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Ruthenium-Catalyzed Tandem Ring-Opening/Ring-Closing/ Cross-Metathesis of 1,6-Cyclopropene-ynes and Olefins for the Construction of the 3-Pyrroline Skeleton

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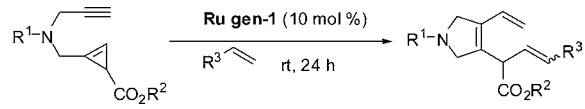
ABSTRACT



Catalyzed by the first-generation Grubbs' ruthenium complex, tandem intramolecular/intermolecular metathesis of 1,6-enynes bearing a cyclopropene ring took place smoothly to produce 3-pyrroline derivatives in satisfactory yields via ring-opening/ring-closing/cross-metathesis processes.

During the 60 years of development,[1] olefin metathesis[2] has emerged as a very powerful tool in organic natural product synthesis because of the great capacity of constructing macrocycles and complex molecular structures.[3] Moreover, alkyne-involved olefin metathesis (enyne metathesis)[4] is also a very important and interesting type of olefin metathesis, which has been extensively studied and has made great progress in the past 20 years. Nowadays, tandem intramolecular/intermolecular enyne metathesis has been widely used to synthesize cyclic/noncyclic 1,3-diene compounds in an atom-economical and environmentally benign way.[5] However, the applications of enyne metathesis are often limited to employing medium/large cycloalkenes (≥five-membered rings) or using straight-chain alkenes as the substrates.[5a] Indeed, the reports on small-ring metathesis are rare.[6] As

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the smallest cycloalkenes, cyclopropenes[7] are highly strained but readily accessible substances,[8] which have been serving as useful building blocks in many organic reactions.[9] For example, 3,3-diphenylcyclopropene has been well-known as an important starting material for the synthesis of valuable ruthenium-involved vinylalkylidene olefin metathesis catalyst via a ring-opening process.[2] Since cyclopropenes cannot be formed by ring-closing metathesis (RCM) due to the highly strained energy,[10] the ring-opening of the ruthenacyclobutane intermediate is irreversible. In such cases, cyclopropenes are more inclined to undergo ring-opening metathesis polymerization (ROMP)[11] rather than ring-opening metathesis/cross-metathesis (ROM/CM). However, several ROM/CM processes involving cyclopropenes have recently been disclosed. For instance, ROM/CM of cyclopropenone ketals has been successfully applied to the synthesis of Bistramide A and Routiennocin.[12] More recently, Hoveyda and co-workers reported enantioselective[13] and diastereoselective[14] ROM/CM of 3,3-disubstituted cyclopropenes, giving functionalized homoallylic carboxylic esters and homoallylic alcohols in moderate to good yields along with good stereoselectivities. Furthermore, Meyer and co-workers also reported intramolecular metathesis reactions of cyclopropenes via a ROM/RCM (ring-rearrangement metathesis) sequence, affording a variety of heterocyclic compounds in moderate to excellent yields.[15] Inspired by these pioneering reports and our previous unsuccessful attempts on using tetra-substituted arylvinylcyclopropenes[16] as substrates in olefin metathesis, we synthesized a series of electron-deficient, sulfonamide-linked 1,6-cyclopropene-ynes **1** via a nucleophilic substitution followed by a rhodium-catalyzed cyclopropenation sequence (Scheme 1; for details, please see the Supporting Information) to examine the enyne metathesis. In this communication, we wish to report a novel and remarkable ROM/RCM/cross-metathesis of 1,6-cyclopropene-ynes and olefins. To the best of our knowledge, this finding constitutes the first report on the ring-closing enyne metathesis (RCEYM) of cyclopropenes.

Scheme 1. Two-Step Synthesis of 1,6-Cyclopropene-ynes **1**

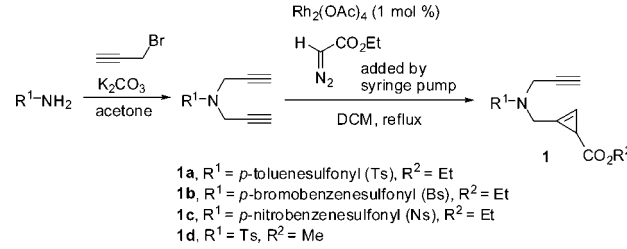

Figure 1 shows the catalysts that are available for ROM/RCM/cross-metathesis of 1,6-cyclopropene-ynes **1** and olefins **2**. **Ru gen-1** and **Ru gen-2** are the first- and second-generation Grubbs' ruthenium complexes that are widely used in olefin metathesis.[3,5] **Ru-3** is a modified Hoveyda−Grubbs catalyst developed by Zhan.[17] Catalyst kits **Ru-4** and **Ru-5** developed by Dixneuf's group have also been widely used in enyne metathesis.[18]

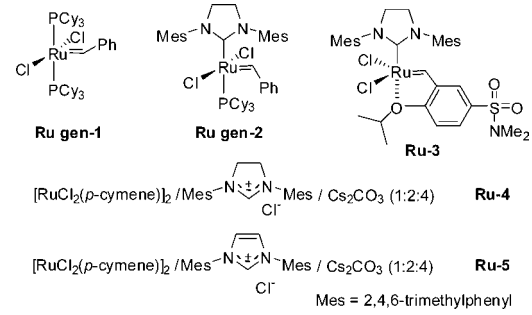

Figure 1. Catalysts used in ROM/RCM/cross-metathesis of 1,6-cyclopropene-yne **1a** in Table SI-2.

Initial examination of the reaction was performed by using ethyl 2-((4-methyl-*N*-(prop-2-ynyl)phenylsulfonamido)methyl)cycloprop-2-enecarboxylate (**1a**, 0.1 mmol) as the substrate in the presence of **Ru gen-1** (10 mol %). We found that using styrene **2a** as the solvent and 10 mol % of catalyst loading (**Ru gen-1**), **3a** can be obtained in maximum overall yields (Please see Table SI-2 in the Supporting Information for the details).

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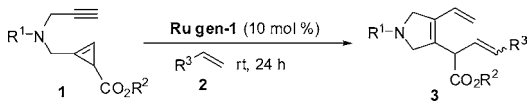
Table 1. Scope of the Tandem ROM/RCM/Cross-Metathesis of 1,6-Cyclopropene-ynes **1** and Olefins **2**



entry[a]	**1** (R^1/R^2)	**2** (R^3)	yield[b] (%) (E/Z)[c]
1	**1b** (Bs/Et)	**2a**	**3b**, 60 (1/1.3)
2	**1c** (Ns/Et)	**2a**	**3c**, 74 (1/0.8)[d]
3	**1d** (Ts/Me)	**2a**	**3d**, 60 (1/1.5)
4	**1a**	**2b** (p-MeC_6H_4)	**3e**, 67 (1/1.3)
5	**1a**	**2c** (m-MeC_6H_4)	**3f**, 71 (1/1.1)
6	**1a**	**2d** (p-$MeOC_6H_4$)	**3g**, 45 (1/0.6)
7	**1a**	**2e** (p-BrC_6H_4)	**3h**, 37 (1/1.0)
8	**1a**	**2f** (m-ClC_6H_4)	**3i**, 35 (1/1.7)
9	**1a**	**2g** (n-pentanyl)	**3j**, 71 (1/2.3)[d]
10	**1a**	**2h** ($PhCH_2CH_2$)	**3k**, 62 (1/2.8)[d]
11	**1a**	**2i** (naphthyl)	**3l**, 78 (1/1.7)[d]
12	**1a**	**2j** (2-benzofuranyl)	**3m**, 51 (1/1.8)[d]
13	**1a**	**2k** [(trimethoxysilyl)ethyl]	**3n**, 60

[a] All reaction were carried out using **1** (0.2 mmol) and **2** (2 mL) in the presence of Grubbs first-generation catalyst (0.02 mmol) at rt for 24 h. [b] Isolated yield. [c] Values in brackets: ratio of two isomers determined by isolated yield. [d] Ratio of two isomers determined by ^{1}H NMR spectroscopy.

With these optimal conditions in hand, we next examined a variety of 1,6-cyclopropene-ynes **1** and olefins **2** in this reaction, and the results of these experiments are shown in Table 1. As can be seen from Table 1, the reactions took place smoothly with *p*-bromobenzenesulfonamide and *p*-nitrobenzenesulfonamide-linked 1,6-cyclopropene-ynes **1b** and **1c**, affording the corresponding products **3b** and **3c** in 60 and 74% yields, respectively (Table 1, entries 1 and 2). On the other hand, the reaction of methyl cyclopropenecarboxylate **1d** with styrene **2a** could also produce the corresponding 3-pyrroline derivative **3d** in 60% yield (Table 1, entry 3). Using electron-rich styrenes **2b**, **2c**, and **2d** as the substrates produced 3-pyrroline derivatives **3e**, **3f**, and **3g** in moderate to good yields (Table 1, entries 4−6). Electron-deficient styrenes **2e** and **2f** strongly retarded the reaction, giving **3h** and **3i** in 37 and 35% yields, respectively (Table 1, entries 7 and 8). The reactions of aliphatic olefins **2g** and **2h** with **1a** produced **3j** and **3k** in 71 and 62% yields along with *Z*-isomers as the major products, respectively (Table 1, entries 9 and 10). Sterically hindered aromatic olefins **2i** and **2j** could also tolerate the standard reaction conditions, producing the corresponding products **3l** and **3m** in 78 and 51% yields, respectively (Table 1, entries 11 and 12). We also observed the formation of ethyl 2-(1-tosyl-4-vinyl-2,5-dihydro-1*H*-pyrrol-3-yl)-5-(trimethoxysilyl)pent-3-enoate **3n** in 60% yield if using olefinic silane **2k** as the substrate on the basis of ^{1}H NMR spectroscopic data and TLC trace of the crude product (Table 1, entry 13).

Using trisubstituted cyclopropene **1e** as the substrate, we failed to isolate the corresponding cross-metathesis products under the standard conditions, presumably due to the steric hindrance of *gem*-substituents on the cyclopropene. Using diethyl-malonate-linked 1,6-cyclopropene-yne **1f** as the substrates, we only recovered ≈80% of **1f** under the standard reaction conditions. Further attempts by increasing the temperature to 50 °C gave complex product mixtures. This unsuccessful metathesis reaction of malonate-linked 1,6-cyclopropene **1f** with styrene **2a** is probably due to the conformational difference of substrates with sulfonamide linkage. The reaction of ether-linked 1,6-cyclopropene-yne ethyl 2-((prop-2-ynyloxy)methyl)cycloprop-2-enecarboxylate (**1g**) and styrene **2a** provided desired product, ethyl 4-phenyl-2-(4-vinyl-2,5-dihydrofuran-3-yl)but-3-enoate (**3o**), in 55% yield along with 1/1.4 ratio of *E*/*Z*-isomers (Figure 2).

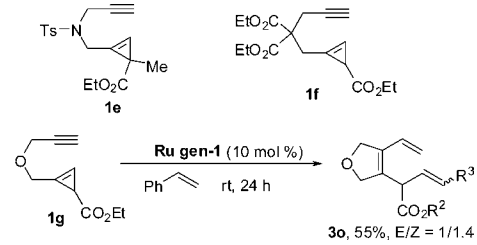
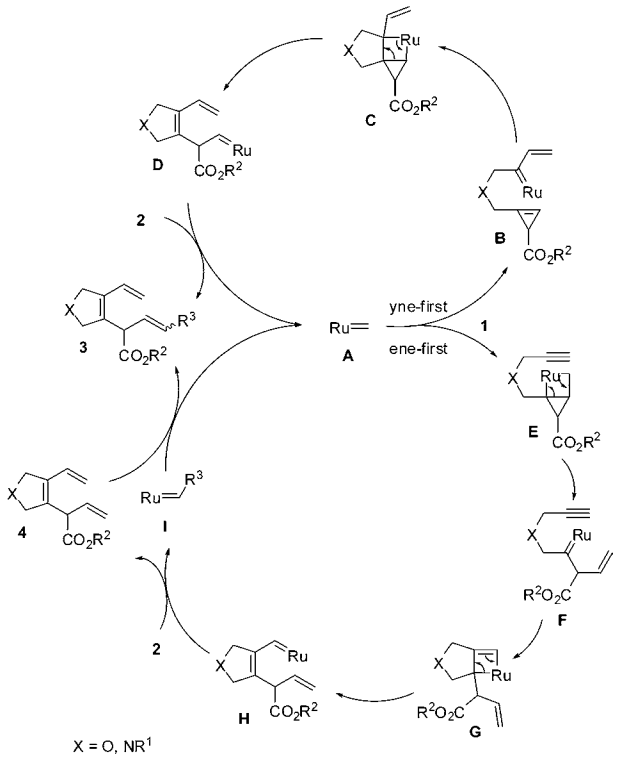


Figure 2. Other attempts of ROM/RCM/cross-metathesis of 1,6-cyclopropene-ynes **1e**, **1f**, and **1g**.

It is well-known that enyne metathesis could be initiated via two relative routes: ene-first pathway or yne-first pathway.[5] A plausible mechanism for the formation of these 3-pyrroline and 2,5-dihydrofuran derivatives based on ene-first and yne-first pathways is outlined in Scheme 2. Initial reaction of **Ru gen-1** with olefin **2** generates methyleneruthenium **A**. The reaction of intermediate **A** with 1,6-cyclopropene-ynes **1** produces internal vinyl carbene intermediate **B**, which is a more general intermediate in intramolecular enyne metathesis, especially in small ring cyclization (yne-first pathway).[5,6] Intermediate **B** undergoes intramolecular cycloaddition to form ruthenacyclobutane **C**. Further ring-opening reaction of **C** generates vinyl carbene intermediate **D**. Subsequent reaction of **D** with olefin **2** produces the desired product **3** and regenerates catalyst **A**. On the other hand, methyleneruthenium **A** can also undergo cycloaddition with 1,6-cyclopropene-ynes **1** to form ruthenacyclobutane **E** (ene-first pathway). Subsequent irreversible ring-opening reaction produces ruthenium carbene species **F**, which undergoes intramolecular cycloaddition to the terminal triple bond to generate ruthenacyclobutene intermediate **G**. The ring-opening reaction of intermediate **G** furnishes the five-membered ring intermediate **H**, which reacts intermolecularly with olefin **2** to give compound **4**. Subsequent cross-metathesis of **4** (which cannot be isolated from the reaction mixtures, presumably due to that compound **4** is highly reactive under the reaction conditions) with **I** produces the final product **3** and regenerates catalyst **A**. At this stage, we cannot determine which one initiates the reaction process.

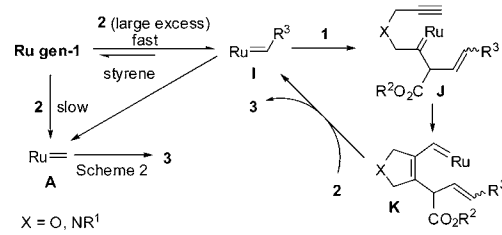
Furthermore, in order to disclose which pathway could be more viable, we examined the reaction of **1a** and stoichiometric amount of **Ru gen-1** in the presence of styrene

Scheme 2. Plausible Reaction Mechanism



(50.0 equiv) in $CDCl_3$ to monitor the disappearance of the protons in cyclopropene and alkyne of **1a** as well as the appearance of new carbene proton resonances. Unfortunately, we failed to monitor the reaction process by NMR spectroscopy because the reaction was completed under the above conditions in less than 2 min, giving **3a** in 70% isolated yield. Using 1.5 equiv of styrene, the reaction produced **3a** in 25% isolated yield within 2 min. These observations reveal that higher catalyst loading can significantly accelerate the reaction. Moreover, according to this observation, the direct addition of alkylidene **Ru gen-1** to cyclopropene followed by enyne metathesis (via intermediates **J** and **K**, Scheme 3) is also possible to produce **3a** in which methyleneruthenium **A** may not be the "real" catalyst during this reaction process. Thus, we examined the reaction of **1a** with **2c** (50 equiv) in DCM in the presence of stoichiometric **Ru gen-1**. It was found that the reaction also completed within 2 min to produce **3f** in 75% isolated yield without formation of **3a**. In comparison, when we reduced the employed amount of **2c** to 2.0 equiv, the reaction completed within 1 h to produce (*E*)-**3a** as a major product along with **3f** as a minor one (for details, please see Scheme 1 in the Supporting Information).

Scheme 3. Alkylidene as Reaction Initiator



This result is not compatible with the methylidene **A** initiated pathway. As methylidene **A** is generated much slower than alkylidene **I** under large excess of olefin,[19] alkylidene (**I** or **Ru gen-1**) could be the real reaction initiator in these cases. As a result, we illustrate a more viable reaction mechanism based on alkylidene as the initiator in Scheme 3. On the other hand, since the reaction proceeded more slowly using catalytic amount of **Ru gen-1**, methylidene-initiated pathways could not be fully excluded at the present stage.

In summary, we have developed a novel tandem ROM/RCM/cross-metathesis of 1,6-cyclopropene-ynes with olefins catalyzed by the first-generation Grubbs' ruthenium complex. This synthetic protocol furnishes 3-pyrroline and 2,5-dihydrofuran derivatives straightforwardly from easily available and simple starting materials in satisfactory yields under mild conditions, partially enriching small-ring metathesis system. A plausible mechanism has also been proposed that is based on an alkylidene-initiated ROM/RCM/cross-metathesis process. Clarification of the detailed reaction mechanism and further application of this chemistry are in progress.

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Supporting Information Available: Detailed description of experimental procedures, full characterization of new compounds shown in Tables 1 and 1, X-ray crystal analysis data of **3c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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