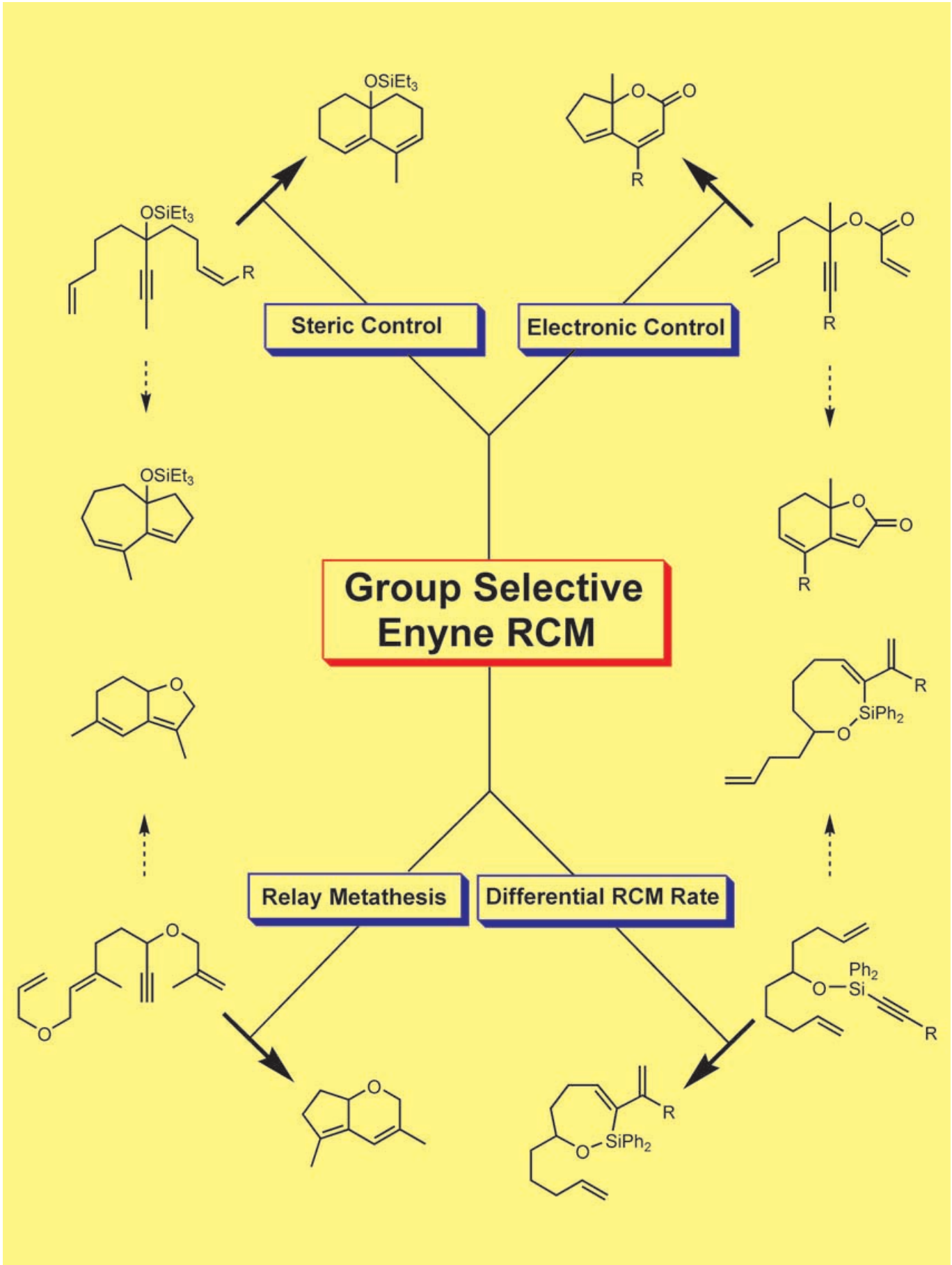

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Group-Selective Ring-Closing Enyne Metathesis

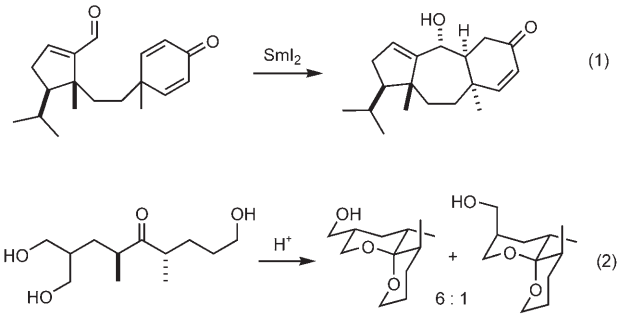
Sarah V. Maifeld and Daesung Lee*[a]

Abstract: The ring-closing metathesis (RCM) of dienynes represents a powerful methodology for the construction of mono- and bicyclic systems containing 1,3-diene functionality. Despite its synthetic potential, the utility of dienyne RCM is significantly reduced due to poor group selectivity. 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. This article highlights a variety of methods to achieve group-selective enyne RCM of dienynes.

Keywords: cyclization · enynes · metathesis · ruthenium

Introduction

Group-selective transformations constitute an important concept in stereoselective synthesis.[1] In this approach, selective conversion of one of the enantiotopic or diastereotopic groups to a new functionality breaks local or molecular symmetry. Group-selective transformations have been realized by employing both irreversible[2] [Eq. (1)] and reversible[3] [Eq. (2)] bond-forming processes.



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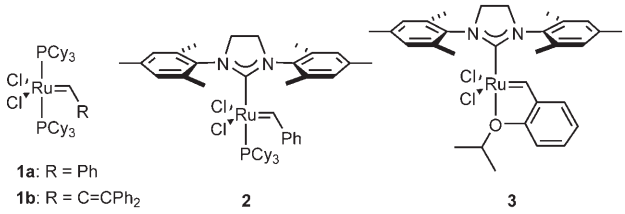
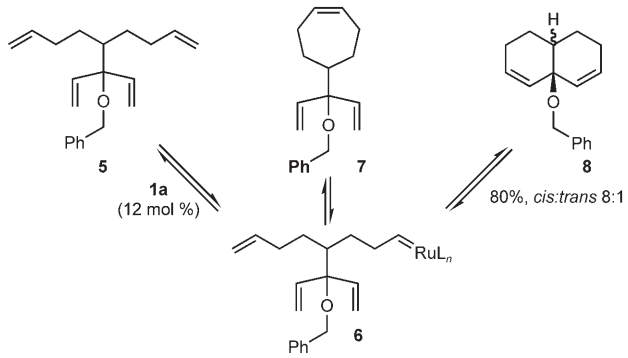
The emergence of metathesis chemistry to build carbo- and heterocyclic structures significantly broadens the scope and utility of group-selective methodology based on reversible carbon–carbon bond forming processes.[4] In particular, the advent of well-defined ruthenium carbene catalysts such as **1**–**3** has enriched the field of metathesis by improving the reaction scope and the selectivity.[5–8]



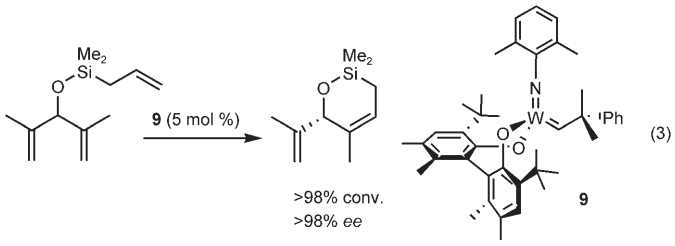
Relying on the inherently reversible nature of the metathesis process, several examples of group-selective metathesis reactions have been reported. For example, Lautens et al. reported a diastereoselective diene RCM reaction of tetraene **5** (Scheme 1).[9] While shorter reaction times gave triene **7**, longer reactions gave rise to bicycle **8** with high levels of *cis*-selectivity, implicating a pre-equilibrium among species **5**–**7**.

In addition, Schrock and Hoveyda have developed a powerful group-selective strategy displaying excellent discrimi-



Scheme 1. Reversibility in the RCM reaction.

nation of diastereo- and enantiotopic alkene functionality. By employing chiral tungsten–alkylidene complex **9**, a chiral cyclic molecule was generated from an acyclic precursor with high yield and enantioselectivity via a diene RCM reaction [Eq. (3)].[10]

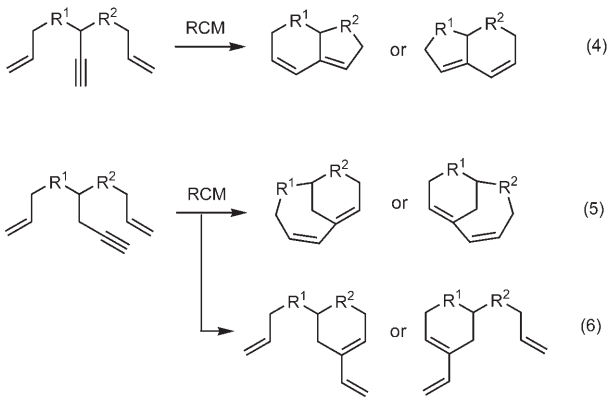


(3)

The catalytic asymmetric desymmetrization described above clearly demonstrates the potential of metathesis-based group-selective transformations. Although the development of reactive metal complexes with broad functional group tolerance and appropriately designed substrate platforms continues to enrich the field of metathesis chemistry, the selectivity in product distribution remains a challenge in many areas of metathesis chemistry.

This shortcoming is most apparent in the body of work concerning enyne RCM reactions.[11] In contrast to diene or diyne metathesis processes, which regenerate the functionality present in the starting material and are thus reversible in nature, enyne metathesis generates a 1,3-diene from an alkene and an alkyne. Although the reversibility of all mechanistic steps throughout the enyne metathesis catalytic cycle has been assumed, it has not been confirmed due to the convolution of several competing reaction pathways involving multiple intermediates (Figure 1).

Despite the poorly understood mechanism and less predictable reactivity profile as compared to its diene counterpart, the prowess of enyne metathesis holds significant promise for further development. The tandem bond-forming nature of enyne metathesis offers a powerful and catalytic framework for the formation of conjugated carbon–carbon double bonds, thereby generating complex molecular structures from simple starting materials in a single synthetic operation. As exemplified by Equations (4)–(6), the desymmetrization of acyclic dienynes by enyne RCM presents a powerful strategy to build fused [Eq. (4)] and bridged [Eq. (5)] bicycles as well as monocyclic structures [Eq. (6)].



Although the catalytic asymmetric desymmetrization strategy described in Equation (3) demonstrates the potential of metathesis-based group-selective transformations, several difficulties hamper the advancement of such methodology based on enyne metathesis. As shown in Figure 2, the asymmetric diene RCM in Equation (3) relies on enantiotopic group differentiation (**A** vs **A**′) by the metal–alkyli-

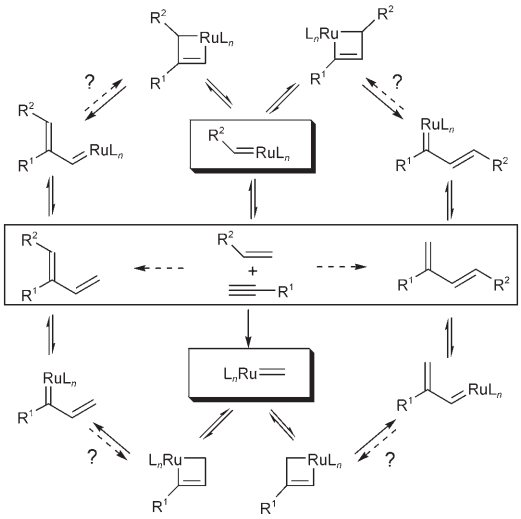


Figure 1. Pathways and intermediates in enyne metathesis.

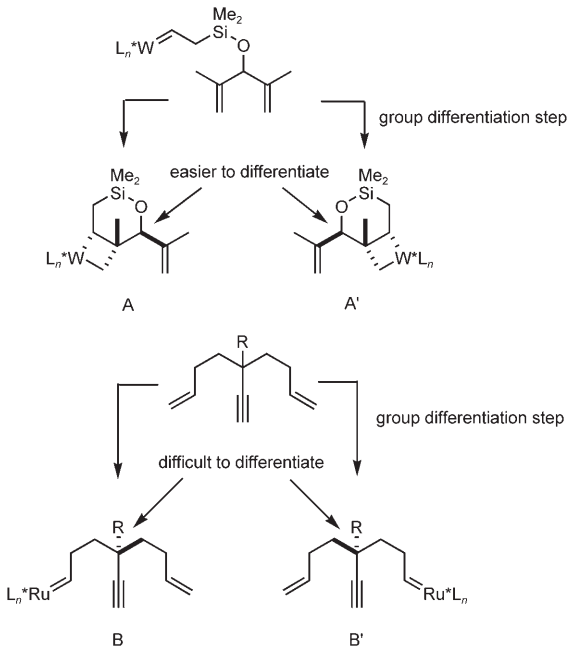


Figure 2. Enantiotopic group differentiation via cyclic and acyclic intermediates in diene and enyne RCM.

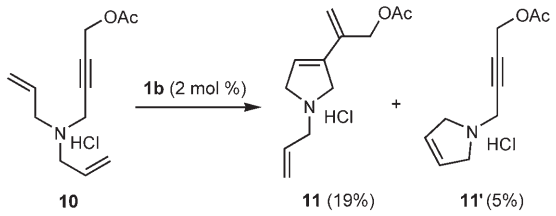
dene complex during ring formation. In contrast, the group differentiation in dienyne systems (**B** vs **B′**) must occur prior to the ring-closure event. The latter represents a more challenging differentiation as the necessary communication between the chiral environment around the metal center and the pro-stereogenic carbon center is further away. However, the realization of such an objective in tandem enyne RCM would surely expand the scope and utility of metathesis chemistry.

To improve the group differentiation between **B** and **B′** as well as the overall selectivity of the RCM of dienynes, four general strategies have been implemented, which include a) steric perturbation, b) electronic perturbation, c) relay metathesis, and d) ring closure rate-based differentiation. The focus of this article is to highlight these concepts that have evolved to enhance the group selectivity in the RCM of dienynes.

Group Differentiation Strategy

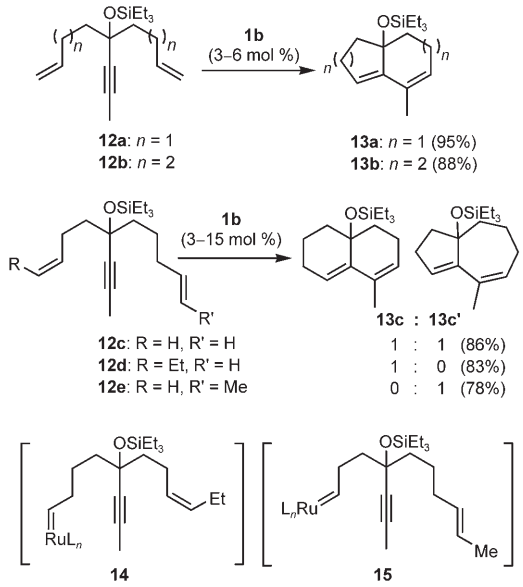
Steric perturbation: Earlier studies in diene metathesis documented that the reactivity of any alkene in a metathesis substrate decreases when alkyl substituents are introduced on or near the alkene. Implementation of this general reactivity-controlling strategy would constitute a useful method to obtain selectivity for a particular reaction manifold in tandem enyne RCM reactions.

While initial reports of enyne metathesis utilized chromium- and tungsten–carbene complexes, Mori and Kinoshita reported the first ruthenium–carbene-mediated enyne metathesis in 1994.[12] Notably, in these reports, the RCM reaction of symmetric dienyne **10** in the presence of 2 mol% **1b** provided enyne RCM product **11** over diene RCM product **11′** (Scheme 2).



Scheme 2.

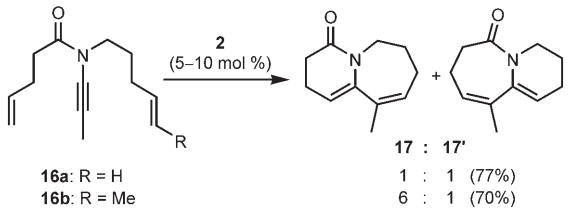
Concurrently, Grubbs et al. reported the tandem enyne RCM of all carbon-based dienynes to form bicyclic 1,3-diene systems (Scheme 3).[13] As seen in the example of Mori and Kinoshita, enyne RCM was preferred over competing diene RCM. Symmetric dienynes **12a** and **12b** gave single products **13a** (95%) and **13b** (88%), respectively. In contrast, a nonsymmetric substrate **12c** generated **13c** and **13c′** (86% combined) as a mixture in a 1:1 ratio. However, the selectivity between **13c** and **13c′** could be controlled by introducing an alkyl substituent on one of the tethered alkenes.



Scheme 3. Selectivity in tandem enyne RCM of all carbon-based dienynes.

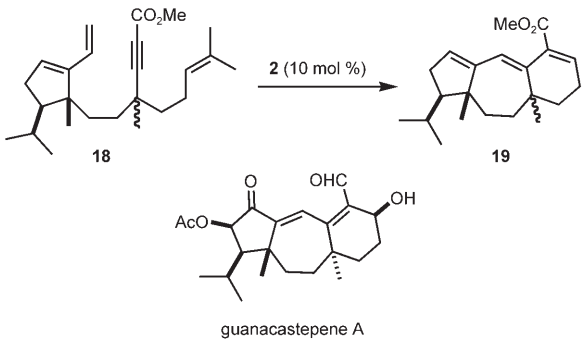
The ethyl group on the shorter alkenyl tether in **12d** selectively directed the formation of propagating alkylidene **14**, thereby giving only **13c**. Likewise, the methyl group on the longer alkenyl tether in **12e** selectively promoted the formation of isomeric intermediate alkylidene **15**, which led to a single cyclized product **13c′**.

Closely related tandem enyne RCM reactions of ynamide-based dienynes were reported by Hsung et al. (Scheme 4).[14] In the absence of steric differentiation between the two tethered alkenes present in **16a**, a 1:1 mixture (77% combined) of isomeric bicycles **17** and **17′** was generated. However, introduction of a methyl group on one of the alkene moieties in **16b** provided much higher selectivity favoring **17**, as the consequence of the preferred intiation on the sterically less hindered alkene.



Scheme 4. Tandem enyne RCM of ynamide-based dienynes.

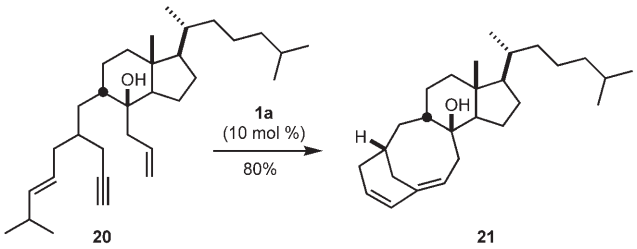
Not surprisingly, group-selective tandem enyne RCM reactions employing the steric perturbation strategy have been applied to the synthesis of natural products. In their effort toward a total synthesis of the guanacastepenes, Hanna et al. constructed tricyclic skeleton **19** from precursor **18** via enyne RCM (Scheme 5).[15] Initiation of the reaction again occurs at the least substituted terminal alkene, a conjugated 1,3-diene moiety, which was followed by a tandem ring clo-



Scheme 5. Formation of the guanacastepene skeleton by tandem enyne RCM.

sure at the alkyne and then the trisubstituted alkene to yield tricycle **19**.

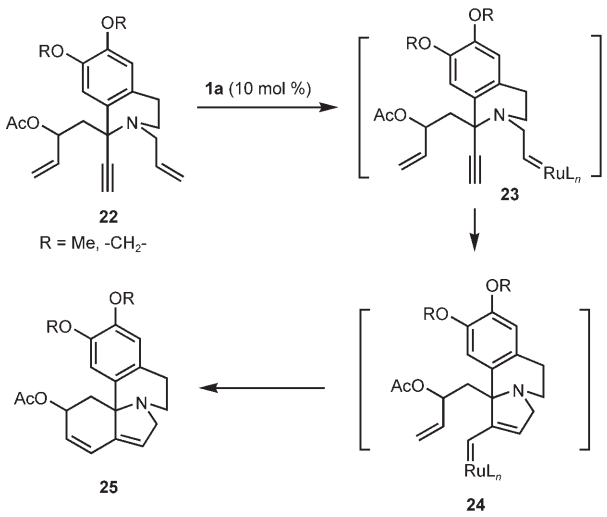
Granja et al. also utilized a similar strategy to promote the formation of a disfavored eight-membered ring over that of a smaller, more favored five-membered ring (Scheme 6).[16] In their synthesis of a bridged bicyclic skeleton **21** by tandem enyne RCM, isopropyl substitution in **20** directed metathesis initiation to the least substituted alkene, which then led to ring closure to the eight-membered ring. Interestingly, this approach represents a rare example of the formation of bridged bicycles possessing a bridgehead double bond.



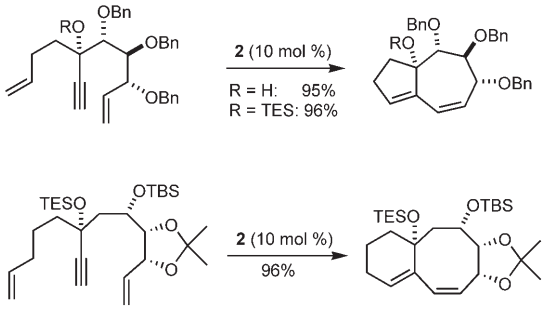
Scheme 6. Construction of a bridged bicycle by tandem enyne RCM.

Since the initiation of a metathesis reaction is impeded not only by substitution on the alkene but also near the alkene, the reactivity of two mono-substituted alkenes of dienyne RCM substrates could be effectively differentiated by the substituents at the allylic positions. Using this concept, the groups of Mori[17] and Hatakeyama[18] have independently reported related enyne RCM strategies to construct the tetracyclic skeleton **25** of the erythrina family of alkaloids (Scheme 7). As expected, the metathesis reaction of **22** initially occurs at the sterically less hindered N-allyl group to generate alkylidene **23**. This intermediate subsequently undergoes ring closure to **24** and finally to tetracycle **25**. In these tandem enyne RCM reactions, none of the regioisomer corresponding to the initial ring closure between alkene bearing allylic substitution and the alkyne moiety was observed.

Hanna et al. also capitalized on this rate difference to synthesize a variety of highly oxygenated bicycles from dienyne



Scheme 7. RCM of dienynes with sterically differentiatiated allylic positions.

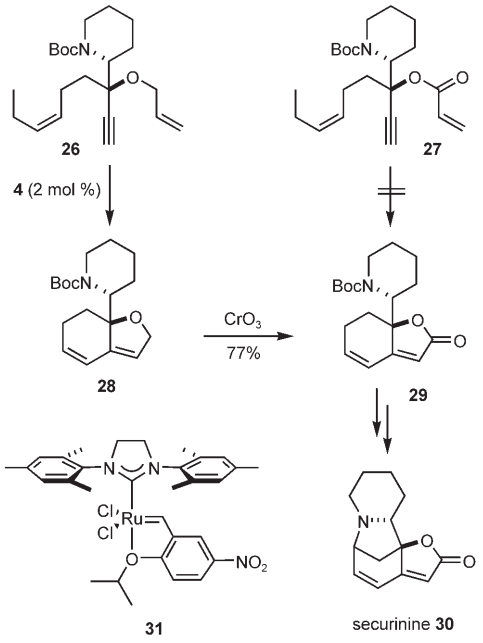


Scheme 8.

precursors (Scheme 8).[19] The cyclization products were derived from reaction initation at the alkene lacking substitution at the allylic position.

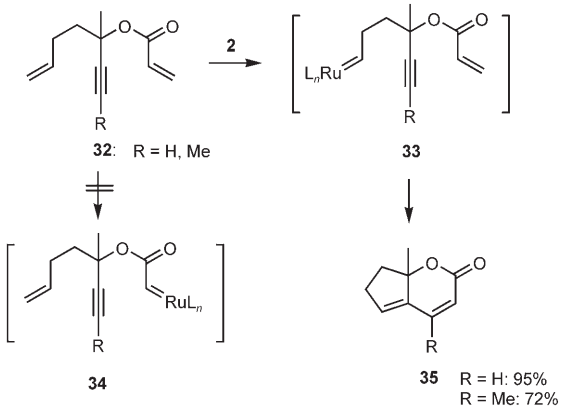
Another example of a group-selective enyne RCM utilizing steric differentiation has been reported by Honda et al. In their approach to securinine **30**, diastereoselective construction of the bicyclic core **29** was envisioned from an enyne RCM reaction initiating from the less hindered alkene in **27** (Scheme 9).[20] However, when acrylate **27** was subjected to the reaction conditions, none of the desired bicycle **29** was observed, likely due to decreased reactivity of the acrylate moiety and the *cis*-disubstituted double bond of **27** toward initiation. In a revised attempt, the cyclization proceeded readily (74%) in the presence of catalyst **31**[21] when an allyl ether was installed instead of the acrylate moiety. Subsequent allylic oxidation on the RCM product employing chromium trioxide yielded the initially intended α,β-unsaturated lactone **29**.

Electronic perturbation: In addition to steric considerations, the introduction of a electronically-biased alkene has also been used to direct the site of catalyst initiation. Grubbs et al. reported that carbenes derived from α,β-unsaturated



Scheme 9. Steric differentiation in a tandem enyne RCM.

carbonyl compounds are less stable and thus less likely to form than other carbenes.[22] For this reason, dienyne **32**, containing two alkenes in similar steric environments but differing by their electronics, underwent a selective enyne RCM to give **35** as the sole product, regardless of substitution on the alkyne (Scheme 10).[23] This observed selectivity is the result of the exclusive formation of the initial alkylidene **33** over less stable enoic alkylidene **34**.



Scheme 10. Electronic effect for selective catalyst initiation.

The manifestation of this electronic biasing effect is noted in the synthesis of a variety of fused bi- and tricyclic ring systems in excellent yields from acrylate-containing dienyne precursors (Figure 3).

Relay metathesis: Hoye and co-workers reported a new strategy for reaction pathway control known as *relay metathesis*.[24] This approach involves the design of substrates that direct the ruthenium carbene through the individual steps of the reaction cascade. The fruition of a successful and selective relay metathesis reaction hinges on the delivery of the propagating metal carbenoid to a less reactive alkene. This delivery occurs by initial formation of the alkylidene at a remote reactive alkene followed by a ring-closing metathesis event with the less reactive alkene.

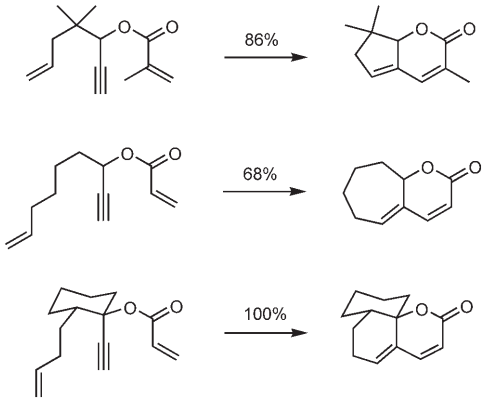
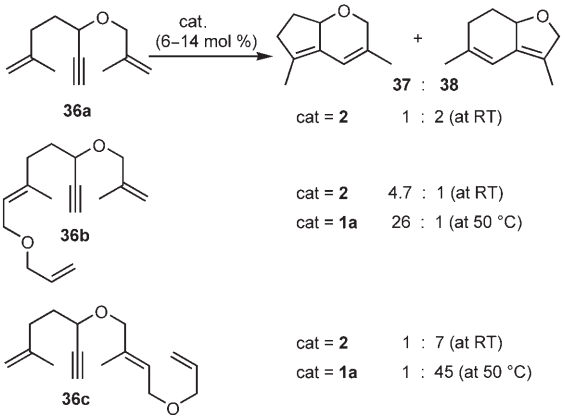


Figure 3. Group selectivity achieved by electronic differentiation.

The efficacy of relay metathesis to control the reaction pathway is illustrated in Scheme 11. Initial ring closure by **2** of the parent dienyne **36a** gave a 1:2 ratio of **37**:**38** due to



Scheme 11. Group-selective enyne RCM by relay ring-closing metathesis (RRCM).

nonselective alkylidenation and closure from either of the similar 1,1-disubstituted alkenes. In contrast, the tethering of a highly active monosubstituted alkene at either end of **36a** increased the selectivity of the ring closure. Importantly, a judicious choice of catalyst was found to amplify the selectivity in this relay metathesis. Reactions employing catalyst **1a** showed a dramatic increase in selectivity; relay substrate **36b** cyclized to **37** very selectively (26:1) while **36c** cyclized nearly exclusively (1:45) to **38**.

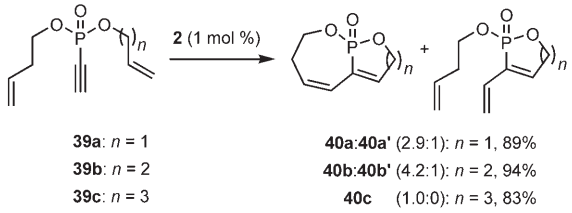
Although the concept of relay metathesis was invented only recently, it has already found important application in

natural product synthesis.[25] The expansion of this approach is expected to develop in both inter- and intramolecular diene and enyne metathesis reactions.

Ring closure rate-based differentiation: In the examples above, selectivity relies on controlling the site of catalyst initiation by modifying the reactivity of the alkene or alkyne moieties with steric and electronic factors. While this has proven successful, the introduction of the biasing elements, in many cases, requires extra synthetic manipulations and may limit the reaction scope.

In the absence of biasing elements, a substrate possessing two alkenes in nearly similar steric and electronic environments will result in reaction initiation at both alkenes. Despite this nonselective initiation, a selective RCM reaction can still be envisioned if the pre-ring closure steps are reversible and occur at higher rates than the nonreversible ring closure step. If these conditions are met, then ring closure rates, rather than rates of initiation influenced by steric and electronic parameters, would govern the selectivity of the tandem enyne RCM. In accordance with this analysis, there are a few examples of group-selective enyne RCM from dienyne precursors possessing unbiased alkenes.

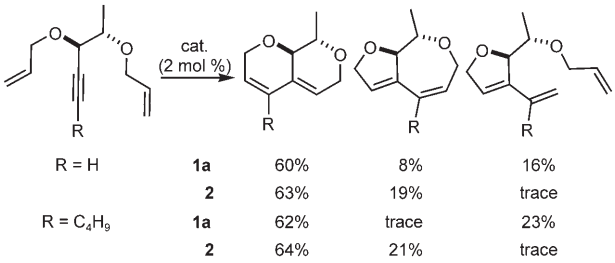
Van Boom et al. reported the synthesis of phosphorus-containing heterocycles from bis(alkenyl)ethynyl phosphonates by enyne RCM (Scheme 12).[26] In the presence of **2**,



Scheme 12. Group-selective enyne RCM of ethynyl phosphonates.

nonsymmetric ethynylphosphonate **39a** cyclized to yield a 2.9:1 mixture of cyclopentenyl products **40a** and **40a′** derived from reaction initiation on the shorter allyl tether. In this example, no products containing a six-membered ring, which would arise by initiation and closure from the tether containing an additional methylene unit, were observed. Symmetric substrate **39b** cyclized cleanly to yield a mixture of bi- and monocyclic products **40b** and **40b′**. Interestingly, nonsymmetric dienyne **39c** was cyclized to form only **40c**. In this case, reaction was initiated on the longer alkenyl tether to yield the seven-membered ring rather than initiation on the shorter tether to yield the six-membered ring. No explanation was given, but the preferred formation of the seven,seven-membered ring suggests a slower rate of cyclization to form the initial six-membered ring from these substrates.

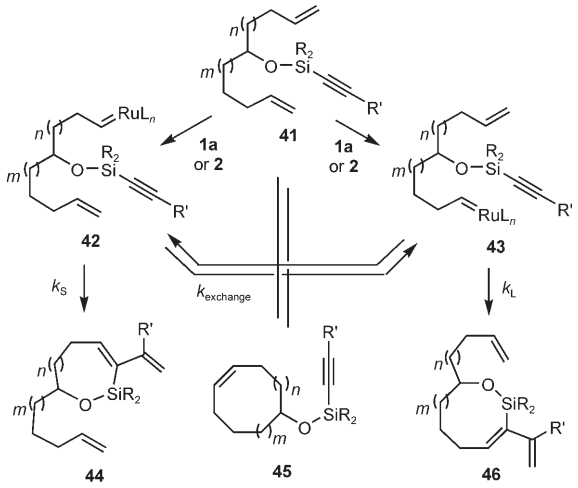
Similarly, Liu et al. reported a moderately group-selective tandem enyne RCM for the synthesis of small-sized fused bicycles (Scheme 13).[27] The dienynes cyclized to form similar ratios of products, consistently favoring the initial ring



Scheme 13. Selectivity of enyne RCM for the formation of fused oxabicycles.

closure to the six- over five-membered ring regardless of the presence of substitution on the alkyne or the catalyst employed (**1a** vs **2**). The observed selectivity could arise from a ring closure rate difference during the initial five- and six-membered ring formation.

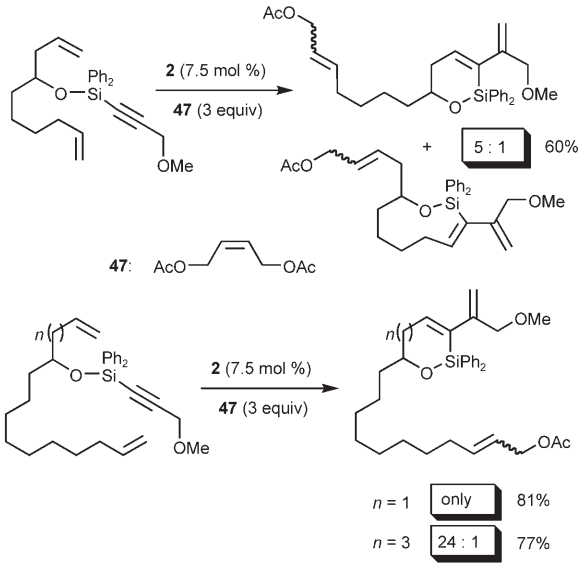
A generalized concept of a ring closure rate-based differentiation of reaction pathways is shown in Scheme 14. In



Scheme 14. Pre-equilibrium of alkylidene intermediates prior to ring closure.

this overall mechanistic picture, it is expected that alkynylsilyloxy-tethered dienyne **41**, possessing two tethered alkenes in nearly equivalent steric and stereoelectronic environments, would be equally partitioned between alkylidenes **42** and **43** during the RCM reaction. Assuming the steric hindrance imparted by the silylalkynyl moiety slows the enyne ring closure rates (k_S and k_L) as compared to rate of alkylidene exchange ($k_{exchange}$), a situation arises where a pre-equilibrium between intermediates prior to ring closure is possible. This equilibrium would permit **42** and **43** to interconvert via alkylidene exchange or possibly via the involvement of diene RCM product **45** and its subsequent ring opening. Assuming that catalyst initiation at the alkyne is negligible and the ring closure rate of the smaller sized ring is faster than that of the larger ($k_S > k_L$), then the selective formation of the smaller ring **44** would be expected over the larger ring **46**.

The tandem enyne RCM reaction of alkynylsilyloxy dienynes that have two terminal alkenes with substantially different tether lengths between the ene and the yne components gave good to excellent selectivity between the two different ring-sized products (Scheme 15).[28] For substrates

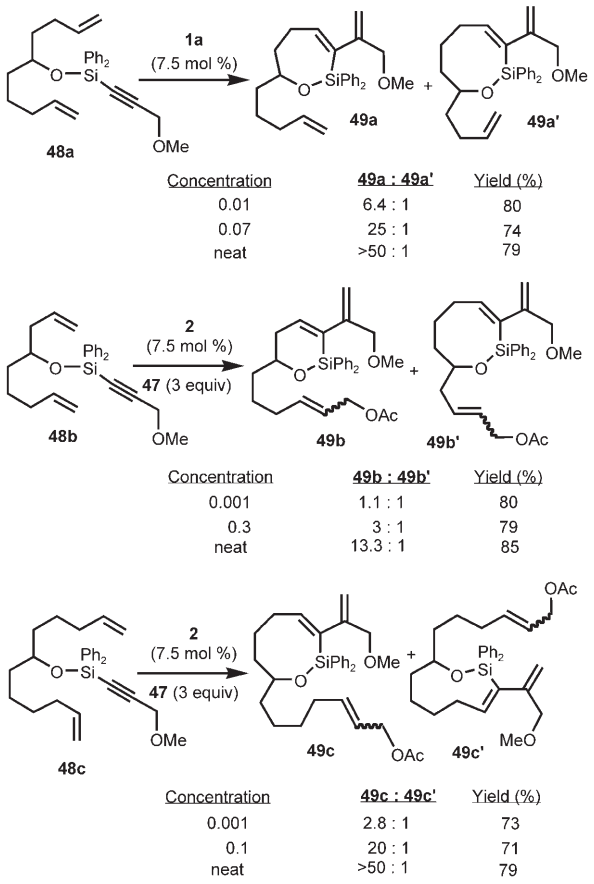


Scheme 15. Group-selective RCM of dienynes with substantially different tether lengths.

showing a high tendency to dimerize after the initial enyne RCM, an external alkene **47**, *cis*-($AcOCH_2CH=)_2$, was added to the reaction. This external alkene impeded dimerization of the ring-closure products, without causing a change of selectivity, by undergoing cross metathesis with the remaining terminal alkene to ultimately give an allylic acetate.

The enyne RCM (0.001 M) 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 above, only marginal selectivity was observed when chain lengths of the two tethered alkenes became similar as in dienynes **48a–c**. This lack of selectivity presumably results from the comparable rates of formation and cyclization of both alkylidene intermediates prior to the establishment of a pre-ring closure equilibrium between these species. Since the equilibration of alkylidene intermediates relies on a bimolecular process requiring the substrate and the propagating catalytic species, we hypothesized that increasing the concentration of the reaction would induce a more effective equilibrium and result in better discrimination between the two ring-closure pathways (Scheme 16). Pleasingly, the RCM reaction of **48a** with catalyst **1a** at gradually increased concentrations provided a remarkable increase in selectivity between seven- and eight-membered rings, providing the highest ratio of **49a** and **49a′** (>50:1) in neat solution (ca. 2.5 M).[29] Treatment of **48b** with the more reactive catalyst **2** in the presence of external alkene **47** exhibited a similar concentration-dependent selectivity profile, generating the highest ratio of **49b** and **49b′** (13.3:1) in neat solution.



Scheme 16. Concentration-dependent group selectivity profile.

The RCM reaction of **48c**, possessing relatively longer alkene chains differing by only one methylene unit, exhibited good selectivity, providing eight- and nine-membered rings **49c** and **49c′** 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).

Closing Remarks

Ring-closing metathesis represents one the most powerful synthetic methods to construct both carbo- and heterocyclic ring systems. Although many examples of tandem enyne RCM suffer from a lack of selectivity, several strategies have evolved to effectively control and direct the reaction outcome. Earlier developments in group-selective enyne

RCM exploited differential rates of reaction initiation by the catalyst at sterically and electronically biased alkenes. By expanding on these findings and further addressing selectivity related issues, more recent innovations, such as relay ring-closing metathesis (RRCM) and ring closure rate-based differentiation, will continue to expand the scope and utility of enyne RCM.

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