A Mechanism Switch in Enyne Metathesis Reactions Involving Rearrangement: Influence of Heteroatoms in the Propargylic Position

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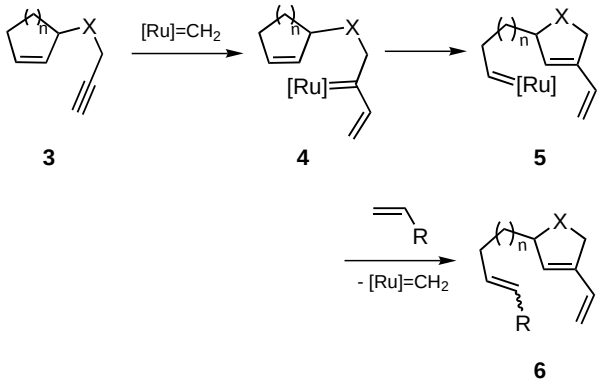
Abstract: Novel findings concerning the mechanism of enyne metathesis reactions involving rearrangement are presented. It has been demonstrated that the presence of either oxygen or nitrogen at the propargylic position leads to opposite regioselectivities in the presence of a cross-metathesis partner. The application of these reactions to domino processes is also described.

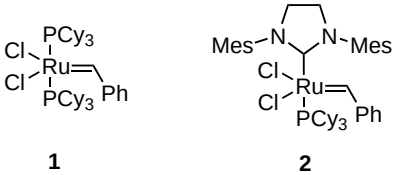
Keywords: alkenes; cycloaddition; enyne metathesis; metathesis; rearrangement; ruthenium



Scheme 1. Proposed rearrangement mechanism.

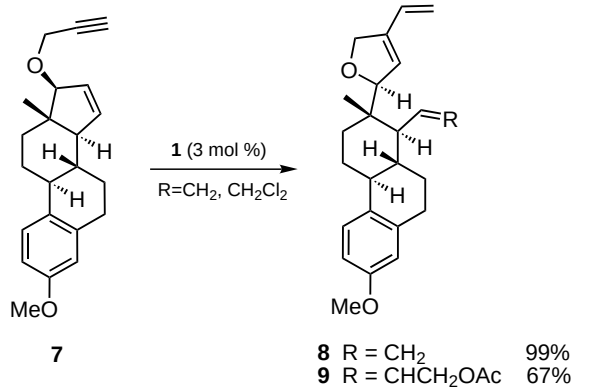
Over the last decade, with the advent of efficient ruthenium alkylidene catalysts such as **1** and later **2** (Figure 1), olefin metathesis[1] has made a significant impact on organic synthesis. In particular ring-closing metathesis (RCM) and ring-opening metathesis (ROM) have received much synthetic attention, while cross-metathesis (CM) and enyne metathesis have been somewhat less exhaustively studied.

Of considerable interest are RCM-ROM reactions of *unstrained* cycloolefins containing alkenyl side-chains, which involve rearrangements. Some of our studies of these processes have resulted in the concise and stereoselective syntheses of heterocyclic natural products.[2] Unlike the alkenyl cases which represent dynamic equilibria driven by formation of a more thermodynamically stable heterocycle, alkynyl side-chains give rise to butadienes which are relatively unreactive to catalyst **1**, thus facilitating irreversible product formation.[3,4] One



1 2

Figure 1. Olefin metathesis catalysts.



Scheme 2. Steroid rearrangement by enyne metathesis.

accepted mechanism of these transformations is depicted in Scheme 1.

In this typical example, the first attack of the ruthenium alkylidene on carbocycle **3** is postulated to occur at the alkynyl side-chain, giving the more substituted (and hence more stable[5]) vinyl alkylidene intermediate **4**, which then reacts with the endocyclic C-C double bond to give the ring rearranged alkylidene **5**. This can then undergo CM in the presence of an added acyclic olefin to give the heterocyclic product **6** along with regeneration of the methylidene propagating species. Following an earlier study concerned with the

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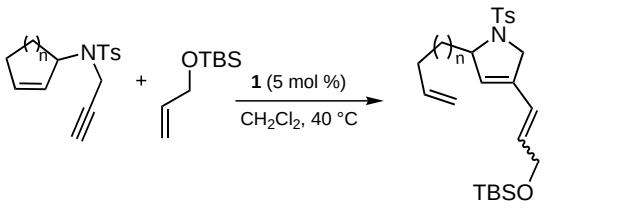
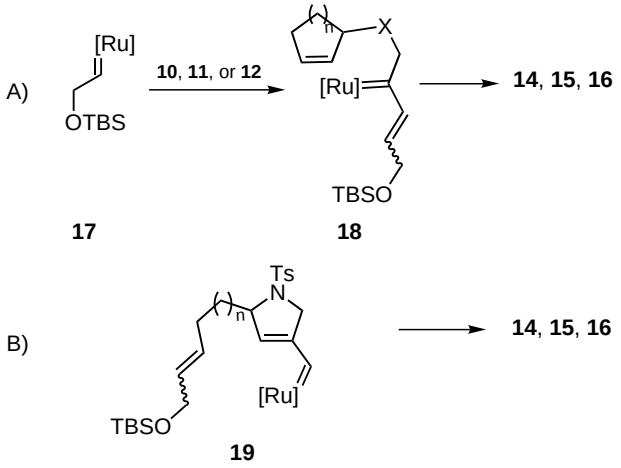
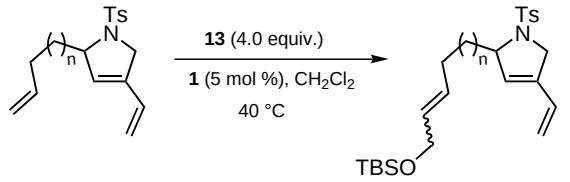


10 n = 1 **13** **14** n = 1, 78%, *E/Z* = 1:1
11 n = 2 **15** n = 2, 85%, *E/Z* = 1:1.6
12 n = 3 **16** n = 3, 81%, *E/Z* = 1:1.4

Scheme 3. Formation of *N*-heterocycles *via* rearrangement.

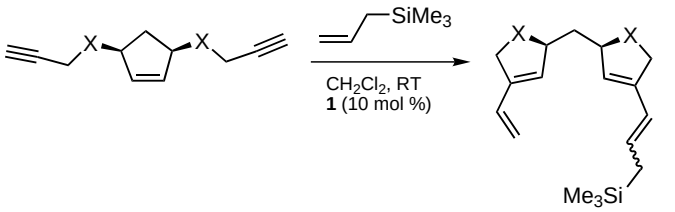


Scheme 4. Possible alkylidene intermediates responsible for the formation of **14**, **15**, and **16**.



20 (n = 3) **21** 49%

Scheme 5. Experiment to determine the CM reactivity of the butadiene moiety.



22 X = O **24** X = O 70%
23 X = NTs **25** X = NTs 88%

Scheme 6. Domino enyne metathesis-rearrangement incorporating a CM step.

synthesis of oxacycles[3] *via* such rearrangements we were interested in extending this methodology. With a view to modifying a steroid skeleton, **7** was treated with 3 mol % **1** in the presence of ethylene at 45 °C for 3 hours (Scheme 2). Under these conditions rearranged product **8** was obtained in quantitative yield. Similarly, use of allyl acetate as the CM partner yielded **9** (67%), consistent with the mechanism proposed in Scheme 1.

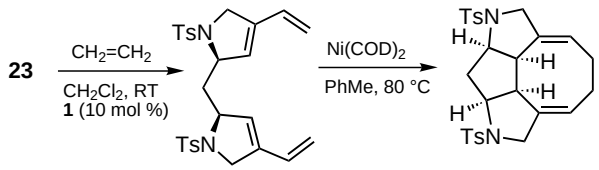
Next we undertook to determine the influence (if any) of the heteroatom on the reaction mechanism. Therefore, simple *N*-substituted 5-, 6-, and 7-membered carbocycles (**10**, **11**, and **12**, respectively) were prepared and rearranged in the presence of 5 mol % **1** with protected alcohol **13** (3.0 equiv.) as the CM partner (Scheme 3).

As expected the transformation proceeded in good yields. However, to our surprise, after rearrangement **13** was incorporated in the butadiene moiety and not in the alkyl side-chain in all three cases. It is also of interest to note that using the more reactive catalyst **2**, no rearranged products were obtainable. If an extremely unlikely[6] initial ring-opening of the carbocycle is discounted, the formation of **14**, **15**, and **16** can be explained (Scheme 4) by two distinct mechanistic rationales: A) initial reaction occurs at **13** giving rise to alkylidene **17**, which then attacks the alkyne to generate **18** with subsequent ring-opening, or B) intra- or intermolecular transfer of the CH_2OTBS-alkylidene unit to the butadiene by CM *after* rearrangement, such as outlined in Scheme 1 *via* vinylidene **19** (itself formed by reaction of the butadiene with [Ru]=CH_2).

Given the dearth of examples of CM involving butadienes in the literature, pathway A seemed more plausible. To prove this, heterocycle **20** was treated with excess **13** in the presence of **1**. Under these conditions butadiene **21** was isolated as the main product in 49% yield (Scheme 5), no evidence for any CM at the butadiene moiety was observed,[7] indicating that **19** is not formed in significant amounts. Whether this change in mechanism when the heteroatom is changed from oxygen[4] to nitrogen is due to an electronic or a chelating effect is unclear at this time. What seems certain is that in the nitrogen case, the alkyne moiety is significantly more reactive towards metathesis than in the *O*-substituted case, as the former preferentially reacts with the kinetic alkylidene **17** instead of with the methylidene propagating species, which is slower to form.[5]

To extend these domino processes, a tandem sequence of RCM-ROM-RCM (combined with a CM step) of bis-substituted unstrained cycloolefins was attempted. Precursors **22** and **23** (readily prepared from the corresponding cyclopentenediol) were treated with **1** in the presence of allyltrimethyl silane (Scheme 6). Both **22** and **23** gave **24** and **25**, respectively, in good yields. These bicycles are obvious precursors for further functionalisation via the Diels–Alder reaction[8] and other cycloadditions.

To demonstrate the potential synthetic utility of these structures, **23** was rearranged in the presence of ethylene to give **26**, which was then treated with $Ni(COD)_2$ at



26 62% **27** 82%

Scheme 7. [4 + 4] Cycloaddition of a domino enyne metathesis-rearrangement product.

elevated temperature[9] to give the [4 + 4] tetracyclic adduct **27** in high yield (Scheme 7).

In summary, it has been shown that heteroatom substituents can play a critical role in these metathesis-rearrangement reactions, with a change in mechanism evident when oxygen is switched for nitrogen in the propargylic position, allowing the possibility for internal olefin formation at either the terminal olefin or butadiene moieties. The application of enyne-RCM-ROM reactions in domino processes, and a new mode of functionalisation of the bis-butadiene products has also been demonstrated.

Experimental Section

Typical Procedure for Ring Rearrangements with Ethylene

Through a solution of 0.35 mmol of the propargylic compound (**7**, R=CH_2 and **23**) and **1** (15 mg) in CH_2Cl_2 (10 mL) was bubbled slowly 50 mL of ethylene at room temperature in a nitrogen-filled glove-box. The reaction vessel was sealed and heated at 50 °C for 3 h. After evaporation of the solvent, the residue was purified by flash-chromatography on silica gel.

Typical Procedure for Ring Rearrangements with Monosubstituted Olefins

Under an argon atmosphere a solution of 1 mmol of the propargylic compound, 3 mmol of the monosubstituted olefin and **1** (44 mg) in CH_2Cl_2 (15 mL) was heated under reflux until TLC analysis indicated completion of the reaction. After evaporation of the solvent, the residue was purified by flash-chromatography on silica gel.

Acknowledgements

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[7] Interestingly, using the more active **2** and methyl vinyl ketone, both selective CM at the side-chain terminal olefin and bis-CM functionalisation were possible in good yields (> 65%) using either 1.2 or 4 equivalents of the CM partner, respectively; to our knowledge the latter is the first example of a butadiene moiety participating in a catalytic CM reaction.

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CORRIGENDUM

In the communication by Stefan Randl, Norbert Lucas, Stephen J. Connon, and Siegfried Blechert in Issue 6+7, 2002, pp. 631 – 633, the *E/Z* ratios in Scheme 3 for products **15** and **16** were reversed by the authors. The correct values are **15**, $E/Z = 1.6:1$ and **16**, $E/Z = 1.4:1$.