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Initiation and Termination Mode of Enyne Cross-Metathesis and Metallotropic [1,3]-Shift Controlled by Remote Substituents

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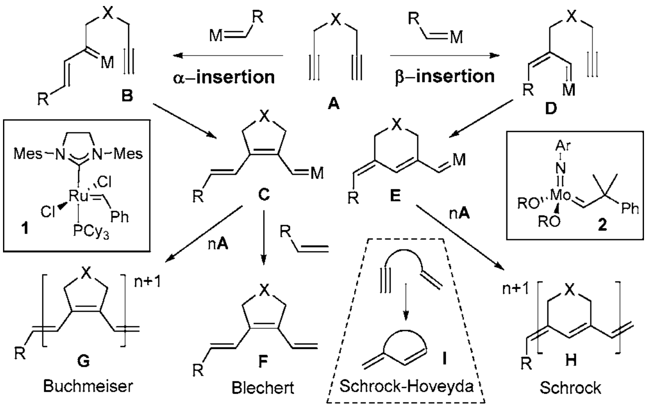
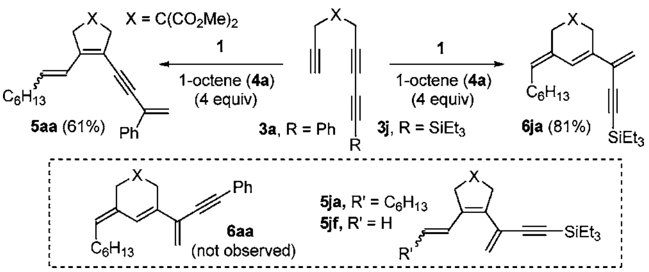
Control over the regio- and stereoselectivity in enyne cross-metathesis (CM) is a challenging problem, and thus it represents a fundamentally important area of investigation.[1,2] The CM of diyne **A** and alkene using Ru-based Grubbs catalyst **1**[3] is known to undergo α-insertion, leading to alkylidenes of type **B** and thus **C**.[4,5] To the best of our knowledge, β-insertion of a ruthenium-based Grubbs type complex to generate a vinyl akylidene **D** from **A** has not been reported.[6] On the other hand, Schrock type molybdenum imido-alkylidene complex **2** prefers β-insertion, generating alkylidenes **D** and thus **E**.[7] Intermediates **C** and **E** derived from the α- and β-insertion would ultimately deliver CM products **F** and **H**, respectively. In cyclopolymerization of 1,6-diyne **A**,[8] the ring size of the repeating unit significantly affects polymer properties,[9] rendering extensive investigation into the regioselective insertion. Investigation by Buchmeiser[4] and Schrock[7] using variants of **1** and **2** to obtain homogeneous polymers **G** and **H** are most notable in this regard. Recently, enyne ring-closing metathesis (RCM) by molybdenum alkylidenes with pyrrolide ligands generated diene **I** via the β-insertion.[10]



In conjunction with divergent metallotropic [1,3]-shift[11] behavior of conjugated multiyne,[12] we envisioned that the tandem process involving enyne CM of **3** followed by RCM and a metallotropic [1,3]-shift sequence would provide access to novel molecular structures with diverse patterns of unsaturation (Scheme 1). Initial studies revealed that the regio- and stereochemical outcome of the products critically depends on the nature of the substituent at the terminating end. For example, the reaction of **3a** bearing a phenyl substituent on the diyne exclusively afforded **5aa** ($E/Z = 10{:}1$) with a catalytic amount of **1** and 1-octene (**4a**). In stark contrast, **3j** carrying a triethylsilyl substituent proceeded with exclusive α-insertion to produce **6ja** as a single regio- and stereoisomer. The other isomers **6aa** and **5ja** were not detected. It is quite striking that the substituent at the diyne remote from the initiation site seems to control the mode of insertion. Moreover, the subsequent metallotropic shift step seems to be directly coupled with the initiation event: a metallotropic shift upon α-insertion, no metallotropic shift upon β-insertion. In this Communication, we report the result of our investigation on this unprecedented control over the regioselectivity of initiation and termination in tandem enyne CM−metallotropic shift processes.

Scheme 1. α- and β-Insertion Mode Selectivity



The generality of the regioselectivity observed in Scheme 1 was further explored by changing the steric and electronic factors on the alkyne and alkene substrates (Table 1). The CM of **3a**−**e** with alkenes **4a**−**e** resulted in the exclusive formation of five-membered ring products (**5aa**, **5ab**, **5ba**, **5ca**, **5da**, **5ea**, **5ec**, **5ed**, **5ee)** in good yields and predicted regio- and stereoselectivity (entries 2−9). Contrary to tertiary alcohol **3e**, however, its acetate and benzyl as well as silyl ether derivatives behave differently. The acetate **3f** did not afford **5fa** (entry 10); instead most of the starting material was recovered unchanged.[13] The benzyl and silyl ethers **3g** and **3h** afforded mixtures of five- and six-membered ring products (**5ga**/**6ga** = 1:1, **5he**/**6he** = 1:3), probably because of the sterically-hindered nature of these groups compared to the tertiary alcohol. The CM of *tert*-butyl group-containing substrate **3i** gave a mixture of **5ia** and **6ia** with a 1:4 ratio, which further supports this hypothesis (entry 13). Interestingly, reaction of triethylsilyl-substituted substrate **3j** with ethylene (**4f**) afforded a mixture of **5jf**[14] and **6jf** (entry 14) but with other alkenes such as 1-octene and TBS-protected allyl alcohol provided exclusively **6ja** and **6jc** (entries 16 and 17). Other silyl group-substituted substrates **3k** and **3l** also provided six-membered ring products **6la**, **6ma**, and **6mb** with slightly reduced yields (entries 18−20).

From Table 1, it is clear that the α-insertion and subsequent metallotropic [1,3]-shift is favorable with sterically unhindered substituents, whereas the hindered ones promote β-insertion without a metallotropic shift. Yet, it is not obvious how these substituents exert their influence to the mode of initiation. To gain more insight into these issues, we explored the reaction of **7a** and **7b** that have a longer tether length between the initiating alkyne and diynes (Scheme 2). Contrary to the selectivity trend with **3a**−**m**, both substrates **7a** and **7b** exhibited identical α-insertion, affording **8a** and **8b**, where the initiation event is not coupled with the termination. These results suggest that the distance between the

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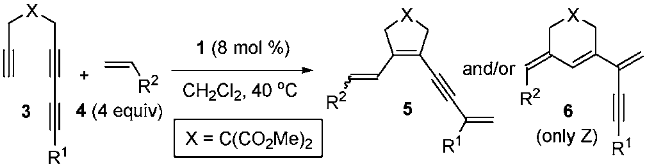
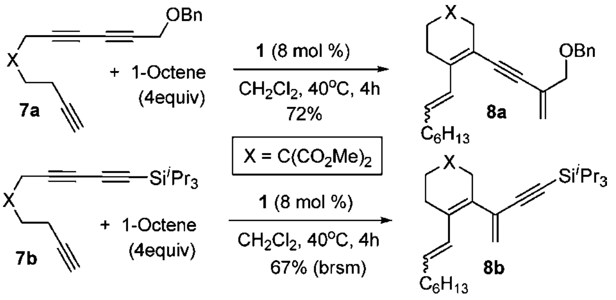
Table 1. Mode Selectivity Controlled by Remote Substituents[a]



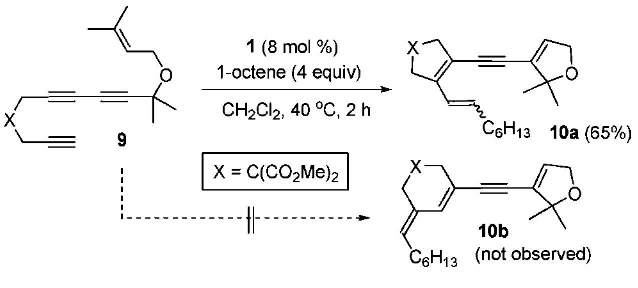
entry	**3**	R^1	**4**	R^2	product			yield (%)[b]
1	**a**	Ph	**a**	$(CH_2)_5CH_3$	**5aa**	(10:1)[c]		81
2	**a**		**b**	CH_2Ph	**5ab**	(1:0)		75
3	**b**	CH_2OBn	**a**	$(CH_2)_5CH_3$	**5ba**	(3:1)		70
4	**c**	CH_2OAc	**a**		**5ca**	(10:1)		80
5	**d**[d]	CH_2OAc	**a**		**5da**	(4:1)		59
6	**e**	$C(CH_3)_2(OH)$	**a**		**5ea**	(3:1)		91
7	**e**		**c**	CH_2OTBS	**5ec**	(3:1)		90
8	**e**		**d**	CH_2TMS	**5ed**	(2:1)		86
9	**e**		**e**	CH_2OAc	**5ee**	(2:1)		85
10	**f**	$C(CH_3)_2(OAc)$	**a**	$(CH_2)_5CH$	–			–[e]
11	**g**	$C(CH_3)_2(OBn)$	**a**		**5ga**	(1:1)[f]	**6ga**	63
12	**h**	$C(CH_3)_2(OTBS)$	**e**	CH_2OAc	**5he**	(1:3)[f]	**6he**	70
13	**i**	*t*-Bu	**a**	$(CH_2)_5CH_3$	**5ia**	(1:4)[f]	**6ia**	69
14	**j**	$SiEt_3$	**f**	H	**5jf**	(2:1)[g]	**6jf**	90
15	**j**		**a**	$(CH_2)_5CH_3$			**6ja**	61
16	**j**		**c**	CH_2OTBS[h]			**6jc**	50
17	**k**[i]		**a**	$(CH_2)_5CH_3$			–	–[j]
18	**l**	$Si(CH_3)_2Bn$	**a**				**6la**	69
19	**m**	Si(*i* -Pr)$_3$	**a**				**6ma**	72
20	**m**		**b**	CH_2Ph			**6nb**	52

[a] Reactions performed with 8 mol % Grubbs II catalyst (**1**) at 40 °C in CH_2Cl_2 for 1–2 h. [b] Total yield (**5** + **6**). [c] *E/Z* ratio. [d] X = NTs. [e] Ruthenium complex formed. [f] Ratio of **5** and **6**. [g] Ratio of **5jf** (in Scheme 1) and **6jf** (see Supporting Information). [h] Allyl acetate and allyltrimethylsilane gave uncharacterizable products. [i] X = NTs. [j] Uncharacterizable material formed.

Scheme 2. CM with Longer Tethered Triynes



Scheme 3. Intramolecular Trapping of the Putative Intermediate



initiating alkyne and the diyne moiety is important for the substituents to influence the initiation event, and the metallotropic shift depends on the nature of the substituent on the diyne and not the mode of initiation.

The possibility of equilibration between intermediates was explored with probe **9**, a close analogue of **3g** (Scheme 3). If the intermediates from the α- and β-insertion pathways are formed reversibly, the putative alkylidene species should be trapped by the ring-closing termination to give respective products **10a** and **10b**. However, contrary to **3g** that gave a 1:1 mixture of five- and six-membered ring products **5ga** and **6ga**, the reaction of **9** generated only **10a** (65%). This result suggests that, at least for **9**, the initiation step should be selective for α-insertion. The discrepancy between **3g** and **9** in product distribution must be due to the difference in their structures although seemingly minor.

In conclusion, we have documented the first examples of β-insertion of Grubbs-type ruthenium alkylidene into terminal alkynes controlled by a bulky substituent at a remote site from the reaction center. While the origin of this regioselective insertion and metallotropic shift remains to be established, direct influence of the substituent on the initiation process through the interaction of the diyne moiety with the ruthenium center seems feasible.

This unprecedented regioselective insertion of a Ru-alkylidene, especially when it is in tandem with a metallotropic [1,3]-shift, would broaden the scope of enyne metathesis as a powerful tool to synthesize a new class of multiply conjugated unsaturated molecules containing alternating double and triple bonds.

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Supporting Information Available: General procedures, characterization for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Complete consumption of **3f** was achieved in the presence of a stoichiometric amount of **1**. See Supporting Information.

(14) The CM of **6jf** and 1-octene did not occur under the reaction conditions.

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