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Nonmetathetic Activity of Ruthenium Alkylidene Complexes: 1,4-Hydrovinylative Cyclization of Multiynes with Ethylene

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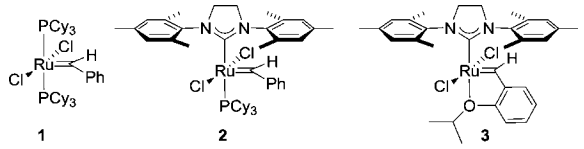
Supporting Information

ABSTRACT: An efficient 1,4-hydrovinylative cyclization reaction of triynes and tetraynes catalyzed by ruthenium alkylidene complexes under ethylene is described. The regioselectivity of vinyl group incorporation can be controlled by the nature of the substituent on the alkyne, and the Grubbs second-generation catalyst is the most effective among typical ruthenium alkylidene complexes.

Grubbs catalysts and their variants, including **1**−**3**, are widely recognized as powerful initiators for olefin metathesis reactions.[1,2] These Ru-based alkylidene complexes have been used in both academic and industrial research for the preparation of natural products, pharmaceuticals, and novel polymeric materials.[3]

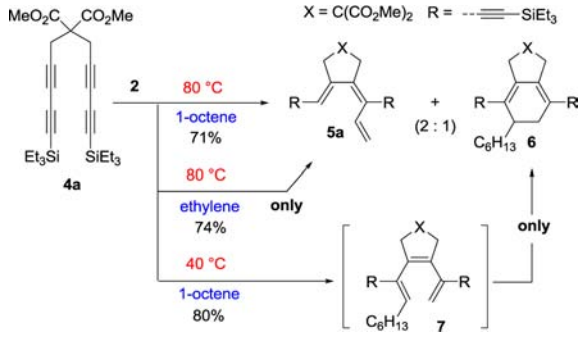


1 2 3

During the past decade, the chemistry of Ru complexes **1**−**3** and their congeners has witnessed explosive growth in diene and enyne metathesis.[3e−g] However the nonmetathetic reactivity[4] of these complexes has gained less attention, and its utility has not been widely demonstrated. This is mainly due to the fact that nonmetathetic processes have been observed as side reactions and are believed to be a consequence of the decomposed ruthenium alkylidene complexes.[4] However, the catalytically active species involved in these nonmetathetic reactions have yet to be identified. Several examples of the nonmetathetic reactivity of Grubbs complexes and their derivatives include Kharasch addition,[5] olefin isomerization,[6] hydrosilylation,[7] hydrogenation,[8] and cycloaddition[9] reactions. The discovery of new nonmetathetic reactivity of ruthenium alkylidene complexes should significantly broaden the scope of the chemistry mediated by Grubbs-type Ru complexes.

We recently reported a regioselective tandem enyne cross-metathesis (CM) and metallotropic 1,3-shift process[10] that delivers diverse patterns of unsaturated molecules, where the remote substituent serves as a controlling element for the high mode selectivity.[11] In our continued effort to expand the scope of this tandem metathesis process, we examined the metathesis behavior of bis-1,3-diyne-containing substrates such as **4a**. To our surprise, under typical metathesis conditions with catalyst **2** and 1-octene (8 equiv, toluene, 80 °C, 6 h), a 2:1 mixture of **5a** and **6** was obtained (Scheme 1). It was obvious that the

Scheme 1. Influence of Temperature and Alkene Structure on Metathesis versus 1,4-Hydrovinylative Cyclization



formation of 1,4-hydrovinylative cyclization[12] product **5a** involved ethylene, presumably formed by homometathesis of 1-octene. This was confirmed by exposing **4a** to ethylene under otherwise identical reaction conditions, which afforded **5a** as the only product in 74% yield. We surmised that bicycle **6** was derived from a thermal 6π-electrocyclization[13] of the CM product **7**. Indeed, when the reaction was run at 40 °C, **7** was formed exclusively and then slowly rearranged to **6**. It is quite remarkable that the same catalyst promotes fundamentally different modes of reaction from a common substrate depending on the nature of the alkene and the reaction temperature. Herein we report a highly efficient 1,4-hydrovinylative cyclization reaction of triynes and tetraynes under ethylene with no additives other than a catalytic amount of a Grubbs-type Ru complex.

First, we briefly screened the catalytic activity of ruthenium alkylidene complexes **1**−**3** at two different temperatures to define their relative effectiveness for the 1,4-hydrovinylative cyclization (Table 1). Clearly, Grubbs second-generation catalyst **2**[1d] was found to be far more effective than the other two at 40 °C. When substrate **4b** was treated with 5 mol % **1** in CH_2Cl_2 at 40 °C for 6 h, product **5b** (Figure 1) was obtained in 64% yield (entry 1). Under otherwise identical conditions, the reaction with **2** provided a quantitative yield of **5b** (>98%; entry 2). On the other hand, Hoveyda−Grubbs catalyst **3**[2a] showed no catalytic activity at this temperature, providing only recovered starting material (entry 3). However, at 80 °C, all three complexes provided **5b** in yields of 95% with **1** (entry 4), >98% with **2** (entry 5), and 72% with **3** (entry 6).

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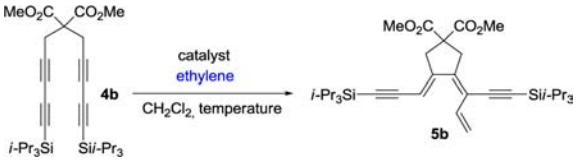
Table 1. Screening of Catalysts and Reaction Conditions[a]



entry	catalyst	T (°C)	time (h)	yield of **5b** (%)[b]
1	**1**	40	6	54
2	**2**	40	6	>98
3	**3**	40	6	0
4	**1**	80	1	95
5	**2**	80	1	>98
6	**3**	80	1	72

[a]The ruthenium complexes $RuCl_3$, $RuCl_2(PPh_3)_3$, $Ru_3(CO)_{12}$, and $[RuCp(CH_3CN)_3]PF_6$ did not provide any hydrovinylative cyclization product. [b]Isolated yields after SiO_2 chromatography.

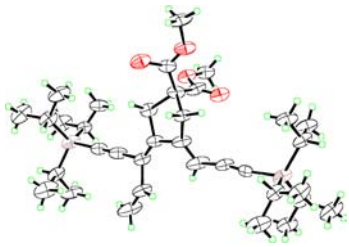
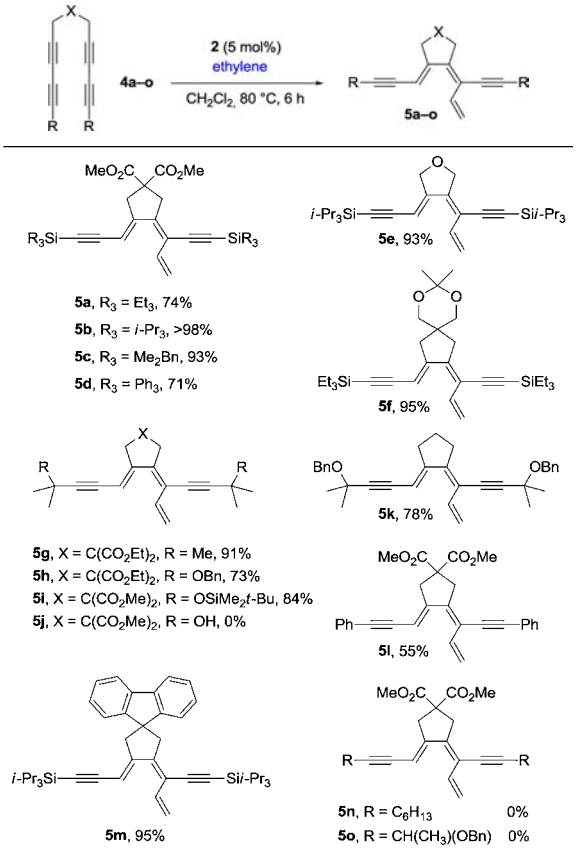


Figure 1. ORTEP diagram of **5b**.

Having established the optimized reaction conditions, we next explored the generality and scope of the 1,4-hydrovinylative cyclization using a variety of tetrayne substrates **4a**–**o** (Table 2).[14] Substrates possessing trialkyl- and triarylsilyl groups afforded products **5a**–**f** in good yields, regardless of the nature of the tether. The substrate containing a *tert*-butyl group also provided product **5g** in 91% yield. Similarly, substrates with benzyl- and silyl-protected tertiary alcohols furnished products **5h** and **5i** in 73 and 84% yield, respectively. However, **5j** was not produced from the corresponding substrate **4j** containing the free alcohol, and the starting material was recovered unchanged. The substrate bearing phenyl groups was marginally effective, providing a 55% yield of **5l**. A substrate possessing a fluorene-derived tether gave **5m** in 95% yield. Unexpectedly, neither the primary nor secondary alkyl group-containing substrate gave the corresponding cyclized product **5n** or **5o**.[15] It is noteworthy that, in all cases, no products derived from the metathesis pathway were detected.

To expand the scope of the reaction, we next examined the reactivity of unsymmetrical triyne-containing substrates **8a**–**i** (Table 3). For triynes, the unconjugated alkyne moiety may be reactive enough toward metathesis. Gratifyingly, the delicate balance between the metathesis and nonmetathetic pathways still favored the latter, providing vinylated cyclic products in excellent yields. Under the optimized reaction conditions, substrates **8a** and **8b** containing a methyl group afforded products **9a**/**9a′** and **9b**/**9b′** in 82 and 77% yield with 1:1.5 and 1.8:1 ratios, respectively (entries 1 and 2). Upon replacement of the methyl group with a phenyl group in substrates **8c**–**f**, the regioselectivity increased progressively depending on the size of the substituents,[16] providing regioisomers **9c**–**f** over **9c′**–**f′** with ratios of up to 9:1 (entries 3–6). Although substrate **8g** with *p*-methoxyphenyl and triisopropylsilyl substituents provided **9g** and **9g′** in a 10:1 ratio (entry 7), substrates **8h** and **8i**

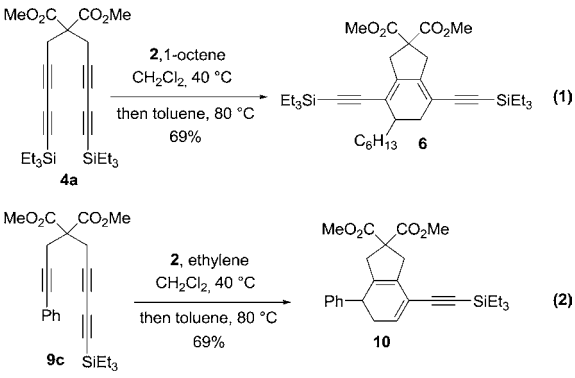
Table 2. Scope with Symmetrical Substrates[a]



[a]Isolated yields after SiO_2 chromatography are shown.

containing phenyl and triisopropylsilyl groups both afforded virtually single regioisomers **9h** and **9i** (>20:1 ratio) in 85 and 69% yield, respectively (entries 8 and 9).

The current 1,4-hydrovinylative cyclization, which creates conjugated trienes with connectivities complementary to those of the metathesis products, should have significant synthetic utility. For example, the trienes generated from metathesis and 1,4-hydrovinylative cyclization are transformed into cyclic dienes with different double-bond locations within similar molecular frameworks. As shown in eqs 1 and 2, selective enyne



metathesis of **4a** and subsequent 6π-electrocyclization of the triene intermediate provided **6**, while 1,4-hydrovinylative cyclization of **9c** followed by electrocyclization gave **10**.

Two possible mechanistic pathways for the present 1,4-hydrovinylative cyclization can be considered (Scheme 2). In path A, the ruthenium hydride[17] derived from decomposition

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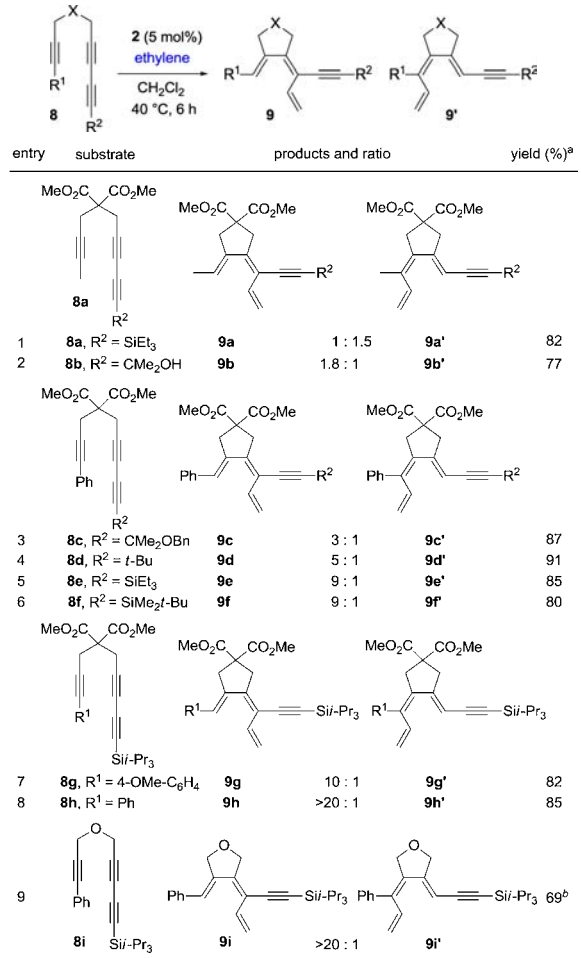
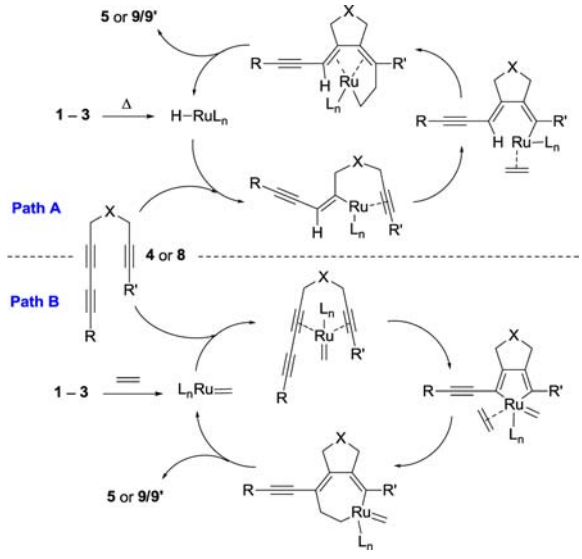
Table 3. Scope and Selectivity with Unsymmetrical Substrates



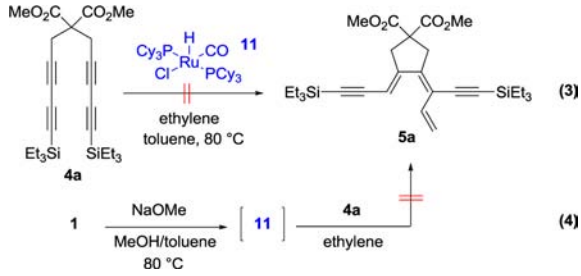
[a]Isolated yields after SiO_2 chromatography. [b]Contaminated with a product of ethylene CM on the 1,3-diyne moiety.

Scheme 2. Two Plausible Mechanisms



of the ruthenium alkylidene would be a catalytically active species, by which an initial hydroruthenation followed by cyclization would occur. Subsequent ethylene insertion and β-hydride elimination would deliver the product and regenerate the catalyst. Alternatively, in path B, formation of a ruthenacyclopentadiene intermediate[12b,18] followed by ethylene insertion, β-hydride elimination, and reductive elimination would deliver the product and regenerate the catalyst.

To gain more insights into the mechanism, we treated **4a** with the ruthenium hydride complex $[(PCy_3)_2COClRuH]$ (**11**) (eq 3).[19] Although this complex is well-known for its reactivity



in hydrovinylation,[17] the expected product **5a** was not produced under these conditions. Also, when **4a** was treated with the ruthenium alkylidene-derived active hydrovinylation catalyst described by Snapper and co-workers,[12c] the 1,4-hydrovinylative cyclization did not occur; instead, **4a** was recovered intact (eq 4). These control experiments indicate that the hydroruthenation pathway catalyzed by ruthenium hydride (path A) may not be operating.[20]

To examine the feasibility of the other reaction manifold in which the intact ruthenium methylidene is the catalytically active species, we added diallyl malonate to the reaction mixture after the hydrovinylation substrate was completely consumed. When catalyst **2** was employed in this experiment, the added diallyl malonate remained intact while 1,4-hydrovinylation continued to occur when more substrate was added to the reaction mixture. On the other hand, when **3** was used, the added diallyl malonate was consumed completely, affording the corresponding ring-closing metathesis product. The lack of metathesis activity with **2** in the former experiment results from the formation of a phosphine-ligated ruthenium methylidene species,[21] which is known to be catalytically inactive toward metathesis. When **3** was used in the latter experiment, however, formation of the metathesis-inactive phosphine-ligated ruthenium methylidene was impossible, so the metathesis activity of **3** remained. NMR monitoring of the reaction clearly proved the formation of an intact ruthenium methylidene species from **2**, and an independently prepared ruthenium methylidene showed a reaction profile indistinguishable from that of the in situ-generated catalyst under ethylene.[22] In light of all this evidence, we conclude that the most probable mechanism for the 1,4-hydrovinylative cyclization involves the ruthenium methylidene species (path B in Scheme 2), where the catalytically active species is either the ruthenium methylidene itself or its tricyclohexylphosphine-dissociated form. This is quite unusual, as without exception the known examples of nonmetathetic activity of Grubbs-type alkylidene complexes have been mediated by ruthenium hydride species such as **11**.[23]

In conclusion, we have shown that the reactivity of multiynes with Grubbs catalysts can be switched from metathesis to nonmetathetic mode by changing the nature of the externally added alkene. Using this new nonmetathetic reactivity of Grubbs complexes, we have developed an efficient 1,4-hydrovinylative cyclization of multiynes under ethylene. For unsymmetrical triyne substrates, high regioselectivity can be

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attained by incorporating appropriate substituents on the alkyne and 1,3-diyne moieties. This study adds another new entry to the already long list of nonmetathetic reactivities of Grubbs-type ruthenium alkylidenes, which we believe should further broaden their utility.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, NMR spectra, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) We surmise that the nonproductive chelation at the distal alkyne moieties prohibits the cyclization event.

(16) The observed selectivity is beyond our current understanding.

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