Ring-Closing Metathesis Dimerizations of Enynes and Deprotections of Propargyl Ethers Mediated by Carbene Ruthenium Complexes

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The ring-forming dimerizations of enynes were catalyzed by the first-generation carbene ruthenium complex, and the effects of the catalysts and ethylene gas were studied. The deprotection of propargyl ethers by the carbene ruthenium complexes is the first to be reported.

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Introduction

With the advance of well-defined and functional-group-tolerant catalysts such as **1** and **2** (Figure 1), olefin metathesis[1] has become a powerful tool for synthetic organic and polymer chemists. Metathesis of dienes, diynes, and enynes have been utilized in many different types of carbon−carbon bond forming reactions. Especially, enyne metathesis[2] generates synthetically useful 1,3-dienes that allow subsequent Diels−Alder reactions with diverse dienophiles to construct complex molecules expeditiously. Despite significant recent advances in enyne metathesis, detailed studies on the reaction pathways of cross enyne metathesis were limited due to complicated mechanisms involved in enyne metathesis. Ring-forming metathesis dimerizations by tandem cross and ring-closing metathesis of dienes have been utilized in the synthesis of symmetric dimers of natural and unnatural molecules such as [*n.n*]-paracyclophanes, sulfones, and lactones.[3] However, to the best of our knowledge, ring-forming metathesis dimerizations of enynes mediated by a tandem process of cross and ring-closing enyne metathesis has not been studied in the literature until now.

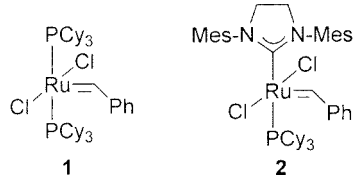
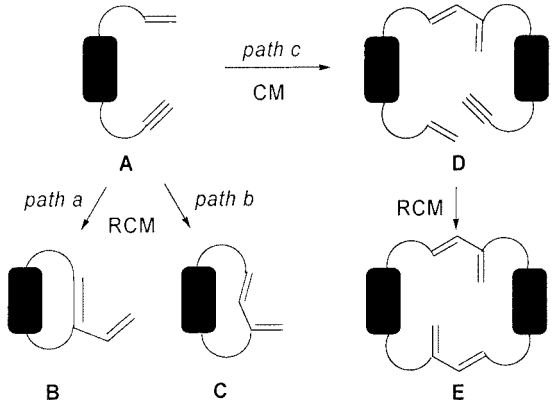


Figure 1. Grubbs' carbene ruthenium complexes

Metathesis of enyne **A** tethered by a linker can proceed by three different ring-forming paths depending on the length of the tether (Scheme 1). The ring-closing enyne metathesis for small-size rings proceeds through *path a* to give *exo*-mode product **B**. If the linker length is long enough, *endo*-mode ring closure occurs to yield 1,3-diene **C** (*path b*).[4] The third option could operate if the linker is too short and the direct cyclization mode is not possible (*path c*). In that case, cross metathesis dimerization can take place to form **D** in which the terminal enyne can further cyclize to give **E**. The overall tandem enyne-CM/RCM process would be a new dimerization reaction to the macrocyclic systems starting from simple enynes. Herein we report the unprecedented ring-forming dimerizations by tandem enyne metathesis and other findings.



Scheme 1. Metathesis pathways of enynes

Results and Discussion

1,4-Disubstituted benzenes and 1,5-disubstituted naphthalenes were selected as the enyne substrates, where the

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alkene and alkyne functions could not participate in the direct ring-forming reactions. Substrates **3**−**6** were prepared readily from commercially available materials (Figure 2).[5]

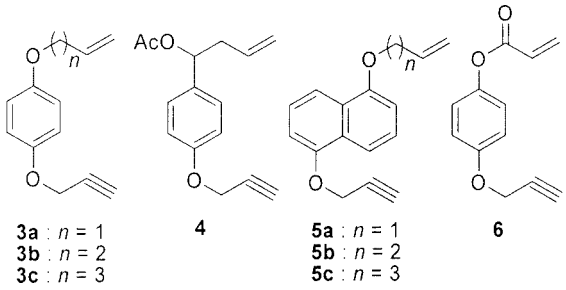
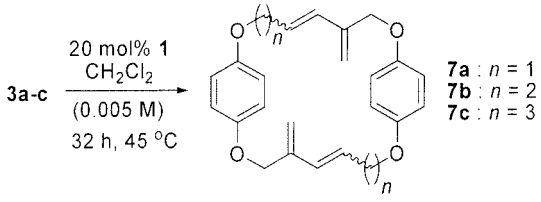


Figure 2. Enyne substrates

By subjecting enyne **3a** to 5 mol % **1** under refluxing dichloromethane, **7a** was produced slowly. Additional catalysts (5 mol % each) were added successively at 8 h intervals until the reaction was completed.[6] With 20 mol % of total catalyst loadings, the starting material was consumed completely within 32 h to give **7a** in 33% isolated yield (Table 1, Entry 1). Conversions of the analogues **3b** and **3c** were also slow and required high catalyst loadings for completion of the reactions (Table 1, Entries 2 and 3). Although the yields were low, no other products were isolated from the reaction mixture. The products were proved to arise from the *exo*-mode cyclization (see Scheme 1), and both 1,3-diene units therefore have the same geometries. Saturation of the alkene isomers by catalytic hydrogenation produced single compounds.[7]

Table 1. Enyne-metathesis dimerizations: the effects of catalyst and ethylene



Entry	3	Catalyst	Ethylene	Products[a]
1	**3a**	**1**	no	**7a** (33)
2	**3b**	**1**	no	**7b** (27)
3	**3c**	**1**	no	**7c** (25)
4	**3a**	**2**	no	**7a** (−)[b]
5	**3b**	**2**	no	**7b** (−)[b]
6 [c]	**3a**	**1**	1 atm	**7a** (31)
7[c]	**3c**	**1**	1 atm	**7c** (36)
8[c]	**3a**	**2**	1 atm	**7a** (−)[d] +**8** (32)

[a] Mixtures of isomers were obtained. [b] Starting materials were recovered. [c] 10 mol % of catalyst, 16 h. [d] **7a** was not detected.

We then examined the more reactive second generation catalyst **2** and the effect of ethylene gas to optimize the reaction conditions (Table 1). In general, catalyst **2** is more effective for enyne-metathesis reactions,[2] and ethylene is known to facilitate the enyne metathesis.[8] However, the story was totally different in the case of the present ring-forming reactions. Treatment of **3a** and **3b** with the second generation catalyst **2** gave none of the expected products **7a** and **7b**, respectively, but only the starting materials, without any other metathesis products except some polymeric materials (Table 1, Entries 4 and 5). The observed reactivity difference between **1** and **2** is unusual and is an interesting feature, and may need further studies for a full understanding.

We then conducted the reaction under an ethylene atmosphere. The effect of ethylene (1 atm) on catalyst **1** was controversial: while the yield of **7c** increased from 25% to 36%, that of **7a** slightly decreased from 33% to 31% (Table 1, Entries 6 and 7). However, the reaction time and catalyst loading were reduced to 16 h and 10 mol %, respectively, for completion of the reactions. On the contrary, an atmosphere of ethylene gas did not have any beneficial effect on catalyst **2** in the dimerization reactions. In this case, cross metathesis between ethylene and the alkyne moiety[9] dominated to give compound **8** instead (Table 1, Entry 8; Figure 3). The less reactive catalyst **1** therefore was better than the more reactive catalyst **2** for the enyne-metathesis dimerizations studied herein.

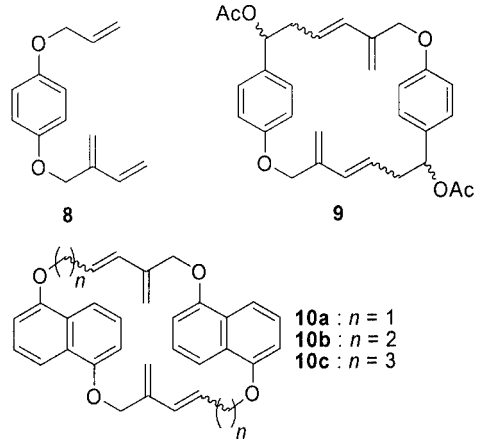


Figure 3. Enyne-metathesis products

Additional dimerization examples using substrate **4** and **5a**−**c** are shown in Table 2. The 1,5-disubstituted naphthalene series **5a**−**c** were more reactive than the hydroquinone relatives in terms of total reaction times. The reactions were completed in 16 h to give 23−44% of macrocyclic dimers (Table 2, Entries 2−4).

At this point, we would like to mention the observed low yields in the enyne-dimerization reactions. In general, intermolecular enyne-metathesis reactions are difficult because of slow reaction rates and competitive pathways such as chelation and oligomerization.[10] Therefore, most of practical intermolecular enyne-RCM reactions employ either excess alkenes or ethylene gas. However, the enyne dimerization studied here could utilize neither of these. The variation of alkene concentration is not optional because it is a

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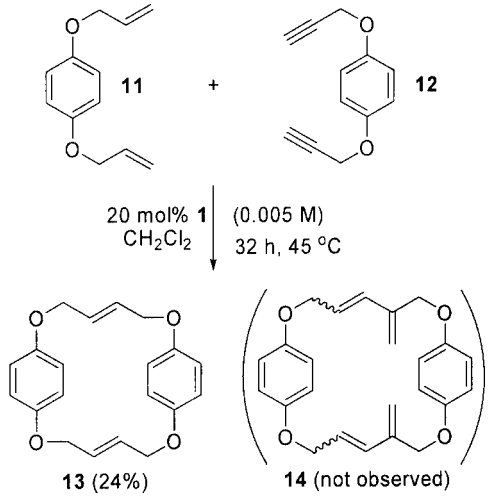
Table 2. Enyne-metathesis dimerizations

Entry[a]	Substrate	Conditions[b]	Products[c]
1	**4**	20 mol % **1**, 24 h	**9** (39)
2	**5a**	10 mol % **1**, 16 h	**10a** (23)
3	**5b**	10 mol % **1**, 16 h	**10b** (30)
4	**5c**	10 mol % **1**, 16 h	**10c** (44)

[a] Reaction conditions: **1**, CH_2Cl_2, 45 °C, 0.005 M. [b] Amount of catalyst **1** used and reaction time. [c] Mixtures of isomers were obtained.

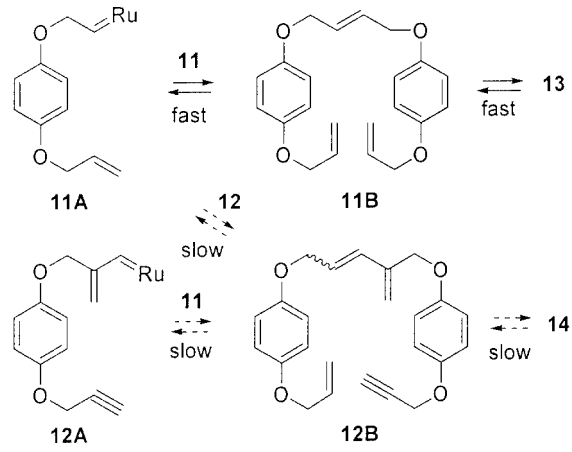
dimerization reaction; the effect of ethylene gas was minimal as mentioned before.

If the above tandem metathesis dimerization operates for the mixture of diene **11** and diyne **12**, we might expect a dimeric macrocycle **14** through a similar process (Scheme 2). Thus, a 1:1 mixture of **11** and **12** was treated with 20 mol % of catalyst **1** under the previous metathesis conditions. However, the expected **14** was not isolated from the reaction mixture, instead dimer **13** was obtained in 24% yield with recovered **12**. This result was obtained because of the dimerization of **11** by a tandem diene-CM/RCM reaction, as shown in our previous report.[3j] This implies that the overall sequence **11A** → **11B** → **13** is most favorable under the reversible conditions, although the initially formed metathesis intermediate could be either **11A** or **12A** (Scheme 3).



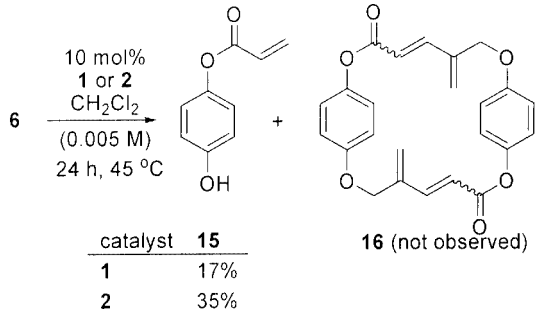
Scheme 2. Metathesis of a mixture of diene **11** and diyne **12**

An enyne substrate with an electron-deficient alkene was also considered for the dimerization. When **6** was subjected to 10 mol % of **1** and **2** under refluxing dichloromethane, the dimer **16** was not obtained, but to our surprise compound **15** was isolated in 17% and 35% yields, respectively (Scheme 4). The propargyl group was removed selectively without any metathesis reactions. Carbene ruthenium catalyzed isomerization of the double bonds of allyl ether to



Scheme 3. Mechanism of cross metathesis of **11** and **12**

vinyl ether and deprotection of allylamines are often encountered in the course of metathesis reactions.[11] These non-metathesis alkene isomerizations mediated by carbene ruthenium complexes were proposed to proceed via ruthenium hydride species, which might be formed by decomposition of the carbene ruthenium species under the reaction conditions.[12] However, isomerization of a triple bond or deprotection of a propargyl group by carbene ruthenium complexes has not been known in the literature until now.



Scheme 4. Deprotection of a propargyl ether

We therefore investigated the scope of the deprotection of propargyl groups[13] in detail by examining different solvent systems and reaction temperatures with catalyst **2**, as shown in Table 3. Conditions **A** (CH_2Cl_2, 45 °C), **B** (benzene, 100 °C), and **C** (toluene, 125 °C) were evaluated with aryl propargyl ethers **17a**–**e**.[6] Condition **A** required longer reaction times, and the yields were low (Table 3, Entries 1 and 2). On the other hand, reactions conducted under condition **C** produced a significant amount of polymeric materials (Table 3, Entries 3–6). The best yields were obtained in benzene solution (condition **B**) with 8–20 mol % of **2**. Aryl propargyl ethers **17a** and **17c** with electron-withdrawing groups at the *para*-position gave poor yields (34% and 29%, respectively) of the corresponding phenols (Table 3, Entries 7 and 9). Compound **17b** and **17e** with electron-donating groups (*p*-OAc and *p*-OMe) proved to be good substrates,

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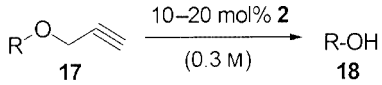
and the deprotection yields were 61% and 81%, respectively (Table 3, Entries 8 and 11). Deprotection of phenyl propargyl ether **17d** was completed in quantitative yield to give phenol (Table 3, Entry 10). The reactions of benzyl propargyl ether **17f** and propargylamine **17g** were also examined, but the reactions were slow, and the yields were rather low relative to those with the aryl propargyl ethers (Table 3, Entries 12 and 13).

Table 3. Deprotection of propargyl groups with **2**

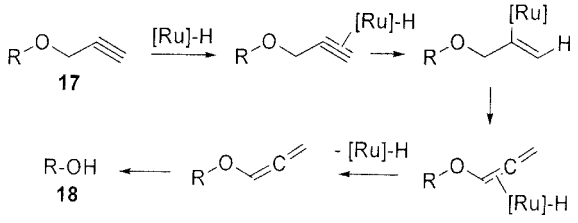


17a: R = (*p*-NO_2)-C_6H_4 **17e**: R = (*p*-MeO)-C_6H_4
17b: R = (*p*-AcO)-C_6H_4 **17f**: R = $C_6H_5CH_2$
17c: R = (*p*-CHO)-C_6H_4 **17g**: RO = C_6H_5N(Boc)
17d: R = C_6H_5

Entry (mol % of **2**)[b]	Substrate time (h)	Condition[a] (%)	Reaction	Yield[b]
1	**17a**	**A** (20)	60	11
2	**17b**	**A** (15)	48	19
3	**17a**	**C** (20)	24	23
4	**17b**	**C** (20)	48	(−)[c]
5	**17c**	**C** (8)	60	25
6	**17d**	**C** (8)	60	11
7	**17a**	**B** (8)	24	34
8	**17b**	**B** (8)	24	61
9	**17c**	**B** (10)	24	29
10	**17d**	**B** (8)	24	99
11	**17e**	**B** (8)	16	81
12	**17f**	**B** (20)	48	20
13	**17g**	**B** (15)	48	24

[a] Condition **A**: **2**, CH_2Cl_2, 45 °C, 0.3 M; Condition **B**: **2**, benzene, 100 °C, 0.3 M; Condition **C**: **2**, toluene, 125 °C, 0.3 M. [b] Catalyst was added in portions (5 mol % each time). [c] Insoluble polymeric materials were obtained.

The detailed mechanism for the deprotection of propargyl ethers by carbene ruthenium complexes is unclear. But the ruthenium-hydride mechanism, which is typically used to explain the deprotection of allyl groups, may also apply in this case. The allenyl ethers generated by the isomerization of the propargyl ethers hydrolyze to the alcohols as shown in Scheme 5.



Scheme 5. A proposed mechanism for the deprotection of propargyl ethers

Conclusion

We have reported a new tandem enyne-metathesis sequence from enyne substrates to macrocyclic compounds. The initial dimeric intermediates formed by cross enyne metathesis were cyclized by ring-closing enyne metathesis to give macrocycles with the use of the first generation Grubbs' catalyst. Deprotections of aryl propargyl ethers by carbene ruthenium complexes are the first to be reported in this communication. The deprotections of propargyl groups were best catalyzed by the second generation Grubbs' catalyst in benzene solutions.

Experimental Section

Procedure for the Metathesis Dimerization: A solution of **3a** (35 mg, 0.16 mmol) and catalyst **1** (7 mg, 5 mol %) in CH_2Cl_2 (32 mL) was refluxed at 45 °C for 7 h under N_2. Additional catalysts (5 mol % × 3) were added at 8 h intervals. A total of 20 mol % of catalyst **1** was added over 32 h before the reaction was completed. The solvent was removed under reduced pressure, and the residue mixture was column chromatographed on silica gel (hexane/EtOAc, 20:1) to give 5.2 mg (15%) of **7c** (*E*/*Z* isomer) and 3.5 mg (10%) of **7c** (*E*/*E* isomer) as colorless solids.

Data for 7c (unsymmetric *E*/*Z* isomer): Colorless solids; R_f = 0.5 (silica gel, hexane/EtOAc, 5:1); m.p. 123−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.75−6.50 (m, 8 H), 6.10 (d, J = 16 Hz, 1 H), 6.05−5.85 (m, 2 H), 5.55−5.45 (m, 1 H), 5.34 (s, 1 H), 5.17 (s, 1 H), 5.13 (s, 2 H), 4.61 (s, 2 H), 4.48 (s, 2 H), 3.84 (m, 2 H), 3.77 (m, 2 H), 2.50−2.35 (m, 2 H), 2.35−2.20 (m, 2 H), 1.95−1.85 (m, 2 H), 1.85−1.75 (m, 2 H) ppm. ^{13}C NMR (128.5 MHz, $CDCl_3$): δ = 153.6, 153.4, 152.6 (2 C), 141.8 (2 C), 132.6, 131.7, 130.4, 128.6, 117.3, 117.1, 116.2, 115.9, 115.6 (2 C), 71.1, 70.0, 67.8, 67.6, 29.5, 29.4, 28.5, 25.4 ppm. IR (neat): $\tilde{\nu}$ = 2978, 2913, 2851, 1656, 1514, 1382, 1237, 1202, 1061, 981, 901, 814 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{28}H_{32}O_4$ [M$^+$]: 432.2301; found 432.2303.

Data for 7c (symmetric *E*/*E* isomer): Colorless solids; R_f = 0.5 (silica gel, hexane/EtOAc, 5:1); m.p. 123−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.74 (d, J = 8 Hz, 4 H), 6.68 (d, J = 9 Hz, 4 H), 6.13 (d, J = 16 Hz, 2 H), 6.00−5.95 (m, 2 H), 5.17 (s, 2 H), 5.13 (s, 2 H), 4.62 (s, 4 H), 3.90 (t, J = 6 Hz, 4 H), 2.35−2.25 (m, 4 H), 1.95−1.75 (m, 4 H) ppm. ^{13}C NMR (128.5 MHz, $CDCl_3$): δ = 153.5, 152.6, 141.6, 131.7, 130.4, 117.3, 116.3, 115.7, 70.0, 67.7, 29.7, 28.6 ppm. IR (neat): $\tilde{\nu}$ = 2940, 2870, 1512, 1482, 1282, 1236, 1213, 1110, 1030, 963, 905, 821 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{28}H_{32}O_4$ [M$^+$]: 432.2301; found 432.2302.

Procedure for the Deprotection of Aryl Propargyl Ethers: A benzene (1.14 mL) solution of **17d** (45 mg, 0.34 mmol) and catalyst **2** (9 mg, 3 mol %) was refluxed at 100 °C (bath temperature) in a sealed tube for 7 h under N_2. Additional catalysts (3 mol % and 2 mol %) were added at 8 h intervals. A total of 8 mol % of catalyst **1** was added over 24 h before the reaction was completed. The solvent was removed under reduced pressure, and the residue mixture was column chromatographed on silica gel (hexane/EtOAc, 10:1) to give 32 mg (99%) of phenol.

Acknowledgments

We thank the Center for Bioactive Molecular Hybrids (CBMH) for financial support.

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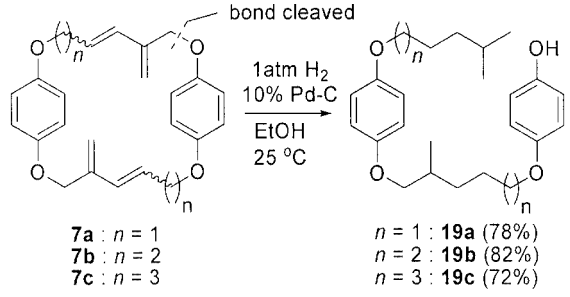
[5] Substrates **3a**−**c** and **5a**−**c** were prepared from hydroquinone and 1,5-dihydroxynaphthalene, respectively, by double alkylations; 1. K_2CO_3, $HCCCH_2Br$, DMF, 35−38% of mono alkylation products, 2. NaH, $Br(CH_2)_nCH{=}CH_2$, DMF, 85% (**3a**), 82% (**3b**), 82% (**3c**), 99% (**5a**), 33% (**5b**), 99% (**5c**). Substrate **6** was synthesized from hydroquinone; 1. K_2CO_3, $HCCCH_2Br$, DMF, 35%, 2. Et_3N, $ClCOCH{=}CH_2$, CH_2Cl_2, 95%. Substrate **4** was prepared from 4-hydroxybenzaldehyde; 1. K_2CO_3, $HCCCH_2Br$, DMF, 66%, 2. $BrMgCH_2CH{=}CH_2$, THF, 83%; 3. Ac_2O, pyr, DMAP, CH_2Cl_2, 99%.

[6] The reactions were performed in sealed tubes, and the temperatures indicated are bath temperatures.

[7] One of the C−O bonds was cleaved under the hydrogenation conditions.



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