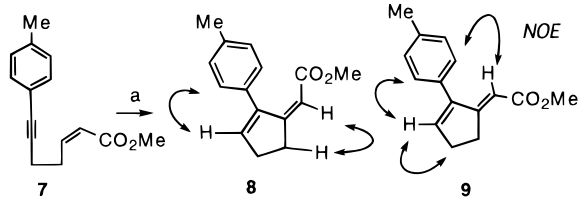
[a] The recovery of **3d** was 48%.

into the Ru−C bond of **III** proceeds and is followed by a syn β-H elimination to produce the cyclized product **2** stereoselectively. On the other hand, in the reaction of **3**, after vinylruthenium complex **IV** (a cis addition product) isomerized to vinylruthenium complex **VI** (via a dipolar intermediate **V**),[10] intramolecular olefin insertion took place, and successive syn β-H elimination produced **5**, exclusively. In both reactions of **1** and **3**, five-membered ring formation preceded all other ring formations.[11] A remarkable characteristic in our reaction is the formation of a cyclopentene moiety conjugated with an *exo*-olefin.

Next, the cyclization of substrate **7** (*Z* isomer of **3b**) was examined (Table 3). After 20 min, cyclized products **8** and **9** were obtained in 33% and 10% yields, respectively, along with 22% of the recovered starting material. NOE experiments clarified the structures of **8** and **9**. The major product **8** had the expected stereochemistry with regard to the α,β-unsaturated ester. The prolonged reaction time (1 h) did not increase the yield of **8** (30%), although it increased the yield of **9** (25%). When **8** was treated under the same reaction conditions, isomerization of **8** into **9** occurred.

Finally, we examined the cyclization of **10**, which does not have an electron-withdrawing group on the alkene functionality. The reaction of **10** with ruthenium complex gave **11** (38% yield) and **12** (29% yield) (Scheme 4). It is notable that intramolecular olefin insertion took place on the alkene without the presence of an electron-withdrawing group.

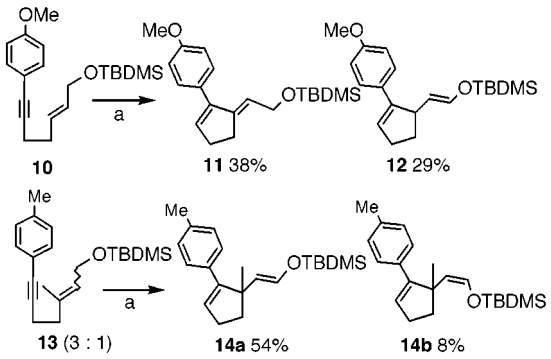
Table 3. Cyclization of 7 (*Z* Isomer of 3b)



a. 5 mol% $RuClH(CO)(PPh_3)_3$, toluene, reflux

		yields (%)		
run	time	**8**	**9**	**7**
1	20 min	33	10	22
2	1 h	30	25	

Scheme 4[a]



[a] Key: (a) 5 mol % $RuClH(CO)(PPh_3)_3$, toluene, reflux, 1 h.

When **13** was treated in a similar manner, the products were only silyl enol ethers **14a** (54% yield) and **14b** (8% yield), and *E* isomer **14a** was the major product.

In summary, we have succeeded in the first example of an intramolecular cyclization of an enyne substrate using $RuClH(CO)(PPh_3)_3$ as a catalyst. Formation of cyclopentene derivatives is a prominent characteristic in our reaction (Scheme 1). Further studies on cyclizations using ruthenium catalysts are in progress.

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Supporting Information Available: Experimental details and characterization for **1b−e**, **2a−e**, **3a−d**, **5a−d**, **6−13**, and **14a**,**b** (12 pages).

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(11) Since the same tendency in the effects of substituents on the aromatic ring was shown in each reaction (Tables 1 and 2), the rate-determining step would be irreversible intramolecular olefin insertion. An electron-withdrawing group on alkyne stabilized the produced vinylruthenium complex through back-donation, which retarded olefin insertion.