Group-Selective Ring-Closing Enyne Metathesis: Concentration-Dependent Selectivity Profile of Alkynylsilyloxy-Tethered Dienynes

Sarah V. Maifeld, Reagan L. Miller, and Daesung Lee*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received July 2, 2004; E-mail: dlee@chem.wisc.edu

Enyne metathesis is a powerful carbon−carbon bond-forming reaction capable of constructing 1,3-dienes.[1] With multiple pathways and products possible in enyne ring-closing metathesis (RCM) reactions, site-selective initiation by the catalyst (**1** or **2**)[2] seems necessary for selectivity.[3] Although the selective initiation can be achieved by modifying the reactivity of the alkene or alkyne moieties with steric and stereoelectronic factors, in many cases, the implementation of these factors requires extra synthetic manipulations.[4] Irrespective of the selectivity in the initiation,[5] a highly selective enyne RCM reaction can still be realized if the pre-ring-closure steps are reversible and occur at higher rates than that of the ring-closure step. As shown in Scheme 1, alkynylsilyl-

Scheme 1
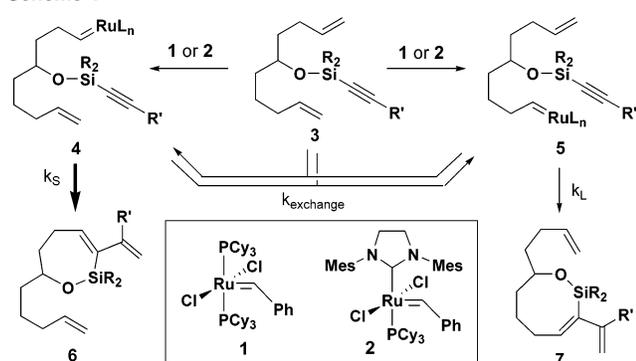
oxy-tethered dienyne **3**,[6,7] which possesses nonsymmetrically tethered alkenes in nearly equivalent steric and stereoelectronic environments, would generate intermediates **4** and **5** in roughly equal amounts when catalyzed by **1** or **2**. If the steric hindrance of the silylalkynyl moiety slows the ring-closure rate as compared to the alkylidene exchange between **4** and **5** ($k_{exchange} \gg k_S$ and k_L), a pre-equilibrium situation arises in which a relatively faster ring-closure rate for the smaller-sized ring (k_S) over that of the larger one (k_L) would preferentially generate **6** over **7** ($k_S > k_L$). We report herein a new type of group-selective enyne RCM reaction of alkynylsilyloxy-tethered dienyne **3** and its concentration-dependent selectivity profile.

To obtain information for a general reactivity profile of silyl-substituted enynes[8] and to address the potential difficulty in differentiating similar product structures (e.g., **6** vs **7**) derived from the RCM of alkynylsilyloxy dienyne **3**, we generated a spectroscopic standard of siloxacycles[9] from symmetrical and sterically well-differentiated bisalkene-containing substrates **8a−e** (Table 1). Regardless of the tether sizes, rapid enyne RCM occurred without interference of diene RCM, providing excellent yields of the cyclic 1,3-diene products **9a−e**. Notably, the chemical shifts of the endocyclic vinyl proton H_β exhibit a distinctive dependency on the ring size. For substrates showing a high tendency to dimerize after the initial enyne RCM, an external alkene (**10**; *cis*-AcOCH$_2$CH═CHCH$_2$OAc) was added to the reaction, thereby retarding dimer-

Table 1. RCM of Symmetric and Sterically Differentiated Dienynes[a]

Entry	Silyl ether	RCM-product	H_β (ppm)	Yield (%)[b]
1 2	**8a**, n = 0 **8b**, n = 1	**9a**, n = 0 **9b**, n = 1	7.0 7.0	86 92
3 4	**8c**, R = **8d**, R =	**9c**, R = **9d**, R =	6.7 6.7	54[c,d] 76
5	**8e**	**9e**	6.4	85

[a] A solution of catalyst **2** (7.5 mol %) and substrate in CH$_2$Cl$_2$ (0.001 M) was heated to reflux for 30 min. [b] Isolated yield. [c] 2 equiv of **10** under reflux for 4 h. [d] Mixture of trans- and cis-isomers (6:1)

Scheme 2
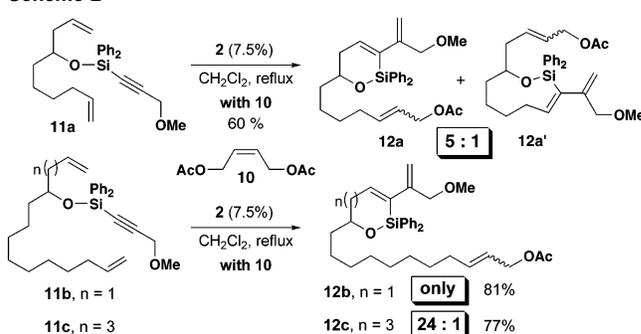
ization and yielding a product resulting from enyne RCM followed by cross metathesis (CM) at the residual terminal alkene (entry 3).[10]

Noting the excellent reactivity of **8a−e**, we next explored the RCM reaction of alkynylsilyloxy dienynes that have two terminal alkenes of similar steric and stereoelectronic character but have substantially different tether lengths between the ene and the yne moieties (Scheme 2).

The RCM reactions (0.001 M) of **11a−c** showed several salient features. First, the enyne RCM is uniformly observed over diene RCM or CM, providing predominantly smaller siloxacycles **12a−c** as a 3:1 to 7.5:1 mixture of trans- and cis-isomers. Second, a larger difference between the tether lengths of unsymmetrical alkynylsilyl ethers results in higher selectivity between ring sizes. This trend is the reflection of a much higher cyclization rate of smaller-sized rings over that of the larger rings[11] in combination with rapid alkylidene exchange of the larger ring-forming intermediate prior to its cyclization.[12]
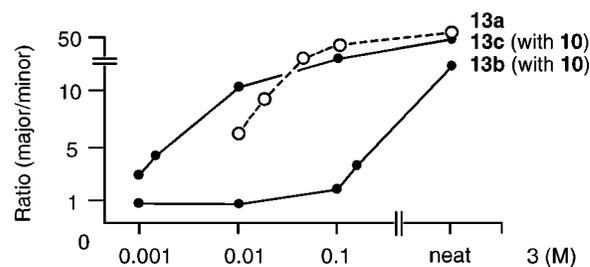
Table 2. Concentration Effect for Dienyne RCM Selectivity

Figure 1. Concentration-dependent RCM selectivity.

a Ratio was determined by ¹H NMR. *b* Isolated yield. *c* Reaction was heated to reflux for 1−3 h with 7.5 mol % of **1**. *d* Combined yields of **14a**, **14a′**, and homo- and heterodimers. *e* 10 mol % **2**. *f* Reaction was heated for 15 min at 70 °C. *g* Reaction was heated to reflux for 4 h with 3 equiv of **10** and 7.5 mol % of **2**. *h* Mixture of trans- and cis-isomers.

The RCM selectivity is marginal when the chain lengths of the two tethered alkenes become similar as in dienynes **13a−c** (Table 2). The low selectivity is believed to result from comparable rates of formation of both alkylidene intermediates followed by their cyclization prior to the pre-equilibrium. Therefore, we hypothesized that the marginal selectivity could be amplified by running these reactions at higher concentrations, whereby the pre-equilibrium of alkylidene exchange can be attained more effectively, leading to better discrimination of the two ring-closure pathways. Pleasingly, the RCM reaction of **13a** with **1** at gradually increased concentrations provided a remarkable increase in selectivity between seven- and eight-membered rings, providing the highest ratio of **14a** and **14a′** (50:1) in neat solution (ca. 2.5 M). Treatment of **13b** with the more reactive catalyst **2** in the presence of external alkene showed a similar concentration-dependent selectivity profile, generating the highest ratio of **14b** and **14b′** (13.3:1) in a neat solution.¹³

The RCM reaction of **13c**, possessing relatively longer alkene chains differing by only one methylene unit, exhibited good selectivity, providing eight- and nine-membered rings **14c** and **14c′** in an 11.5:1 ratio even at a lower concentration (0.01 M). At higher concentrations, the selectivity of this reaction was improved immensely (>50:1 in neat solution). The enyne RCM selectivity profile for **13a−c** is plotted in Figure 1 to show the general trend. The RCM selectivity of **13a** and **13c** possessing one methylene unit difference in the two alkene moieties shows a more sensitive concentration dependency compared to that of **13b**, which has a two methylene unit difference.

In conclusion, we have developed the alkynylsilyloxy-tethered dienyne as an effective enyne RCM platform and examined its metathesis-based ring-closing behavior. High selectivity for smaller ring sizes was noted from the RCM reaction of dienynes run at high concentration, providing a new insight into achieving group selectivity in the enyne RCM process. Further investigation to elucidate the origin of this increased selectivity at higher concentration is in progress.

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

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(12) Replacement of the diphenyl groups on silane **11b** with diisopropyl groups did not change the outcome of the RCM-CM reaction.
(13) No interconversion was observed when the terminal alkene-containing six- and eight-membered ring compounds derived from **13b** were resubjected to reaction conditions.

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