Search for Solutions to the Reactivity and Selectivity Problems in Enyne Metathesis

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ABSTRACT
Enyne metathesis is a powerful carbon−carbon bond-forming reaction to generate 1,3-dienes from an alkyne and an alkene. Different from the diene and diyne metathesis, the enyne metathesis suffers from both regio- and stereoselectivity problems, yet there is no general solution to these problems. This Account briefly describes the evolution of various new strategies and substrate platforms from these laboratories to address the reactivity and selectivity issues in the enyne metathesis processes.

1. Introduction

Olefin metathesis is one of the great advances in organic synthesis of our time, a fact highlighted by the recent awarding of the Nobel Prize in this area. Metathesis can be classified into three major categories depending upon the types of olefins (alkene or alkyne) participating in the metathesis process: diene,[1] enyne,[2] and diyne metathesis[3] (Figure 1). Enyne metathesis is unique among these three in that it generates a new functionality in the product different from that of starting materials. Another unique feature of the enyne metathesis is its capacity to perform tandem sequences of reactions, thereby allowing the formation of more than one carbon−carbon bond in cyclic and acyclic product structures. This is a consequence of the net addition of a metal alkylidene across the π bonds on the alkyne, thus generating an intermediate, where the alkene-metathesized product moiety is directly connected to the propagating alkylidene (Scheme 1).

This powerful aspect of enyne metathesis in terms of forming multiple bonds and rings could be broadly exploited in organic synthesis. However, since the first paper[4] on enyne metathesis by Katz and Sivavec in 1985, its development has lagged behind that of its diene counterpart because of the less predictable nature of substrate reactivity, regio- and stereoselectivity, as well as the poorly understood reaction mechanism. Recently, fueled by the development of effective ruthenium-based catalysts[5] and the significantly improved metathesis performance protocol of using an ethylene atmosphere,[6] the scope of enyne metathesis has been significantly expanded to include new substrate platforms, which allows for a host of exciting

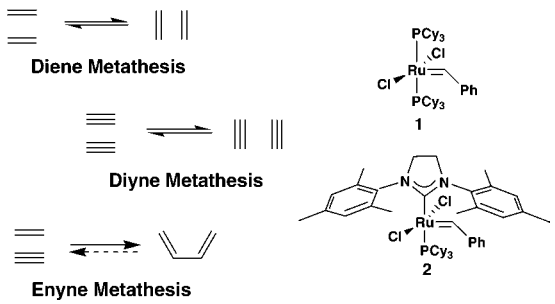
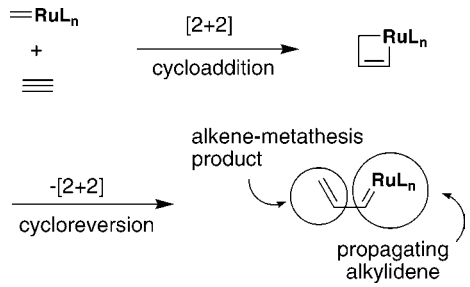


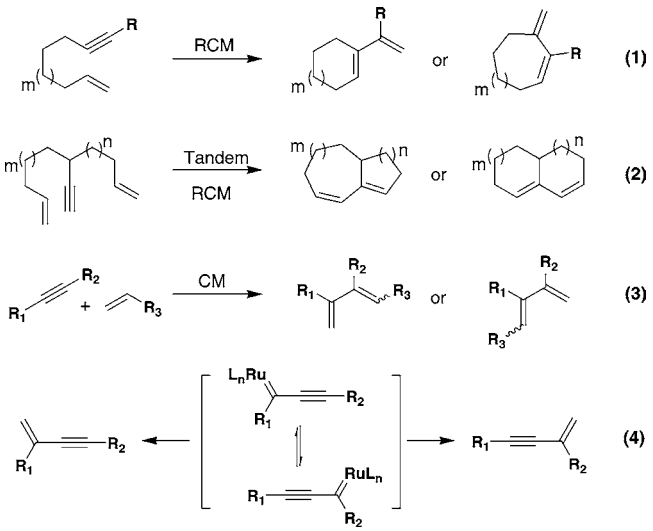
FIGURE 1. Metathesis processes and typical catalysts.

Scheme 1



new applications. Notwithstanding the significant improvement, the ring-closing metathesis (RCM) of enynes has been limited to the synthesis of small-sized rings. Similarly, the cross-metathesis (CM)[7] has been limited to the parings of terminal alkyne and alkene substrates because of low regioselectivity with internal alkynes.

In this Account, we describe our approaches toward enyne RCM and CM reactions focusing on a variety of selectivity problems: *exo*/*endo*-mode selectivity in RCM (eq 1), group selectivity in tandem RCM (eq 2), regio- and stereoselectivity in CM (eq 3), and site selectivity in relay metathesis and the metallotropic [1,3]-shift of alkylidene species (eq 4). These selectivity problems are specific to the enyne metathesis, and thus, most of them do not arise in the diene or diyne metathesis processes.



Eric Hansen graduated from Calvin College in 2001. He then moved to the University of Wisconsin—Madison, where he is carrying out his Ph.D. with Prof. Daesung Lee, focusing on new methodologies involving ruthenium-catalyzed enyne-coupling reactions.

Daesung Lee obtained his Ph.D. at Stanford University in 1998. After postdoctoral training at Harvard University, he took an assistant professor position at the University of Wisconsin—Madison in 2000. His major research interest involves the development of enyne metathesis and its application to natural-product synthesis.

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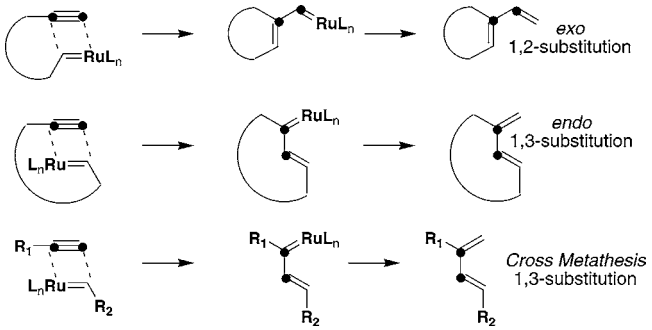
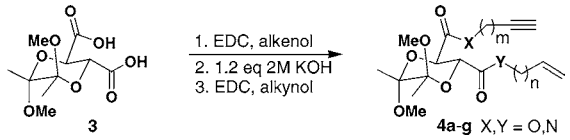
Scheme 2. Definition of *Exo*/*Endo* Selectivity



Scheme 3. Tartrate-Derived Enyne RCM Substrates



2. *Exo*/*Endo*-Mode Selectivity in Macro-RCM

Exo/*endo*-mode selectivity arises in enyne RCM because of two possible orientations of the metal alkylidene during the addition to the alkyne, leading to different connectivity patterns of 1,3-dienes (1,2- and 1,3-substituted 1,3-dienes derived from *exo*- and *endo*-mode RCM, respectively.) The definition of *exo*/*endo*-mode is based on the position of the carbon−carbon bond derived from the triple bond of the alkyne in the final product (Scheme 2). Thus, *exo*-mode RCM gives a product where the original C−C bond is in an exocyclic position, whereas *endo*-mode RCM gives a product with the original C−C bond in an endocyclic position. Consequently, the ring size formed from *endo*-mode cyclization is one carbon larger than the corresponding *exo*-mode products.

When we initiated our study, it was well-known that enyne RCM forming small- to medium-sized rings (five−nine-membered rings) follows the *exo*-mode ring closure path when terminal ene and yne subunits are involved.[2,8] *Endo*-mode selectivity had only been observed in one example for the formation of a 16-membered ring;[9] however, the regiochemistry of the enyne CM reaction (ring size = ∞) was known to be identical to *endo*-mode products. Because the enyne RCM forming 10−15-membered rings had not yet been reported, we set out to define the inherent trend of *exo*/*endo*-mode selectivity based on ring size.

2.1. Development of Tartrate Tether. To study the general reactivity feature of the macrocyclic enyne RCM reaction in the range of 10−15-membered rings,[10] we required a substrate platform that allowed the tether length between ene and yne subunits to be easily adjusted to give a variety of ring sizes while at the same time facilitating efficient ring closures. Tartaric acid derivatives **4**, which can be easily derived from **3**, suited our needs perfectly (Scheme 3).

2.1.1. RCM without Ethylene. Substrates **4a**−**g** were synthesized and subjected to typical RCM conditions (0.02 M in CH_2Cl_2, 5−10 mol % of **1** or **2**, reflux), and macrocycles **5a**, **5b**, and **6b**−**g** were obtained smoothly in good

Table 1. Direct Macrocyclic Enyne Metathesis[a]

Entry	Enyne substrate	Macrocycle product exo	Macrocycle product endo	*E*:*Z*	Yield (%)
1	**4a** m = n = 1, X = Y = O, R = H	**5a** (R = H)		0:1	52
2	**4b** m = 1, n = 2, X = Y = O, R = H	**5b**	(1 : 1) **6b**	1:1 (for endo)	50
3	**4c** m = 1, n = 2, X = NH, Y = O, R = H	**6c**		1:0	35
4	**4d** m = 2, n = 1, X = Y = O, R = H	**6d**		1:1	70
5	**4e** m = 2, n = 2, X = Y = O, R = H	**6e**		0:1	61
6	**4f** m = 3, n = 2, X = Y = O, R = H	**6f**		2:1	54
7	**4g** m = 3, n = 3, X = Y = O, R = H	**6g**		1:1	55

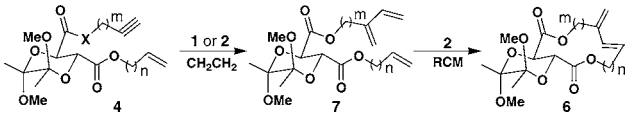
[a] With 10 mol % **2** in CH_2Cl_2 at 40 °C.

yields (Table 1). A clear trend immediately emerged from our data, wherein a transition from *exo*-mode selectivity for small- and medium-sized rings to *endo*-mode selectivity for macrocycle formation (12−15-membered rings) was observed. In only one case (**4b**, entry 2) was a 1:1 mixture of 11-*exo* and 12-*endo* products formed. Interestingly, changing the functionality in the tether to a propargylic amide (**4c**) as well as changing the relative position of ene and yne subunits (**4d**) led exclusively to 12-*endo* products **6c** and **6d**, respectively. This indicates that the mode selectivity depends upon not only the size of the incipient macrocycles but also the functionality within the tether. The *E*/*Z* selectivity for RCM reactions of **4a**−**g** varies from complete selectivity to a 1:1 ratio.

2.1.2. RCM under an Ethylene Atmosphere. We next turned our attention to the effect of ethylene in macrocyclic enyne RCM. The beneficial effect of ethylene in enyne RCM has been attributed to the protection of the catalyst from unproductive resting states in the catalytic cycle[6] and to an acceleration of the transfer of methylidene to the vinyl alkylidene in the catalytic cycle.[11] However, in macrocyclic enyne metathesis, the slow ring-closure rate can be outrun by competitive CM of the alkyne with ethylene to form triene products. Diene RCM of these products could lead to *exo*- or *endo*-mode RCM products, depending upon whether the proximal or distal double bond of the 1,3-diene participates in the process.

It was found that the treatment of enynes **4a**−**g** under mild conditions (Grubbs catalyst **1** or **2** under an ethylene atmosphere at room temperature) led to **7a**−**g** in good

Table 2. Macrocyclic Enyne Metathesis under Ethylene



entry	enyne	percent yield **7**	percent yield **6** (one step)	*E*/*Z* (one step)
1	**4a**	96	25[a]	0:1
2	**4b**	65	91 (70)	1:0 (2.5:1)
3	**4c**	77	78	1:0
4	**4e**	77	65 (75)	1:0
5	**4f**	92	85 (99)	1:0
6	**4g**	88	90 (92)	15:1 (20:1)

[a] A significant amount of a cyclopropane-containing side product was observed.

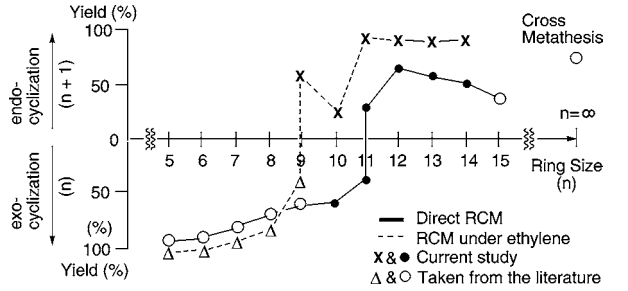


FIGURE 2. Mode of Ring Closure and Efficiency of Enyne RCM.

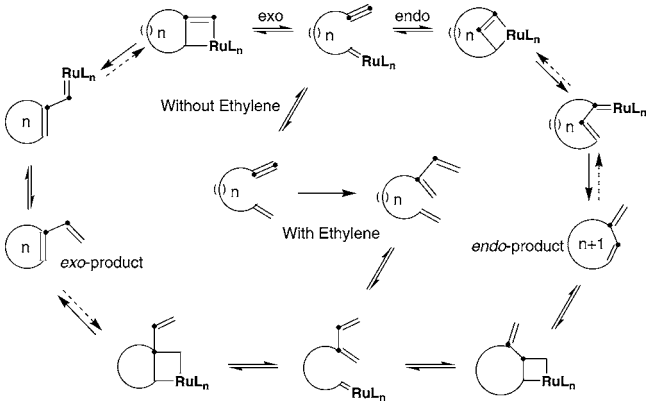
yields (Table 2). Subsequent RCM with **2** in refluxing dichloromethane yielded *endo*-mode products **6a**−**g** with almost complete selectivity for the *E* isomer. We also found that treatment of **4** with **2** under an ethylene atmosphere at room temperature until the complete consumption of starting material, followed by removal of ethylene and heating, gave superior results. Using this protocol, substrates that inherently give *exo*-mode products can be diverted to give *endo*-mode products.

Figure 2 summarizes the general trend for both mode selectivity and cyclization efficiency for enyne RCM reactions with and without ethylene. Our study, in combination with the small-membered ring formation from the literature (△ and ○), reveals a general feature of the enyne RCM reaction; the direct RCM of enynes without ethylene forming 11-membered rings and smaller gives invariably *exo*-mode products, whereas that forming 12-membered rings or larger, including CM, provides *endo*-mode products exclusively. Using an ethylene atmosphere, *endo*-mode products can be obtained for nine-membered rings or larger with improved yields and selectivity.

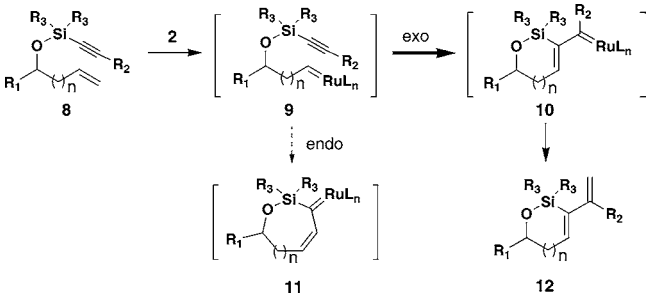
The mode and *E*/*Z* selectivity of the enyne metathesis without ethylene represents the inherent selectivity of the macrocyclic RCM reaction, leading to the kinetic distribution of *endo*/*exo* and *E*/*Z* isomers. The selectivity seen under an ethylene atmosphere is the consequence of a thermodynamically driven equilibration.

Mechanistic Consideration. Dependent upon whether the reaction initiates on the alkyne or alkene of an enyne RCM substrate determines the overall pathway including the key propagating species. Alkyne initiation[12a] was originally proposed for enyne RCM; however, on the basis

Scheme 4. Possible Mechanistic Pathways



Scheme 5

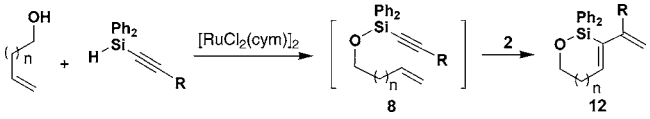


of this hypothesis, it is difficult to explain the transition from *exo* to *endo* mode. It is unlikely that a small change in the tether length would have a significant effect on the regiochemistry of the addition of the propagating alkylidene to the alkyne prior to ring closure. We favor an explanation involving alkene initiation, because this is the only pathway where the *endo*/*exo*-discriminating step coincides with the ring closure (Scheme 4). Therefore, the selectivity is the consequence of the ring strain associated with respective intermediates in the *exo* and *endo* pathways. A growing body of experimental[11,12b−d] and theoretical evidence[13] supports this mechanistic hypothesis. For the reactions under an ethylene atmosphere, the enyne substrate is transiently modified to a triene intermediate, thereby converting the ring closure to a more facile diene RCM.

2.2. Development of Silicon-Tethered Enyne Metathesis: 2.2.1. *Exo*-Mode Selectivity. The tartrate-based enyne RCM provided a valuable insight into the *exo*/*endo*-mode selectivity. Using ethylene in this system, we were able to achieve a formal *endo*-mode enyne RCM product selectively. Aiming at finding a more versatile tether and possibly providing *exo*-mode selectivity, we developed alkynyl silyloxy tether **8** (Scheme 5).[14] With this silicon-tethered enyne system, the *endo*-mode RCM would be disfavored because of the formation of the sterically hindered silicon-substituted alkylidene **11** compared to the *exo*-mode RCM intermediate **10**, which would deliver product **12**.

The above hypothesis was readily tested with silyloxy-tethered enynes **8a**−**g**, which were obtained from the $[RuCl_2(p\text{-cymene})]_2$-catalyzed silylation of alcohols with alkynyl silanes. Enyne RCM of these substrates provided

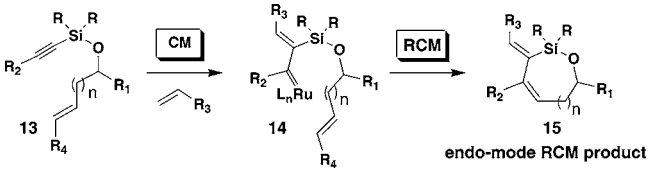
Table 3. Consecutive Ru Catalysis for Siloxacycle Synthesis[a]



entry	silyl ether	*n*	R	RCM product	yield (%)
1	**8a**	0	CH_2OMe	**12a**	52
2	**8b**	1	CH_2OMe	**12b**	85
3	**8c**	2	CH_2OMe	**12c**	67
4	**8d**	2	H	**12d**	81
5	**8e**	3	CH_2OMe	**12e**	50
6	**8f**	4	H	**12f**	63
7	**8g**	8	CH_2OMe	**12g**	30

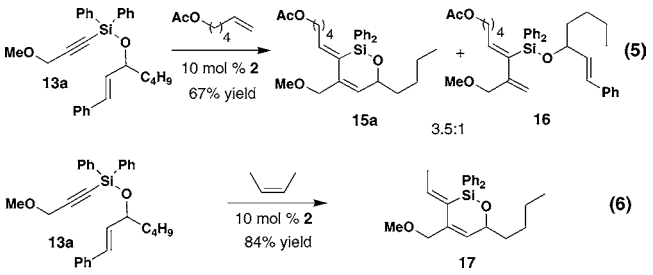
[a] A total of 0.5 mol % $[RuCl_2(p\text{-cym})]_2$ for silyl ether formation. RCM reactions with 7.5 mol % catalyst **2** at 0.003 M in refluxing CH_2Cl_2.

Scheme 6

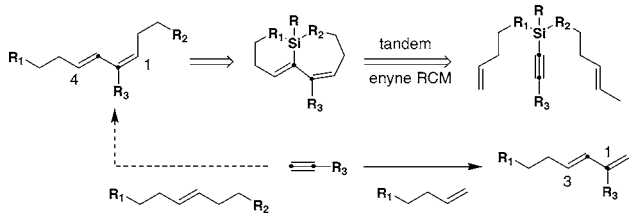


only the *exo*-mode products **12a**−**g** possessing *Z* stereochemistry of the endocyclic double bond regardless of the tether size (Table 3). We believed that the observed *exo*-mode selectivity is the consequence of the sterically hindered nature of the silyl group, directing the formation of the *exo*-mode intermediate. The exclusive formation of the *Z* isomer differs from that of the macrocyclic enyne RCM reactions with the tartrate tether, which normally generates mixtures of *E* and *Z* stereoisomers.[10]

2.2.2. Formal *Endo*-Mode Selectivty. Not wanting to be restricted to *exo*-mode products with this system, we surmised that a formal *endo*-mode product could be achieved through a tandem CM/RCM procedure (Scheme 6). Assuming that the same regio- and stereoselectivity exerted by the bulky silane substituent that gives excellent *exo*-mode selectivity in the RCM reaction could be extrapolated to the CM reaction between silylated alkynes and alkenes, we envisioned that cyclization of alkylidene **14** would provide products with the same connectivity as *endo*-mode cyclization. To achieve this goal, the double bond of enyne **13** must have a lower reactivity than the triple bond to allow for the initial CM reaction to occur between the alkylidene derived from the external alkene and alkyne to generate **14**. If the rate of ring closure of **14** is faster than that of intermolecular methylene transfer, **15** would be formed. Steric deactivation of the alkene moiety of substrate **13a** proved enough to facilitate initial CM followed by RCM (eqs 5 and 6).[15] It was found that methylene transfer from the terminal alkene was competitive with the ring closure, giving a mixture of products **15a** and **16**. However, under "methylene-free conditions"[16] with *cis*-2-butene, **13a** gave CM−RCM product **17** in 84% yield without the formation of the CM-only product.



Scheme 7



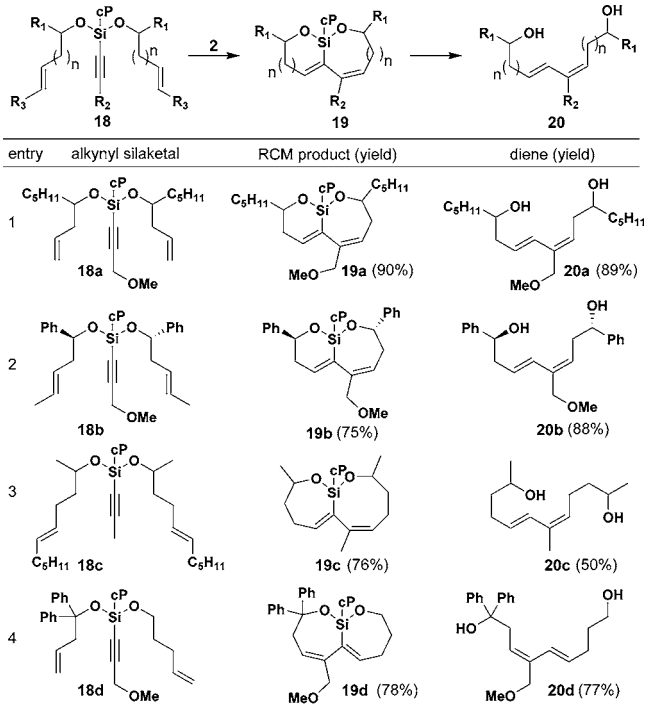
Another merit of using the silicon-based tether[17] is the implementation of a new connectivity pattern of 1,3-diene. In general, 1,3-substituted 1,3-dienes are formed from enyne metathesis between terminal alkynes and alkenes. Given that 1,4-substitution is more frequently found in many natural products and synthetic intermediates, this limitation of the scope of enyne RCM is detrimental. We surmised that the CM−RCM sequence shown in Scheme 6 could be converted to a *tandem dienyne ring-closing metathesis*[18] by tethering a second alkene to the silicon center (Scheme 7). This would allow for an initial enyne RCM followed by diene RCM, generating a bicyclic structure, which, upon removal of the silicon tether, would provide a 1,4-substituted *E,Z*-1,3-diene.

A variety of *symmetrical* silaketals **18a**−**d** were prepared and cyclized to the corresponding bicycles **19a**−**d** in good yield (Table 4). Cyclization of **18a** and **18d** proceeded at 40 °C in CH_2Cl_2, whereas the reaction of **18b** and **18c**, with disubstituted alkenes, required a higher temperature (110 °C, toluene). Treatment of siloxanes **19a**−**d** with an excess of TBAF yielded diols **20a**−**d** in moderate to good yield with retention of double-bond geometry.[19] In the case of unsymmetrical silaketal **18d**, although diasteriomeric products are expected, a single product **19d**, derived by initial cyclization of the longer chain, was obtained, which, upon protodesilylation, gave **20d**. The origin of this group selectivity is most likely due to the gem-diphenyl groups being proximate to the alkene, preventing the initiation of the catalyst at this center. This result prompted us to explore the group-selective RCM of unsymmetrical dienynes.

3. Group Selectivity in Tandem RCM

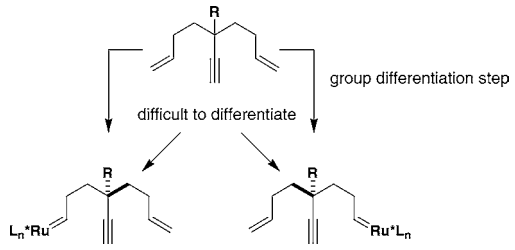
3.1. General Strategies. Group-selective transformations break local or molecular symmetry by the selective conversion of one of the enantiotopic or diasterotopic functionalities.[20] Group selectivity, realized using both

Table 4. Tandem RCM Reaction of Silyloxy-Tethered Enynes[a]



[a] With 7.5 mol % catalyst **2**. cP = cyclopentyl.

Scheme 8

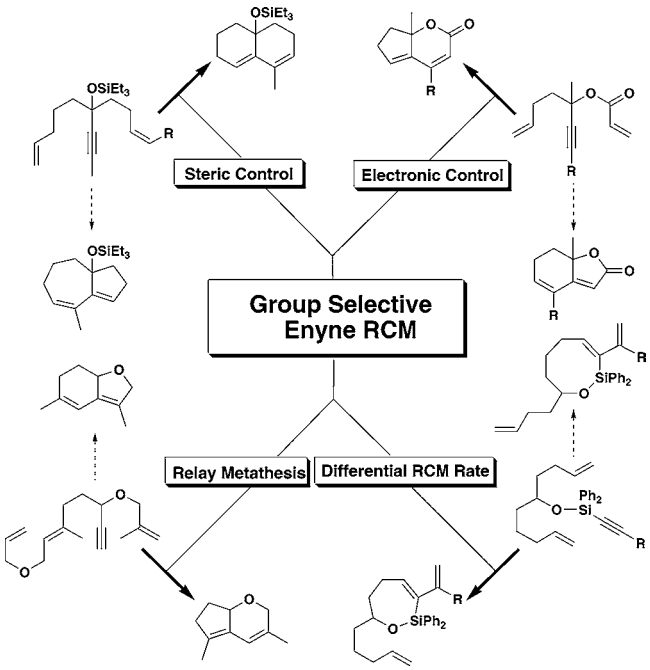


reversible and irreversible bond-forming processes, constitutes an important concept in stereoselective synthesis.

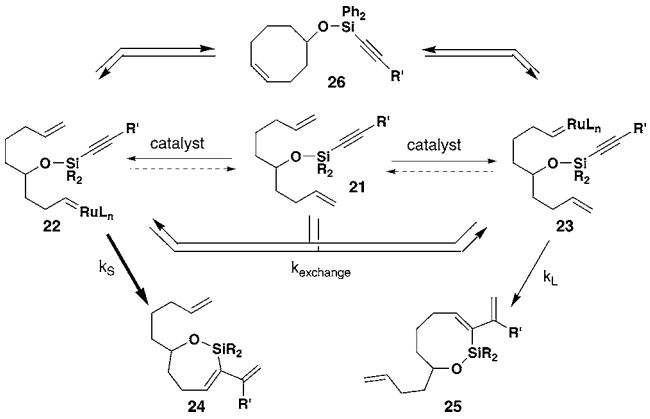
Relying on the reversible nature of the diene metathesis process, several examples of group-selective metathesis reactions have been reported.[21] We assume that not all steps of enyne metathesis are reversible;[13] therefore, selectivity is dependent upon the site of catalyst initiation. In the case of dienynes, differentiation of two alkene groups in similar steric and electronic environments is difficult (Scheme 8). To circumvent this shortcoming, several strategies utilizing steric hindrance, electronic variation, relay metathesis, and ring-closure kinetics have been implemented to exert control over the reaction pathways. For the examples in Scheme 9,[22] selectivity relies on controlling the site of catalyst initiation by modifying the reactivity of the alkene or alkyne moieties with steric and stereoelectronic factors.[18] While this has proven successful, the introduction of the biasing elements, in many cases, reduces the reaction scope.

3.2. Ring-Closure Rate-Based Differentiation. A generalized concept of ring-closure rate-based differentiation of reaction pathways is shown in Scheme 10.[23] In this mechanistic picture, alkynyl silyloxy-tethered dienyne **21**,

Scheme 9



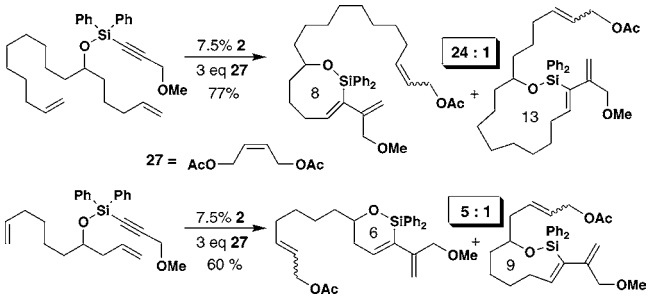
Scheme 10. Pre-equilibrium of Alkylidene Intermediates Prior to Ring Closure



possessing two tethered alkenes in nearly equivalent steric and stereoelectronic environments, would be equally partitioned between alkylidenes **22** and **23**. Assuming that the steric hindrance imparted by the silylalkynyl moiety slows the enyne ring-closure rates (k_S and k_L) as compared to the rate of alkylidene exchange ($k_{exchange}$), a situation arises where a pre-equilibrium between intermediates prior to ring closure is possible. This equilibrium would also be possible via the involvement of diene RCM product **26**. Regardless of the exchange mechanism, because of the faster ring closure of smaller sized rings ($k_S > k_L$),[24] the selective formation of smaller ring **24** is expected over the larger ring **25**.

The tandem RCM of alkynylsilyloxy dienynes bearing two terminal alkenes with substantially different tether lengths between the ene and yne components gave good to excellent selectivity between the two different ring-sized products (Scheme 11). For substrates showing a high tendency to dimerize after the initial enyne RCM, external alkene **27** was added to the reaction. This external alkene

Scheme 11

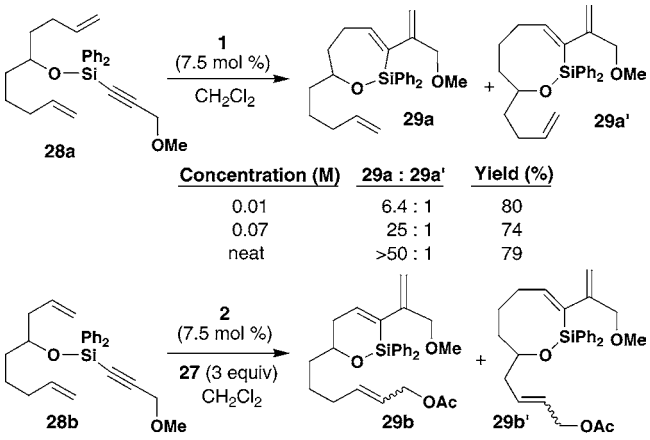


undergoes CM of the remaining terminal alkene to ultimately give an allylic acetate without causing a change in selectivity.

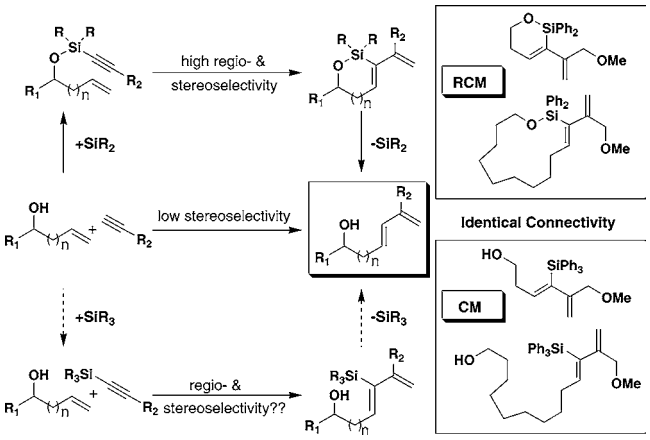
The enyne RCM showed several salient features. First, enyne RCM was uniformly observed over diene RCM, and predominantly, the smaller siloxacycle was produced as a mixture of *trans* and *cis* isomers. Second, a larger difference between the tether lengths of nonsymmetric alkynylsilyl ethers resulted in greater selectivity between ring sizes. As expected, this trend reflects the higher cyclization rate of smaller sized rings over that of larger rings, while rapid alkylidene exchange of the larger ring-forming intermediate is occurring prior to its cyclization.

In contrast to the highly group-selective reactions shown in Scheme 11, only marginal selectivity was observed when the chain lengths of the two tethered alkenes became similar as in dienynes **28a**−**c**. This lack of selectivity presumably results from the comparable rates of formation and cyclization of both alkylidene intermediates prior to a pre-ring-closure equilibrium between these species. We hypothesized that, if the equilibration of alkylidene intermediates relies on a bimolecular process, the reaction at higher concentration would induce a more effective equilibrium and, thus, result in better discrimination between the two ring-closure pathways (Scheme 12). Pleasingly, the RCM reaction of **28a** with catalyst **1** at gradually increased concentrations provided a remarkable increase in selectivity between seven- and eight-membered rings, providing the highest ratio of **29a** and **29a′** (>50:1) in neat solution (ca. 2.5 M). Treatment of **28b** with a more reactive catalyst **2** in the presence of external alkene **27** exhibited a similar concentration-dependent selectivity profile, generating the highest ratio of **29b** and **29b′** (13.3:1) in neat solution. The RCM reaction of **28c**, possessing relatively longer alkene chains exhibited good selectivity, providing eight- and nine-membered rings **29c** and **29c′** in a 20:1 ratio even at a lower concentration (0.1 M). At higher concentrations, the selectivity of this reaction improved immensely (>50:1 in neat solution).

Scheme 12



Scheme 13

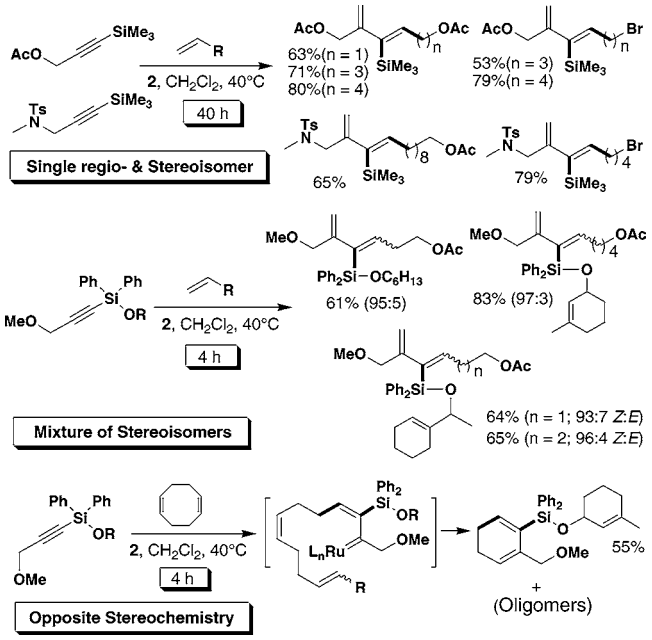


4. Regio- and Stereoselectivity in CM

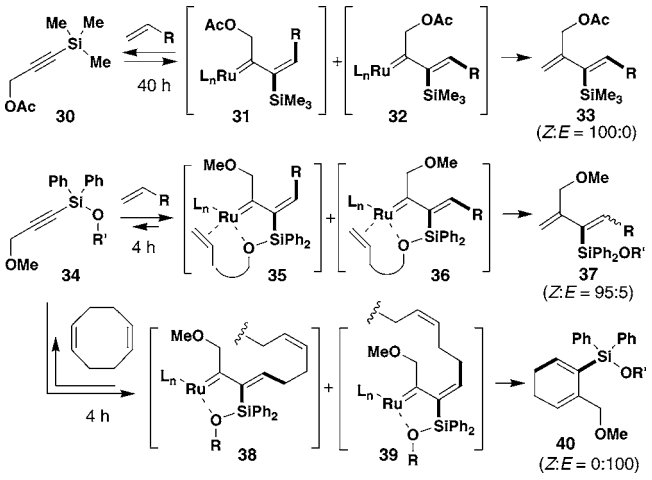
4.1. Silylated Alkynes. Applications of enyne CM have been limited because of low regio- and stereoselectivity. The issue of chemoselecivity (homo- versus heterocoupling) further complicates enyne CM. To circumvent the selectivity problems, the enyne CM reaction has been confined to the pairings of internal alkyne−ethylene[25a] and terminal alkyne−terminal alkene.[25b] To the best of our knowledge, the stereoselective CM reaction between unsymmetrical internal alkynes and unsymmetrical alkenes has not been realized. We envisioned the known steric and stereoelectronic biasing effect of a silyl functionality in RCM reactions could be applied to the corresponding CM of silylated alkynes, thereby producing 1,3-diene products of the same connectivity (Scheme 13).

The selectivity of the enyne CM was first tested with TMS-substituted alkynes with several terminal alkenes (top of Scheme 14).[15,26] Although the reactivity was low, requiring 40 h for complete consumption of starting materials, the diene products were isolated as single regio- and stereoisomers. The selectivity in the CM process

Scheme 14



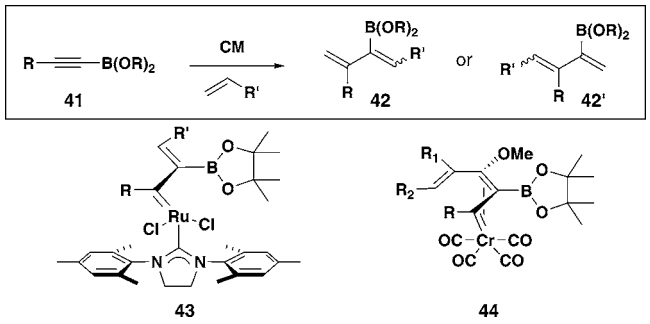
Scheme 15



correlated exactly to that of the RCM process, giving only the *Z* isomer. When the silyl group on the alkyne contained an alkoxy substituent, a dramatic increase in reactivity was observed, giving complete conversion in only 4 h (middle of Scheme 14). This increase in reactivity was accompanied by a slight decrease in *Z*/*E* selectivity, giving 5−10% of the *E* isomer. Interestingly, when cyclooctadiene was used as the alkene partner, 55% of the cyclohexadiene product was observed (bottom of Scheme 14). This requires the opposite stereochemical outcome in the initial CM event to allow for the subsequent ring closure.

The dramatic increase in reactivity caused by the oxygen substituent on the silicon is intriguing. We speculate that this arises from some type of complexation of the ruthenium metal to the oxygen (Scheme 15).[27] The increased reactivity in concert with the decreased *Z*/*E* selectivity in the CM reaction of **34** relative to **30** and the complete reversal of *Z*/*E* selectivity for the formation of **40** indicate that the metathesis steps to form early

Scheme 16



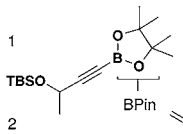
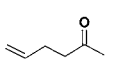
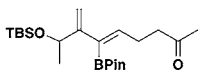
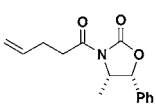
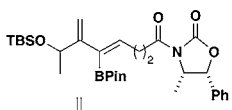
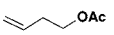
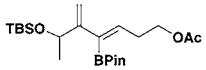
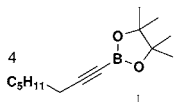
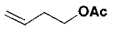
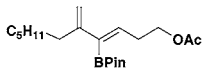
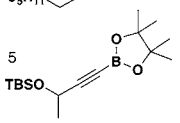
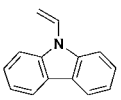
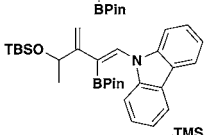
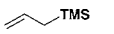
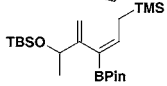
intermediates (e.g., **31**, **35**, and **38**) are reversible. Therefore, the rate for the formation of **31** and **32** from **30** and their reversion rates are comparable, while only **32** slowly turns over to the major compound **33**. On the other hand, once the intermediates **35** and **36** are formed from **34**, their reversion rates are slower compared to those of **31** and **32** because of the presumed chelation of the oxygen and possibly the tethered alkene[28] that stabilize these intermediates. The slower reversion rate maintains the higher concentration of these reactive intermediates, which is the source of the reduced reaction time. The reduced reversion rate of **35** will allow for some fraction of this intermediate to turn over to the minor product. In the metathesis reaction of **34** with 1,5-cyclooctadiene, the intermediate **39** has proper *cis* geometry between the double bond and the alkylidene to undergo facile cyclization, thereby providing 1,3-cyclohexadiene products, whereas the other intermediate **38** possessing *trans* geometry between the double and alkylidene can only react intermolecularly to generate oligomers or revert back to **34**.[16]

4.2. Borylated Alkynes. We envisioned that borylated alkynes **41** in CM would provide vinyl boronates **42** or **42′** (Scheme 16).[29] Having no precedent for this reaction, the regio- and stereochemical consequence could not be predicted. However, a putative intermediate **43** leading to **42** might be inferred by analogy to a Fisher carbene complex **44** formed from borylated alkynes as an intermediate in the benzannulation reaction.[30] Indeed, we found a strong directing effect of the boron substituent, providing a general and stereocontrolled synthesis of vinylboronates.

Selected examples of CM between borylated alkynes and terminal alkenes are shown in Table 5. In general, complete CM occurred using 5 mol % catalyst **2** in dichloromethane at 40 °C within 2 h. Single regioisomers of the type **42** were isolated in moderate to good yield. High *E* selectivity was observed in many cases, although the stereoselectivity was highly dependent upon the alkene functionality. Vinyl carbazole, which would generate a Fisher carbene-like stable alkylidene intermediate provided a high yield of CM product with excellent *E* selectivity (entry 5). Interestingly, the reaction with allyltrimethylsilane gave only the *Z* isomer in moderate yield.

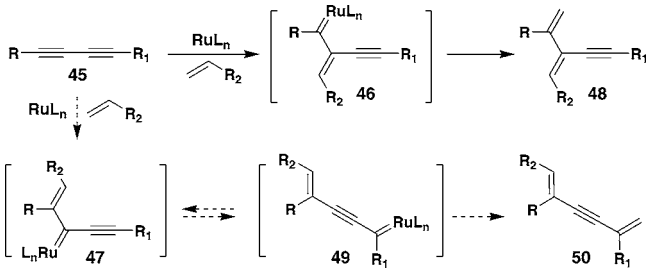
4.3. Diyne CM. On the basis of successful regio- and stereoselectivity control in CM reactions of silylated and borylated alkynes, we became interested in using 1,3-

Table 5. CM of Alkynyl Boronates[a]

entry	alkyne	alkene	1,3-diene	yield (%)	*E*/*Z*
1				76	99 : 1
2				63	97 : 3
3				60	93 : 7
4				61	83 : 17
5				92	95 : 5
6				60	0 : 100

[a] A total of 2 equiv of alkene, with 5 mol % **2**, refluxing CH_2Cl_2, 2 h.

Scheme 17



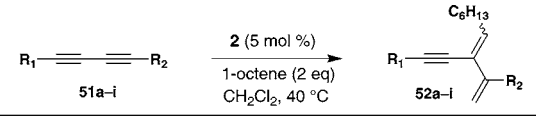
diynes as a new class of substrate.[31] During the CM of one of the alkynes in **45**, the adjacent alkyne should have an influence over the formation of either intermediate **46** or **47**. The formation of **46** would lead to product **48**, whereas **47** could undergo a metallotropic [1,3]-shift to generate a new alkylidene **49**, which may lead to the fully conjugated 1,5-diene-3-yne **50**. Two recent papers involving CM and RCM of diynes by Grubbs[32] and van Otterlo,[33] respectively, show both discouraging and encouraging support to our hypothesis (Scheme 17).

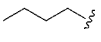
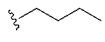
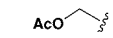
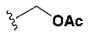
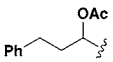
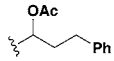
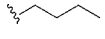
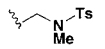
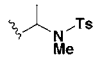
Treatment of symmetrical diyne **51a** and 1-octene (2.5 equiv) with catalyst **2** (5 mol %) provided CM product **52a** as a single regioisomer with no *E*/*Z* selectivity (Table 6). Substrates **51b** and **51c** containing a propargylic acetate gave excellent yield and *Z* selectivity for products **52b** and **52c**. Similarly, CM of unsymmetrical diynes **51d**−**f** provided **52d**−**f** in high yields (entries 4−6). The substrates possessing branched and heteroatom-functionalized propargylic carbons gave excellent *Z* selectivity (entries 3 and 6), whereas the unbranched ones gave mixtures of *E*/*Z* isomers (entries 4 and 5). Unfortunately, throughout the CM reaction of diynes, the anticipated metallotropic [1,3]-shifted products were not observed.

5. Site Selectivity

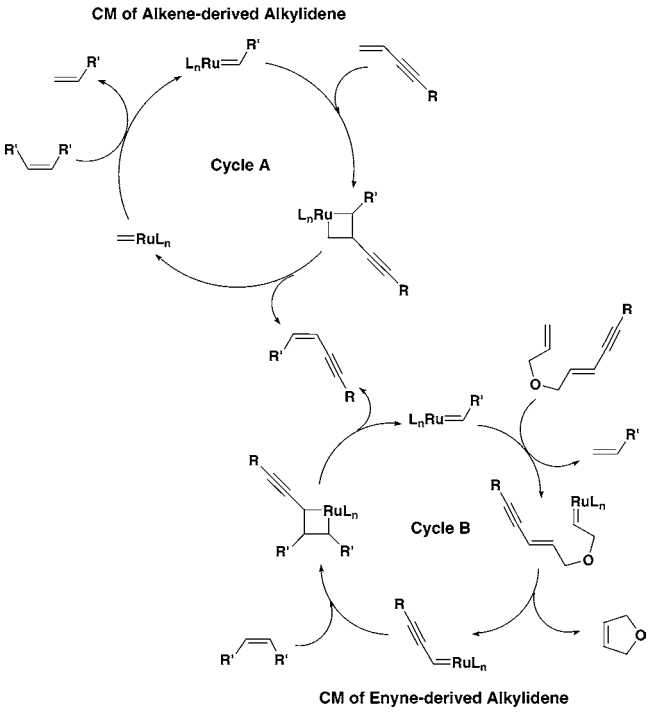
5.1. Relay Metathesis. Despite the natural tendency for the formation of regioisomeric alkylidene **46** in the CM of diynes, we remained interested in the possibility of a

Table 6. CM of Symmetric and Unsymmetric 1,3-Diynes



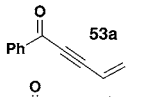
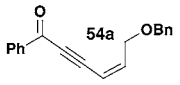
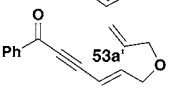
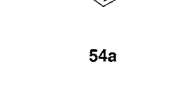
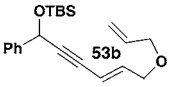
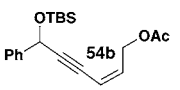
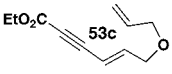
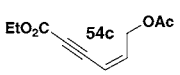
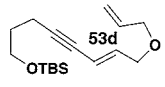
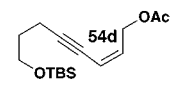
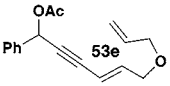
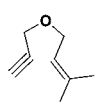
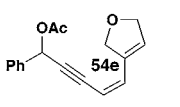
entry	diyne	R_1	R_2	enyne	*Z* / *E*	yield (%)
1	**51a**			**52a**	50:50	62
2	**51b**			**52b**	95:5	72
3	**51c**			**52c**	98:2	88
4	**51d**	Et_3Si—		**52d**	41:59	77
5	**51e**	Et_3Si—		**52e**	43:57	91
6	**51f**	Et_3Si—		**52f**	98:2	91

Scheme 18



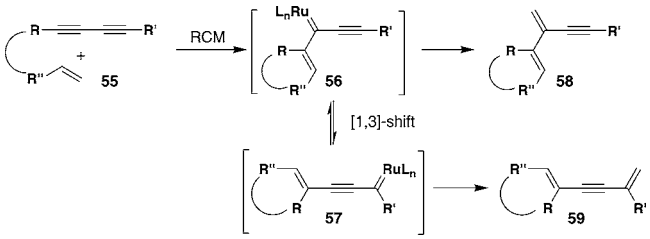
metallotropic shift that could occur from a conjugated alkynyl alkylidene as in **47**. A simple way of generating an alkynyl alkylidene would be through the use of a terminal 1,3-enyne. However, in CM reactions, the low inherent reactivity of conjugated enynes precludes initiation of the catalyst on this substrate. Instead, the propagating species is derived from the alkene counterpart as in Cycle A (Scheme 18). As a way of achieving the desired site selectivity in the CM of conjugated enynes, we would need to develop a new type of enyne substrate that would participate in the metathesis reaction with a completely different reaction manifold. Hoye had shown that attaching an allyl ether appendage to sterically hindered or electron-deficient alkenes will selectively "relay" the catalyst to that site.[34] When our enyne substrates are adapted with this appendage, the CM process will be initiated at the allyl group, generating the conjugated alkynyl alkylidene after the extrusion of dihydrofuran (Cycle B). The

Table 7. Relay CM of Conjugated Enynes[a]

entry	enyne	alkene	CM product	*Z*/*E*	yield (%)
1				7:1	38
2				4:1	65
3				10:1	85
4				20:1	66
5				7:1	61
6				1.5:1	65

[a] A total of 2 equiv of alkene, with 5−10 mol % catalyst **2**, refluxing CH_2Cl_2.

Scheme 19

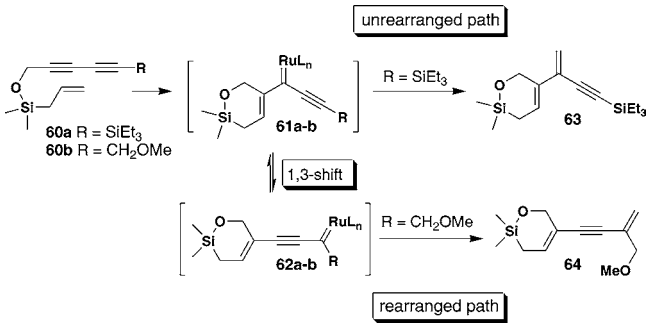


subsequent reaction of the alkylidene with an external alkene would provide CM products.

The relay metathesis strategy for generating the terminal alkynyl alkylidene was tested with the CM reaction of enynes **53a**−**e** with a symmetric internal alkene (Table 7).[35] Treatment of enyne **53a**, which does not contain a relay tether, produced **54a** in low yield and a 7:1 *Z*/*E* ratio, presumably via Cycle A above. Incorporation of the relay tether in **53a′** changes the reaction pathway to Cycle B and gives a higher yield (65 versus 38%) and somewhat lower *Z*/*E* selectivity for **54a**. Relay substrates **53b**−**e** yielded the expected enyne products **54b**−**e** in good to moderate yield and variable *Z*/*E* selectivity. The conjugated alkynyl alkylidene generated from **53e** could even undergo CM with an alkyne partner (entry 6), generating **54e** after a subsequent intramolecular ring closure.

Unfortunately, no products derived from the metallotropic [1,3]-shift[36] were observed. It is possible that the initially formed alkylidene and the 1,3-shifted alkylidene are in rapid equilibrium, but subsequent CM occurs only from the least sterically hindered initially formed alkylidene. We envisioned that a differently substituted alkylidene could be formed, and its metallotropic shift behavior can be examined by the RCM of enediynes (Scheme 19). The formation of **58** and **59** should therefore depend upon both the equilibrium between **56** and **57** and their relative

Scheme 20



reactivity, which will depend upon the steric and stereoelectonic properties of substituents.

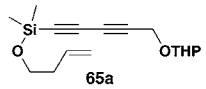
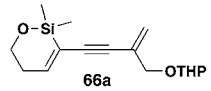
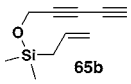
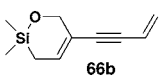
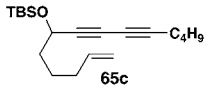
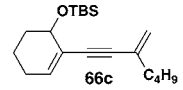
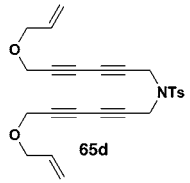
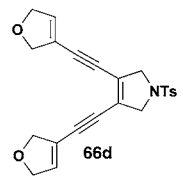
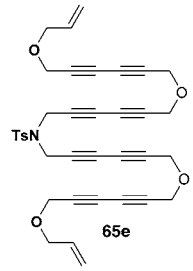
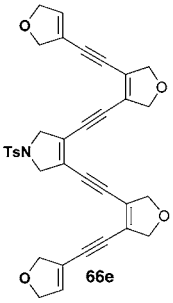
5.2. Metallotropic [1,3]-Shift. To test our hypothesis, enediynes **60a** and **60b** were synthesized and treated with catalyst **2** in dichloromethane.[31] The reaction of **60a** produced a single product **63** in quantitative yield, while the RCM of **60b** generated **64** exclusively. We believe that both **60a** and **60b** underwent an initial RCM to generate intermediates **61a** and **61b**, which then followed divergent reaction paths depending upon the steric size of the alkynyl substituents. Alkylidene **60b**, possessing a less hindered methoxymethylene at the terminal position of diyne, underwent [1,3]-shift to **62b**, which turned over to the observed product **64**. On the other hand, the bulky silyl substituent at the terminal position of the alkyne of **61a** prevented the formation of **62a**, providing **63** exclusively. Another plausible scenario is based on a lower barrier of **62b** to **64** compared to that of **61b** to the corresponding final product, while **61b** and **62b** are in rapid equilibrium (Scheme 20).

Next, we examined the generality of RCM and [1,3]-shift behavior with enediynes **65a**−**e**. Gratifyingly, the RCM reactions with these substrates provided an efficient metallotropic [1,3]-shift (Table 8). RCM with both internal and terminal diynes provided the expected [1,3]-shifted products (entries 1−3). Substrates **65d** and **65e** containing more that one suitably positioned diynes undergo consecutive RCM-metallotropic shifts,[37] providing enediynes **66d** and **66e** (entries 4 and 5). The efficient formation of these products can be rationalized by the sequence of enyne RCM−[1,3]-shift−RCM as depicted in Scheme 19.

Conclusions and Outlook

Our studies have successfully identified some of the important factors for controlling selectivity and identified new substrate platforms that give increased selectivity. We have shown the importance of ring size on *exo*/*endo* selectivity and the use of ethylene in macrocyclization to give *endo* products with high *E* selectivity. Conversely, the use of silylated alkynes allows for the formation of *exo* products for all ring sizes with high *Z* selectivity. Silyl-substituted as well as boron-substituted alkynes allow for excellent regiochemical control of the CM of internal alkynes. We have also contributed to a host of group-selective metathesis processes by demonstrating the differential RCM rate-based enyne metathesis. The use of

Table 8. RCM-Induced Metallotropic [1,3]-Shift[a]

entry	enediyne	product	yield (%)
1	 65a	 66a	66
2	 65b	 66b	69
3	 65c	 66c	96
4	 65d	 66d	86
5	 65e	 66e	45

[a] With 5 mol % catalyst **2**, refluxing CH_2Cl_2, 4−6 h.

diyne substrates, combined with the inherently tandem nature of the enyne metathesis process and new insight into the control over the selectivity issues, has led to the discovery of the facile metallotropic [1,3]-shift of alkynyl ruthenium alkylidene species. The use of enyne metathesis along with the metallotropic shift allows for the formation of not only a wide range of 1,3-dienes but also various multiconjugated molecular connectivity patterns useful in organic synthesis and materials chemistry.

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