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Citation: Lee, Yeon-Ju, Richard R. Schrock, and Amir H. Hoveyda. "Endo-Selective Enyne Ring-Closing Metathesis Promoted by Stereogenic-at-Mo Monoalkoxide and Monoaryloxide Complexes. Efficient Synthesis of Cyclic Dienes Not Accessible through Reactions with Ru Carbenes." Journal of the American Chemical Society 131, no. 30 (August 5, 2009): 10652-10661.

As Published: http://dx.doi.org/10.1021/ja904098h

Publisher: American Chemical Society (ACS)

Persistent URL: http://hdl.handle.net/1721.1/82540

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Published in final edited form as:
J Am Chem Soc. 2009 August 5; 131(30): 10652–10661. doi:10.1021/ja904098h.

Endo-Selective Enyne Ring-Closing Metathesis Promoted by Stereogenic-at-Mo Monoalkoxide and Monoaryloxide Complexes. Efficient Synthesis of Cyclic Dienes Not Accessible through Reactions with Ru Carbenes

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Abstract

Stereogenic-at-Mo monoalkoxide and monoaryloxide complexes promote enyne ring-closing metathesis (RCM) reactions, affording the corresponding *endo* products with high selectivity (typically >98:<2 *endo*:*exo*). All catalysts can be prepared and used *in situ*. Five-, six-, and seven-membered rings are obtained through reactions with enyne substrates that bear all-carbon tethers as well as those that contain heteroatom substituents. The newly developed catalytic protocols complement the related *exo*-selective Ru-catalyzed processes. In cases where Ru-based complexes deliver *exo* and *endo* products nondiscriminately, such as when tetrasubstituted cyclic alkenes are generated, Mo-catalyzed reactions afford the *endo* product exclusively. The efficiency of synthesis of *N*- and *O*-containing *endo* diene heterocycles can be improved significantly through structural modification of Mo catalysts. The modularity of Mo-based monopyrrolides is thus exploited in the identification of the most effective catalyst variants. Through alteration of *O*-based monodentate ligands, catalysts have been identified that promote enyne RCM with improved efficiency. The structural attributes of three Mo complexes are elucidated through X-ray crystallography. The first examples of catalytic enantioselective enyne RCM reactions are reported (up to 98:2 enantiomer ratio and >98% *endo*).

Introduction

Catalytic enyne ring-closing metathesis (RCM) is an effective method for preparation of cyclic dienes.[1] Various mechanistic aspects of this class of transformations, nearly all reported cases of which are promoted by Ru-based carbenes, have been elucidated;[2] the utility of this important branch of catalytic olefin metathesis has been demonstrated on several occasions in the context of natural product total synthesis.[3] Nonetheless, solutions to a number of unresolved problems in reactivity and selectivity[4] would substantially enhance the utility of metal-catalyzed enyne RCM.

Herein, we detail our studies regarding the development of Mo-catalyzed enyne RCM reactions,[5] which in contrast to Ru-,[1] W-,[6] and Cr-catalyzed[7] processes deliver cyclic *endo*

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diene isomers. None of the previously reported olefin metathesis-based methods allow selective access to *endo* products.[8] Five-, six-, and seven-membered-ring *endo* dienes (vs *exo* dienes generated predominantly by Ru-based carbenes) bearing di-, tri-, and tetrasubstituted alkenes are obtained in 41–90% yield. Reactions generally proceed with exceptional *endo* selectivity (typically >98:<2 *endo*:*exo*). Ring-forming processes are promoted by readily prepared stereogenic-at-Mo complexes, which bear only monodentate ligands.[9] Such attributes allow for modification of Mo complexes so that reactivity and selectivity of enyne RCM reactions are enhanced. We introduce several structurally modified stereogenic-at-Mo complexes that initiate enyne RCM with degrees of efficiency and selectivity not achievable through the use of previously reported catalysts. We conclude by presenting the first examples of efficient metal-catalyzed enantioselective enyne RCM reactions.[10]

The key challenge facing us in the course of investigations detailed herein originates from the availability of various pathways[2] through which a catalyst might promote an enyne RCM reaction: a metal-based alkylidene may first either associate with the alkyne (pathways 1 and 2, Scheme 1) or the alkene (pathway 3, Scheme 1) unit of the substrate ***i***. Transformation through complex ***ii*** gives rise to *β*-substituted metallacyclobutene ***iii***, where the metal center forms a bond with the terminal carbon of the alkyne; conversion of ***iii*** to conjugated terminal alkylidene ***iv*** would then be followed by RCM to afford cyclic diene *v* (*endo* product). A metal alkylidene might alternatively coordinate to the alkyne in such a manner that, as depicted in pathway 2 in Scheme 1, generation of α-substituted metallacyclobutene ***vii*** is preferred; cycloreversion to disubstituted alkylidene ***viii*** culminates in the formation of the *exo* product ***ix***. Pathway 3 (Scheme 1) commences by initial interaction of the catalyst with the alkene unit ***x***, affording terminal carbene ***xi***, which through an intramolecular cycloaddition is converted to α,*β*-metallacyclobutene ***xii***. Subsequent transformation gives rise to cyclopentene-substituted terminal carbene ***xiii***, which through a cross-metathesis process with another enyne substrate (***i***) affords *exo* product ***ix*** and regenerates terminal carbene ***xi***.

Extensive previous research has established that when Ru-based carbene complexes are used to promote enyne RCM, the formation of *exo* products, represented by ***ix*** (Scheme 1), is strongly favored.[1] Our interest in examining the ability of stereogenic-at-Mo complexes, recently developed in these laboratories to address a number of unresolved issues in selective catalytic olefin metathesis, arose from the principle that high oxidation state complexes should favor reaction through a pathway that commences with association with the alkyne site of an enyne substrate.[11] The above considerations, together with the preference of the sterically demanding Mo center to form a bond with the terminal carbon of an alkyne, led us to surmise that *β*-metallacyclobutenes should prove to be favored intermediates, leading to selective formation of *endo* RCM products (pathway 1, Scheme 1). We were also aware, however, that the strong preference for formation of Mo-alkyne complex could lead to competitive oligomerization processes, involving reaction of intermediate alkylidenes (e.g., ***iv*** or ***viii***, Scheme 1) with an alkyne of another substrate molecule. We will demonstrate that such complications can be addressed through modification of the catalyst structure so that intramolecular processes that lead to RCM products are preferred over intermolecular reactions that result in formation of oligomers.

Results and Discussion

1. Selective Synthesis of *endo*-1,3-Carbocyclic Dienes through Mo-Catalyzed Enyne RCM

1.1. Initial Evaluation of Mo- and Ru-Based Complexes—We began by examining the ability of representative Mo-based complexes to catalyze RCM of enyne **1** (Scheme 2). Use of Mo alkylidene **4**[10b] (5 mol %) does not lead to formation of either the *endo* or the *exo* cyclic diene isomer (**2** and **3**, respectively; 22 °C, 30 min). In contrast, under identical

conditions, monopyrrolide–monoalkoxide **5**[5] delivers *endo* RCM product **2** in 72% yield (<2% *exo* isomer **3**, detected by 400 MHz ^{1}H NMR spectroscopy). As has been described previously, stereogenic-at-Mo complexes, represented by **5**, are prepared and often used *in situ*[9a,b] through reaction of a bispyrrolide (e.g., **6**) with an alcohol.[12] As also shown in Scheme 2, the latter precursor complex does not exhibit any catalytic activity in this case (<2% conversion). Ru-based carbene **7**[13] initiates enyne RCM, albeit less effectively than **5** (2 h vs 30 min of reaction time). It is only the *exo* isomer **3** that is isolated in the Ru-catalyzed process (Scheme 2).[14] When the RCM promoted by carbene **7** is performed under an atmosphere of ethylene,[14c] after 1 h there is only 24% conversion to **3**, which is obtained along with a byproduct that is derived from homo-cross-metathesis of the product (**3**, 26%; ~50% recovered substrate).

1.2. Enyne RCM Promoted by Monoalkoxide Mo Complex 5—The findings summarized in Table 1 demonstrate that, through the use of Mo complex **5**, a range of cyclic dienes can be accessed. Thus, five-, six-, and seven-membered ring products are isolated in 70–82% yield after purification; reactions proceed readily and selectively with terminal alkynes as well as 1,1-disubstituted alkenes (e.g., entry 3, Table 1). The RCM process in entry 4 of Table 1, involving enyne **11**, which contains an internal alkyne and a disubstituted olefin, leads to the formation of a tetrasubstituted cyclic alkene; as a result, unlike cases where di- or trisubstituted olefins are generated (5 mol % **5**), higher catalyst loading (20 mol %) is required for achieving complete substrate consumption. When 5 mol % **5** is used, there is only 23% conversion, and with 10 mol % Mo-alkylidene, 42% of the desired *endo* product is obtained after 30 min [70% conversion after 24 h; the remainder of the enyne remains unreacted (i.e., <2% oligomerization)]. Additional points regarding the RCM processes in Table 1 are worthy of note: Although most reactions described above are performed with 5 mol % **5**, in at least some cases, efficient transformation can be achieved with lower catalyst loading. For example, RCM of **1** (Scheme 2) carried out in the presence of 1 mol % **5** proceeds to >98% conversion within 30 min at 22 °C to afford endocyclic diene **2** (Scheme 2) in 74% yield.

High *endo* selectivity is observed in most instances (entries 1 and 3–4), except for the reaction of internal alkyne **9** (entry 2), where a mixture of *endo* and *exo* dienes is formed (75:25). It is plausible that the presence of the methyl substituent and the attendant steric repulsion that entails Mo alkylidene–alkyne association, represented by ***ii*** (Scheme 1, pathway 1), leads to partial reaction through pathway 3, involving initiation at the olefin site; some of the *exo* product could also result from reaction via ***vi*** and the corresponding α-metallacyclobutene ***vii*** (Scheme 1, pathway 2).[15] The complete *endo* selectivity (<2% *exo*) observed in RCM of enyne **11** (entry 4, Table 1), which bears an internal alkyne in addition to a 1,1-disubstituted alkene (vs a terminal olefin in **9**), is noteworthy; with the more substituted olefin, the Mo alkylidene likely initiates exclusively at the site of the internal alkyne. When Ru-based carbenes are used to promote RCM reactions of enynes bearing a terminal alkyne and a disubstituted alkene (e.g., **11**), nearly equal mixtures of *exo* and *endo* isomers are generated.[14g]

To probe further the effect of steric factors on *endo* vs *exo* selectivity, we prepared several acetonide-containing enynes (Table 2) and examined the corresponding RCM reactions (vs diesters in Table 1). Catalytic cyclizations of enynes **12** (entry 1, Table 2) and **15** (entry 4, Table 2) proceed to afford the *endo* products exclusively (>98:<2). Unlike the reaction of diester **8** (entry 1, Table 1), however, RCM of acetonide–enyne **13** (entry 2, Table 2) gives rise to a 75:25 mixture of *endo* and *exo* isomers. Similar to catalytic RCM of internal alkyne **9**, illustrated in entry 3 of Table 1, acetonide **14** undergoes transformation readily to generate a mixture of *endo* and *exo* dienes (66:33 *endo*:*exo*). We suggest that, in the case of **13**, *exo* isomer formation is competitive since generation of the α-metallacyclobutene intermediate (pathway 2, Scheme 1) is rendered more favorable as a result of reduced steric repulsion between the metal complex and the less sterically cumbersome and geometrically constrained acetonide moiety (vs the diester units of **8**). The latter scenario does not lead to diminution of product

selectivity in RCM of the structurally related acetonide–enyne **12** (entry 1, Table 2), likely because of the sterically accessible terminal alkyne and because the *endo* product is a readily generated six-membered-ring diene. In contrast, *endo* selectivity in RCM of acetonide–enyne **13** results in the generation of a less readily formed seven-membered-ring product (*exo* isomer is a six-membered ring). It merits mention that the validity of some of the scenarios mentioned depends on reversibility of some of the steps within the catalytic cycle (Scheme 1); a more sophisticated appreciation regarding any mechanistic preferences must await the outcome of more detailed studies.

The above observations illustrate that the degree of *endo*:*exo* selectivity in Mo-catalyzed RCM of enynes can depend on whether the typically favored mode of reaction (via Mo-alkyne complex ***ii*** and *β*-metallacyclobutene ***iii*** in Scheme 1) engenders unfavorable steric repulsion between any of the substrate substituents and the relatively sizable ligands of the Mo center. Furthermore, diminished selectivity may arise if the *endo* product represents a ring size (e.g., a cycloheptadiene) that is typically formed more slowly than that which corresponds to the *exo* isomer (e.g., a cyclohexadiene).

2. Selective Synthesis of *endo*-1,3-Heterocyclic Dienes through Mo-Catalyzed Enyne RCM

A significant consequence of the ability of Mo-based monoaryloxide–monopyrrolides to promote selective formation of *endo*-1,3-cyclic dienes is the possibility of applying such protocols toward preparation of the corresponding heterocyclic structures.[16] Accordingly, we investigated the effect of the presence of a heteroatom within the tether separating the alkyne and alkene units on the efficiency and selectivity of the catalytic RCM processes.

2.1. Mo-Catalyzed RCM of *N*-Containing Enynes

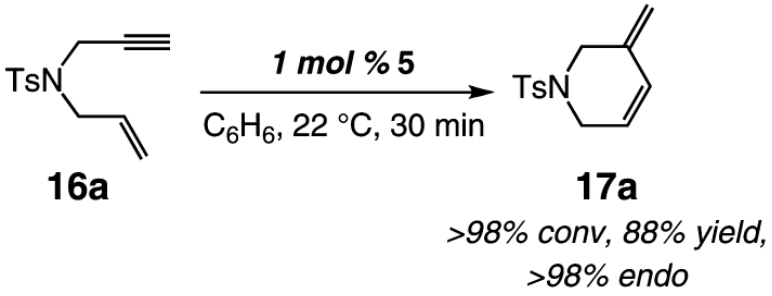
2.1.1. Catalytic RCM of Enynes Bearing Different *N*-Substituents: We began by investigating the RCM of a small set of enynes with various *N*-substituents. As the data summarized in Scheme 3 illustrate, in the presence of 5 mol % of Mo-based alkylidene **5**, tosylamide **16a** readily undergoes RCM to afford **17a** in >98% *endo* selectivity and 92% yield after purification. Catalytic ring closure of **16b**, carrying the more easily removable *o*-nosylamide, is equally efficient: the desired *N*-containing cyclic *endo*-1,3-diene **17b** is isolated in 85% yield with only slightly diminished product selectivity (97:3 *endo*:*exo*). When Boc-amide **16c** serves as the starting enyne (Scheme 3), oligomer formation is competitive with the desired RCM, which furnishes **17c** in 48% yield and >98% *endo* selectivity. Adventitious oligomerization competes with formation of **17c**, likely because the adjacent Boc unit renders the alkyne sterically more accessible (vs Ts or *o*-Ns), causing the intermolecular reaction to be favored. As the data below will demonstrate (see eq 5), it is less likely that the reduced conformational constraint imposed by the Boc-amide plays a significant role in the lower yield in which **17c** is isolated.

2.1.2. Selective Mo-Catalyzed RCM of Enynes Bearing an *N*-Tosylamide Tether: A range of *N*-containing enynes readily undergo RCM reactions to afford the derived cyclic diene products with high *endo* selectivity (Table 3). Similar to previous cases, even when a tetrasubstituted olefin is generated (entry 4, Table 3), the *endo* isomer is generated exclusively. As illustrated in entry 2 of Table 3, in only one case is a small amount of the *exo* product formed (*endo*:*exo* = 84:16). The arguments discussed above, regarding reactions of substrates bearing an internal alkyne and a terminal olefin, are likely valid here as well.

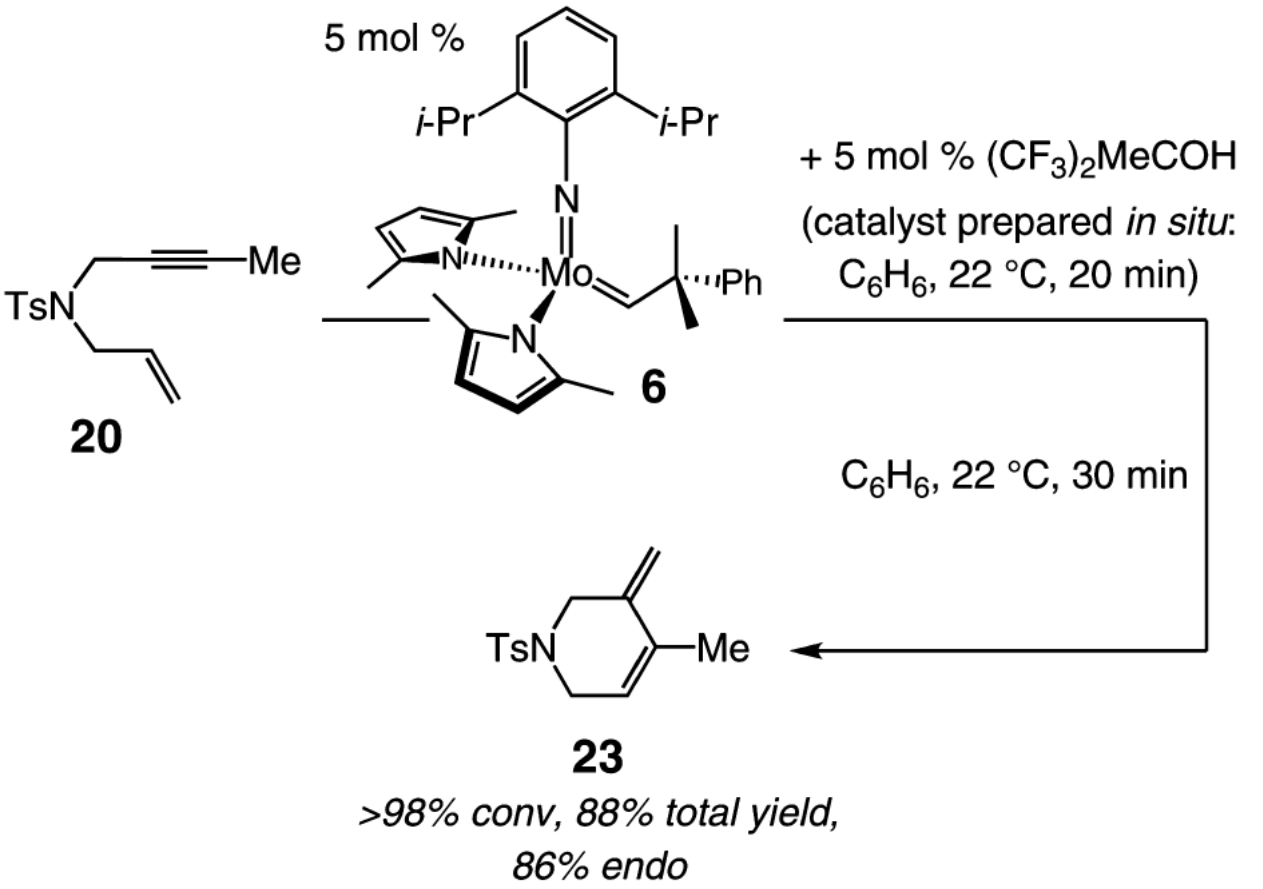
In cases where a medium ring is generated (entry 1, Table 3) or when the rate of ring closure is retarded due to increased substitution at the alkyne and/or the alkene site (entries 2–4, Table 3), the reaction must be performed under conditions that are designed to minimize oligomerization. That is, whereas the transformations in Schemes 2 and 3 and Tables 1 and 2

were performed in 0.16 M solutions, RCM processes in entries 1, 3, and 4 of Table 3 were carried out under more dilute conditions (1.3×10^{-3}, 2×10^{-3}, and 2×10^{-3} M, respectively).[17] It is noteworthy, however, that even when substrate concentration is decreased significantly, the stereogenic-at-Mo complex remains highly effective as an olefin metathesis catalyst.

As the example illustrated in eq 1 demonstrates, Mo-catalyzed RCM reactions involving terminal alkynes and alkenes readily proceed to >98% conversion with only 1 mol % **5**, delivering the corresponding *endo* products efficiently and with outstanding selectivity (>98:<2 *endo*:*exo*). In cases where the alkyne or the olefin unit is more sterically hindered, 5 mol % catalyst loading is required for complete conversion; for example, with 1,6-enyne **20** (entry 2, Table 3) as the substrate, RCM in the presence of 2.5 mol % **5** leads to 68% conversion after 90 min. It should also be noted that the Mo catalyst can be readily generated and used *in situ* without any diminution in reaction efficiency or product selectivity; the example illustrated in eq 2, regarding the preparation of *endo* diene **23**, is representative.



(1)



(2)

The transformations illustrated in Scheme 4 involve RCM reactions of *N*-substituted 1,7-enyne substrates (vs 1,6-enynes examined above). We find that, with 5 mol % **5**, aryl-substituted enyne **24** is converted within 30 min to seven-membered *endo* diene **25** in >98% selectivity (<2% *exo* product **26**) and 68% yield. When Ru-based complex **7** is used, *exo* diene **26** is formed as the sole product (<2% *endo* product, **25**) in 70% yield (Scheme 4). In contrast, when 1,7-enyne **27**, bearing a less sterically congested alkyne unit (vs the benzylic alkyne in **24**), is treated with the same conditions as mentioned above, only rapid oligomerization ensues.

To address the aforementioned complication, we turned to the modified stereogenic-at-Mo monopyrrolide complex **28**,[9a] where the hexafluoro-*tert*-butoxide ligand of **5** has been replaced by a bulkier 2,6-di(isopropyl)phenoxide. We surmised that the presence of the more sizable aryloxide would discourage the competing intermolecular processes, leading to oligomeric products (vs the desired RCM). As illustrated in Scheme 4, in the presence of Mo monoaryloxide–monopyrrolide **28**, the efficiency of the RCM is increased significantly: a mixture of *endo*-**29** and *exo*-**30** is obtained in 41% yield; the remainder of the substrate is consumed toward side reactions. The low *endo*:*exo* selectivity is likely due to favorable formation of the derived Mo-arylidene complex (derived from the styrenyl alkene) that gives rise to the competing mode of transformation (pathway 3, Scheme 1) involving initiation of the catalytic cycle at the styrenyl site of enyne **27**. Ru-catalyzed RCM with **27**,[18] as indicated in Scheme 4, leads to formation of unidentified product mixtures when carried out under N_2; when ethylene atmosphere is used at 22 °C, low efficiency is observed. It has, however, been

previously reported that, with 5 mol % Ru carbene **7**, RCM of the acetamide derivative of **27** proceeds readily at 80 °C (toluene, under N_2 atm, reaction time not specified) to deliver the corresponding *exo* isomer in 65% yield.[18d]

2.2. Mo-Catalyzed RCM of *O*-Containing Enynes

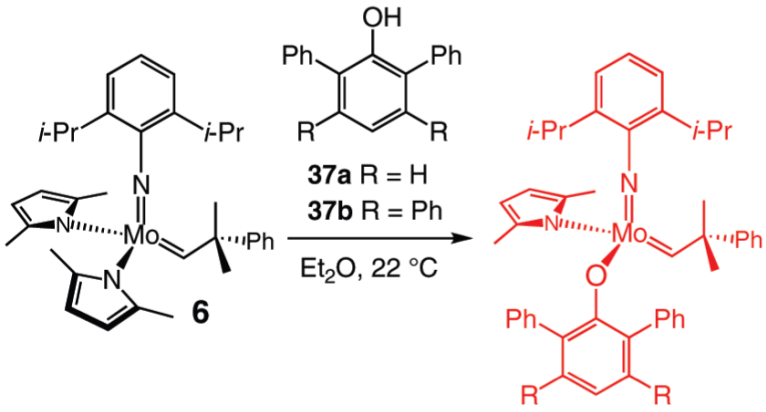
2.2.1. Initial Studies: We began our studies by treatment of **31** with 5 mol % **5**, which resulted in the formation of pyran **32** in 46% yield and >98% *endo* selectivity; a significant amount of oligomer generation accounts for complete consumption of the substrate. With the more sterically hindered monoaryloxide **28**, there is little or no competing oligomerization, but there is only 20% conversion to the desired product (>98% *endo*), and **32** is obtained in 15% yield. When enyne **34** is used, a similar trend in selectivity is observed (Scheme 5). The lower yield of the *endo* diene **35** versus that of **32** is likely because the sterically less hindered alkyne unit of **34** is more prone to undergo the intermolecular cross-metathesis reactions that deliver oligomeric products. As indicated in Scheme 5, when performed under an atmosphere of ethylene, RCM with Ru complex **7** affords the *exo* products with high efficiency; otherwise, only a complex mixture of products is obtained.[19]

2.2.2. Improved Mo-Catalyzed RCM Efficiency and Minimization of Competitive Oligomerization through the Use of Coordinating Solvents: To enhance the efficiency of RCM reactions of *O*-containing enynes, we first turned our attention to investigating the effect of the reaction medium in diminishing the rate of competitive oligomerization. We reasoned that, in the presence of a coordinating solvent, which might associate with the metal center, the steric requirements of the substrate coordination site as well as the Lewis acidity of the Mo might be altered, such that oligomerization reactions, for reasons delineated above regarding the preparation and examination of monoaryloxide **28** (Scheme 4), would be rendered relatively sluggish. We have successfully used the above strategy in enhancing the enantioselectivity of RCM reactions of dienes promoted by chiral Mo diolates.[20]

Whereas reactions performed in Et_2O proceed in a similar fashion as in benzene (Table 4, entries 1 and 5), when THF is used the desired RCM pathway becomes significantly more competitive: **32** and **35** constitute 76% and 46% of the mixture (entries 2 and 6, Table 4; vs 46% and 22%, respectively) and are isolated in 75% and 44% yield. The suggestion that the positive effect of THF is, at least partly, due to its coordinating ability is supported by the findings that, when 2-methyl-THF (entries 3 and 7, Table 4) and the more sizable 2,5-dimethyl-THF (entries 4 and 8) serve as solvent, reaction efficiency is improved.

2.2.3. Enhancement of RCM Efficiency and Minimization of Competitive Oligomerization through Catalyst Modification: We next turned our attention to altering the structure of the Mo catalyst. We reasoned that, although with alkylidene **28**, bearing a 2,6-di(isopropyl)phenoxide, formation of unsaturated pyran **32** is less efficient than when complex **5** is used (see Scheme 5), other modified catalyst structures might furnish superior selectivity based on the aforementioned rationales (see Scheme 4 and related discussion). Several monoaryloxides were thus prepared *in situ* through treatment of bispyrrolide **6** with the appropriate phenol (Table 5), and their ability to promote RCM of enyne **31** was investigated. In two cases (entries 1 and 4, Table 5), a substantial amount of unreacted enyne is recovered; with the catalyst derived from 2,3,5,6-tetraphenylphenol (entry 4, Table 5), the desired heterocycle **32** constitutes a substantial portion of the product mixture (55% conversion of the substrate, 32% yield of **32**). Furthermore, the Mo complex derived from 2,6-diphenylphenoxide (entry 3, Table 5) delivers the desired monomeric product **32** in 62% yield after purification (>98% *endo*; complete consumption of enyne **31**).

In light of the promising activity and selectivity levels furnished by the two modified stereogenic-at-Mo alkylidenes, we isolated and characterized complexes **38a**,**b** which, as illustrated in eq 3, are generated in 80% and 76% yield, respectively. The ability of **38a**,**b**, prepared and used *in situ*, to promote RCM reactions of a select number of *O*-containing enynes was then probed.



38a R = H: *1 h, >98% conv, 80% yield*
38b R = Ph: *4 h, >98% conv, 76% yield*

(3)

As the data in Table 6 indicate, the two modified monoaryloxides allow access to the desired *O*-substituted cyclic *endo* dienes in useful levels of efficiency; none of the corresponding *exo* product isomers are detected (as judged by analysis of 400 MHz ^{1}H NMR spectra). It is noteworthy that Mo-catalyzed RCM reactions of sterically congested vinylsilanes **39** and **41** (entries 5–8) proceed readily to afford the desired cyclic unsaturated siloxanes in up to 85% yield. A notable feature of the findings in Table 6 is the difficulty of gauging *a priori* whether the diphenylphenoxide **38a** (e.g., in the case of **31** and **41** in entries 1–2 and 7–8) or the more sterically hindered tetraphenylphenoxide **38b** promotes a more efficient reaction (e.g., with enynes **34** and **39** in entries 3–6). A significantly improved ability to predict the outcome of RCM reactions requires a more detailed understanding of the mechanistic nuances of the catalytic process, including the relationship between the structure of a Mo complex and the level of *endo*:*exo* selectivity.

Several additional points regarding the data in Table 6 merit mention: (a) The reaction performed in the presence of **38a** (entry 1, Table 6), although superior to that involving Mo complex **5** (62% vs 46% yield of **32**), remains less efficient than when **5** is utilized in THF (see entry 2, Table 4: 75% yield of **32**). In the RCM involving enyne **34**, however, it is the tetraphenylphenoxide **38b** that delivers **35** with the highest degree of efficiency (entry 4, Table 6: 67% yield vs 22% and 44% yield with alkylidene **5** in C_6H_6 and THF, respectively). (b) The amount of catalyst required depends on the structure of the substrate. Thus, 5 mol % loading is sufficient for achieving >98% conversion with enyne **34**, which bears the less sterically congested alkyne (vs 10 mol % for **31**). The same amount of **38a**,**b** engenders complete conversion in reactions of vinylsilanes **39** and **41** (entries 5–8, Table 6). The higher degree of efficiency observed for RCM of **39** (vs **31**) is likely due to the favorable entropic (Thorpe–Ingold) effects due to the tetrasubstituted Si-based tether within such substrates. Finally, it should be noted that use of complexes **38a**,**b** in THF (see Table 4) does not give rise to any additional increase in RCM efficiency. It is plausible that association of the Lewis basic solvent with the metal center is less favorable with the more sterically demanding aryloxide ligands.

3. Structural Attributes of Stereogenic-at-Mo Monopyrrolide Complexes

Several stereogenic-at-Mo complexes, bearing different *O*-based ligands, have played a critical role in the development of enyne RCM reactions described above. A brief analysis of some of the structural features of these alkylidenes is thus warranted. The X-ray structures of monopyrrolide monoalkoxide complex **5** as well as monoaryloxides **38a**,**b** are illustrated in Scheme 6. The structural details of complex **28** (Scheme 4) have been previously disclosed.[8a]

Selected bond lengths and angles are depicted in Scheme 6. Noteworthy is the relatively long Mo–O bond in 2,6-diphenylphenoxide **38a** and 2,3,5,6-tetraphenyphenoxide **38b**, a characteristic that is likely the result of minimization of unfavorable steric interactions between the sizable aryloxides and the other ligands. Similar considerations can be used to offer a rationale for the unusually large C–Mo–O angle in **38b** (115.03° vs ~109° for **5** and **28**). The above attributes can give rise to a more spacious binding pocket, allowing for facile RCM reactions of sterically demanding enyne substrates. Two noteworthy examples within this context are the reactions of vinylsilanes **39** and **41**, shown in entries 5–8 of Table 6. In contrast to RCM promoted by monopyrrolides **38a** and **38b** (>98% conversion, 61–85% yields), <2% consumption of the substrates is observed with Mo-based complexes **5** and **28** (as well as the Ru-based carbene **7**).

Somewhat surprisingly, Mo complex **38a** (138.51°) has the smallest Mo–O–C and C–Mo–O angles of the four complexes. This unusual attribute may be due to π-stacking associations[21] between the phenyl unit of the neophylidene substituent and the aryloxide group, as suggested by the distance between these two aromatic planes (see X-ray of **38a**, Scheme 6). Such an interaction would be less favored with the sterically more demanding tetraphenylphenoxide of **38b**. It is important to note that, upon initiation and loss of the neophylidene group, the Mo–O–C angle of the complexes derived from **38a** would likely resemble that of **38b**. Thus, in general, whereas the bond length values shown in Scheme 6 may prove to be relevant to the properties of the catalytically active complex in solution, the corresponding bond angles might be largely influenced by crystal packing forces and steric interactions that arise from the presence of the neophylidene unit. One set of observations supports the validity of such a caveat: The alkylidene proton in **38b** resides only ~28 Å above the π surface of an aryl unit of the aryloxide ligand, as observed in the X-ray structure of this complex (Scheme 6), and would thus be expected to appear more upfield as a result of well-established anisotropic effects. The ^{1}H NMR spectrum of **38b** (in C_6D_6), however, exhibits a signal at δ 11.67 ppm, which is closely related to the chemical shifts detected for the alkylidene proton in **38a** (δ 11.70 ppm).

4. Enantioselective Mo-Catalyzed Enyne RCM Reactions

Varying degrees of progress have been achieved in connection with enantioselective versions of several types of olefin metathesis reactions.[22-24] One subset of transformations that has not yet yielded to enantioselective catalysis is the RCM reactions of enynes. Based on the outcome of the investigations summarized above, and encouraged by the recent discoveries regarding the exceptional ability of stereogenic-at-Mo complexes to promote enantioselective RCM[9a-b] and ring-opening/cross-metathesis reactions of olefinic substrates,[9c] we set out to establish whether the same class of chiral alkylidenes can promote the formation of enantiomerically enriched cyclic *endo* dienes.

Treatment of dienyne **43** with 10 mol % of **44a**, prepared and used *in situ*, leads to complete consumption of the substrate (Scheme 7). The product from enantioselective RCM affords the *endo* cycloadduct **45** in 79:21 enantiomer ratio (er) and 30% yield after purification; a significant portion of the product mixture consists of oligomeric materials. We then surmised that if the RCM process is performed under an atmosphere of ethylene (vs N_2), the efficiency with which the monomeric heterocycle is generated might be improved. This strategy,

previously utilized in relation to Ru-catalyzed enyne metathesis reactions,[14c] is based on the principle that initial cross-metathesis of the alkyne unit with ethylene might deliver tetraene **46** (Scheme 7), which would undergo RCM to generate endocyclic product **45**. Increased RCM efficiency would arise from the more expeditious removal of the terminal alkyne, largely responsible for the formation of oligomeric side products. When RCM of **43** is carried out under an atmosphere of ethylene (Scheme 7), unsaturated tosylpiperidine **45** is isolated in 60% yield (vs 30% under N_2) in the same degree of enantiomeric purity (79:21 er). Enantioselectivity is improved with di-iodo complex **44b**: the *endo* product is obtained in 85:15 er. Although unreacted substrate is recovered when **44b** is used (69% conversion), there is minimal oligomerization: *endo* product **45** is formed in 63% yield after purification (Scheme 7). It should be noted that, despite repeated attempts, we did not detect the purported diene intermediate **46** (see below for an additional related observation).

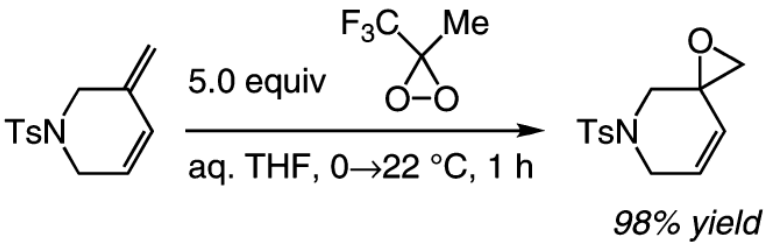
Next, we evaluated the corresponding transformation of dienyne **47**, which bears two 1,1-disubstituted alkenes (vs terminal olefins in **43**, Scheme 7). As shown in Scheme 8, treatment of **47** with 10 mol % **44a** under an atmosphere of ethylene gives rise to >98% conversion within 2 h at 22 °C. Tetraene **48** is isolated in 70% yield, and none of the expected RCM product is detected (**49**, as judged by analysis of the 400 MHz ^{1}H NMR spectrum of the unpurified mixture). Resubjection of **48** to 5 mol % **44a**, this time under an atmosphere of N_2, gives rise to formation of **49** in >98% *endo* selectivity, 92% yield, and 98:2 er. Minimal oligomerization is observed in the transformations depicted in Scheme 8. It should be noted that there is <10% conversion when **47** is subjected to 10 mol % **44a** at 22 °C under an atmosphere of N_2; longer reaction times do not lead to additional transformation. The origin of the aforementioned lack of reactivity is not clear at the present time; it is feasible, however, that initial oligomerization leads to formation of an unreactive Mo alkylidene, resulting in sequestration of all catalytically competent complexes. The two-step procedure shown in Scheme 8 can be carried out in a single vessel: treatment of **47** with 10 mol % **44a** in benzene under ethylene atmosphere for 10 min, followed by removing the balloon and allowing the mixture to stir for 12 h, delivers **49** in 62% yield and 95:5 er.

Initial investigations indicate that use of an ethylene atmosphere as the means to improve the efficiency of an enyne RCM process does not apply to all substrate classes. As an example, when *O*-containing enyne **34** (Table 6) is subjected to 10 mol % Mo-based monopyrrolide complex **38b** (prepared and used *in situ*, as with **44a**,**b**) under an ethylene atmosphere, after 2 h at 22 °C, there is >98% substrate consumption but *endo* product **35** is obtained in 42% yield (vs 67% yield under N_2; see entry 4, Table 6). It is plausible that sterically less congested alkynes (e.g., those bearing an allylic ether vs an NTs unit) undergo oligomerization at a rate with which ethylene cross-metathesis cannot effectively compete.

Attempts to promote Mo-catalyzed enantioselective RCM reactions of the related enyne substrates bearing all-carbon or *O*-containing tethers proved significantly less selective (<65:35 er). Clearly, development of chiral catalyst variants that exhibit a wider range of substrate generality is required; studies along these lines are in progress.

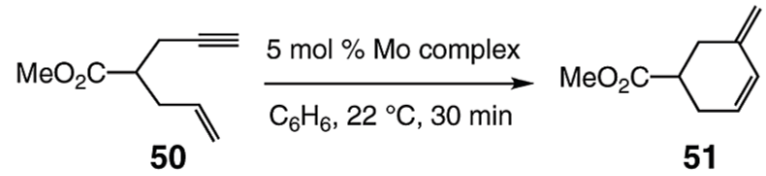
Conclusions

We report the first *endo*-selective set of protocols for catalytic RCM of enynes, including those that bear an *N*- or an *O*-based tether. Cyclization reactions typically proceed with high *endo*:*exo* selectivity and in yields that render the method of utility, particularly since, in most instances, the Ru-catalyzed reactions deliver the corresponding *exo* products. The *endo* cyclic dienes, as illustrated by the highly site-selective oxidation[25] in eq 4, can be functionalized to allow access to a range of useful heterocyclic small organic molecules (e.g., through alkylations or substitution reactions of the allylic epoxide).[26]



(4)

Reactions are promoted by stereogenic-at-metal monoalkoxide– or monoaryloxide–monopyrrolide Mo complexes, prepared from the corresponding bispyrrolide (**6** in Scheme 2) and the appropriate alkyl or aryl alcohols. Isolation and purification of the metal complexes is not required, as they can be synthesized and used *in situ*. The above characteristic, together with the fact that the Mo-based catalysts bear only monodentate ligands, lends itself to facile modification of the catalyst structure. The latter attribute has been used in this study to alter the catalyst structure in order to maximize the efficiency of certain enyne RCM reactions (e.g., Tables 5and 6). The present investigations have therefore led to identification of several new catalyst variants that enhance the utility of this class of transformations. An additional example is provided in eq 5. Catalytic RCM of enyne **50** with Mo complex **5** affords diene **51** in only 45% yield as a result of a significant oligomerization, likely due to the absence of the quaternary carbon, which facilitates intramolecular cyclization (compare to RCM of **1** in Scheme 2). The catalysts bearing substituted phenoxide ligands, however, promote formation of **51** with substantially higher efficiency; complex **38a** furnishes the desired product in 80% yield with a similarly exceptional degree of *endo* selectivity.



with complex **5**: *>98% conv, endo:exo = >98:<2, 45% yield*
with complex **38a**: *>98% conv, endo:exo = >98:<2, 80% yield*
with complex **38b**: *>98% conv, endo:exo = >98:<2, 65% yield*

(5)

The first examples of enantioselective enyne RCM reactions are presented as well. Products are obtained in up to 98:2 er and >98:<2 *endo*:*exo* selectivity through desymmetrization reactions of *N*-containing dienynes in transformations promoted by enantiomerically pure stereogenic-at-Mo complexes, which have been shown to be exceptionally effective for RCM of various diene substrates. Many shortcomings remain to be addressed, including identification of catalysts that promote enantioselective reactions of enynes with *O*-containing tethers, a class of substrates particularly prone toward oligimerization. It is important to note that not only will discovery and development of new chiral catalysts be beneficial to enantioselective variants of *endo*-selective enyne RCM reactions, but such chiral complexes may prove to be superior catalysts in general and highly effective in cases where the desired product is achiral. Every Mo complex used in the present investigation is chiral; this class of chiral catalysts, used in the racemic form, promotes efficient *endo*-selective reactions. As has been described previously, the stereogenic Mo center and the attendant stereoelectronic

attributes of such chiral catalysts render the complexes examined here effective RCM catalysts.[9b,c] These investigations provide a clear example of the principle that chiral catalysts should not be considered as potentially viable solutions only in cases where control of enantioselectivity is desired.

Future studies will be directed toward the design of more efficient catalysts for enyne RCM reactions, further development of the enantioselective variants, and applications to the synthesis of biologically active molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The NIH (GM-59426) provided financial support. We are grateful to Dr. Bo Li (Boston College) for obtaining the X-ray crystal structures. We thank S. J. Malcolmson and S. J. Meek (Boston College) for valuable discussions. Mass spectrometry facilities at Boston College are supported by the NSF (DBI-0619576).

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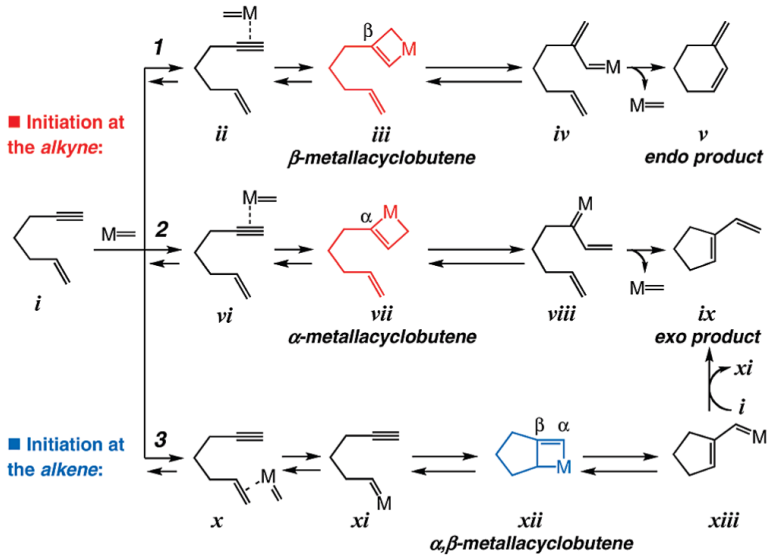
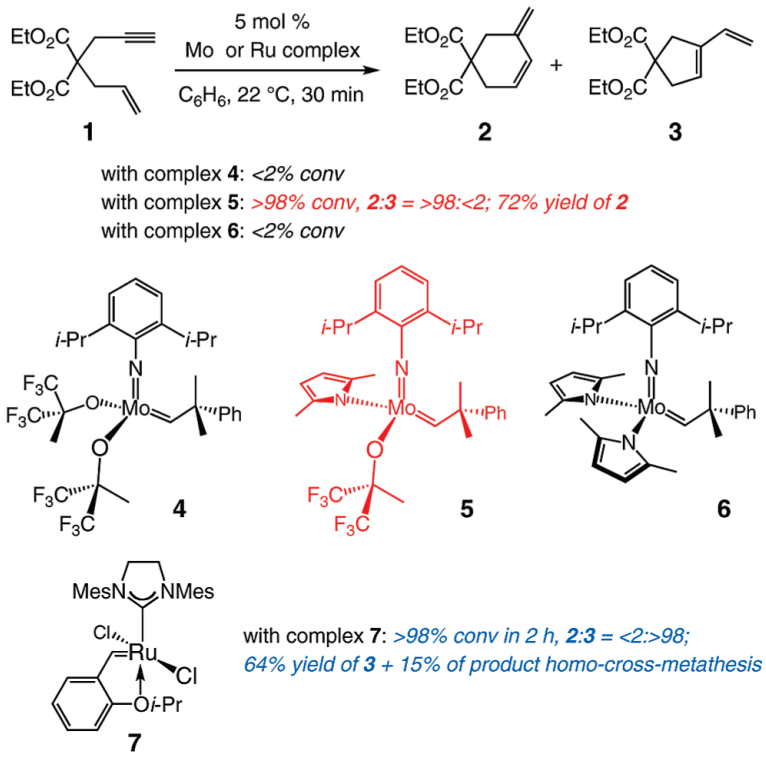


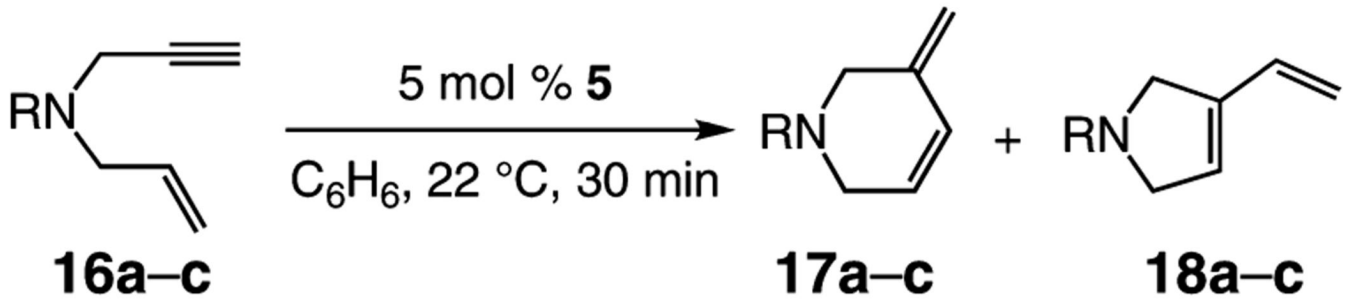
Scheme 1.
Various Modes of Reaction in Metal-Catalyzed Enyne RCM



Scheme 2.

Mo and Ru Complexes as Enyne RCM Catalysts[a]

[a] Mes = 2,4,6-$(Me)_3C_6H_2$.



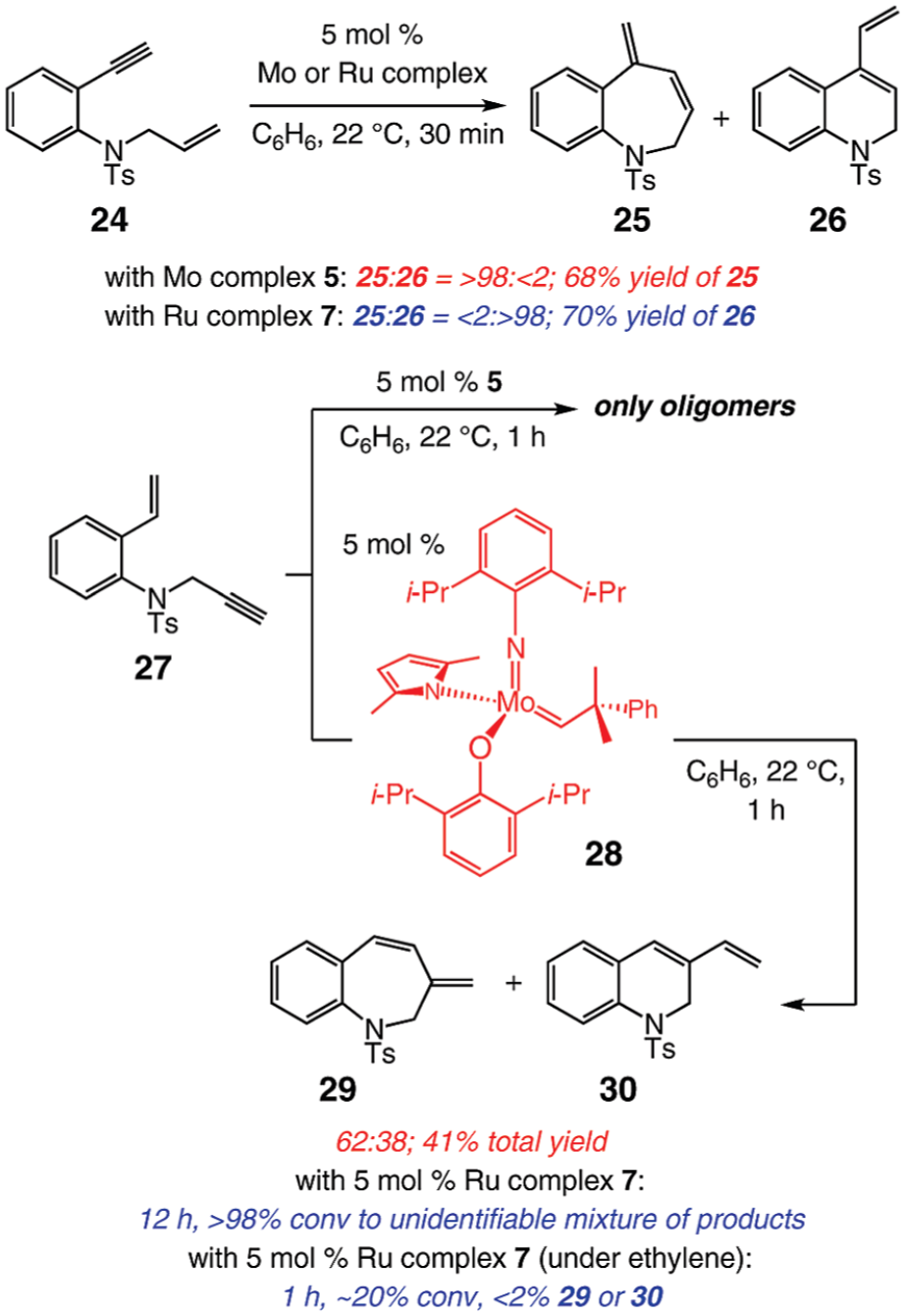
R = Ts (**a**): **17a**:**18a** = *>98:<2; 92% yield of* ***17a***

R = *o*-Ns (**b**): **17b**:**18b** = *97:3; 85% yield of* ***17b***

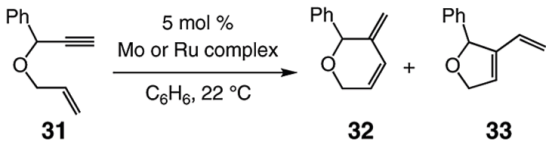
R = Boc (**c**): **17c**:**18c** = *>98:<2; 48% yield of* ***17c***

>98% substrate consumption in all cases

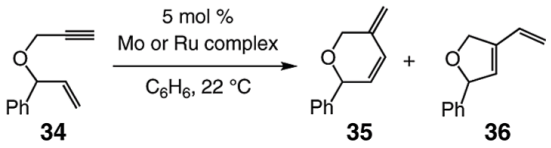
Scheme 3.
Initial Examination of Mo-Catalyzed RCM of Various *N*-Containing Enynes



Scheme 4.

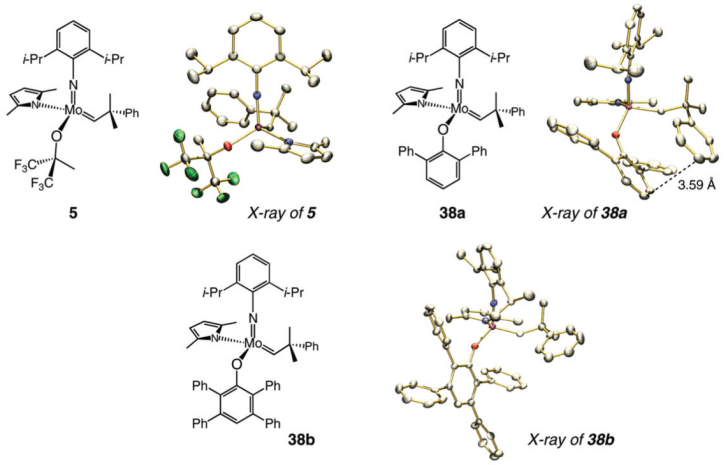


with Mo complex **5**: *10 h, >98% conv, **32:33** = >98:<2; 46% yield of **32***
with Mo complex **28**: *12 h, 20% conv, **32:33** = >98:<2; 15% yield of **32** (<2% oligomer)*
with Ru complex **7**: *12 h, >98% conv, **32:33** = <2:>98, 15% yield of **33***
with Ru complex **7** (under ethylene): *1 h, >98% conv, **32:33** = <2:>98, 70% yield of **33***



with Mo complex **5**: *3 h, >98% conv, **35:36** = >98:<2; 22% yield of **35***
with Mo complex **28**: *12 h, 50% conv to oligomers*
with Ru complex **7**: *12 h, 60% conv, **35:36** = <2:>98, 12% yield of **36**, 13% product homo-cross-metathesis*
with Ru complex **7** (under ethylene): *1 h, >98% conv; 54% yield of **36**, 20% product homo-cross-metathesis*

Scheme 5.
Initial Study of Mo-Catalyzed RCM of *O*-Containing Enynes[a]
[a] All reactions performed under N_2 atmosphere, unless otherwise noted.



Bond Lengths

	5 (Å)	28 (Å)	38a (Å)	38b (Å)
Mo–N (imido)	1.723	1.736	1.733	1.720
Mo–C	1.863	1.892	1.863	1.880
Mo–O	1.916	1.915	1.942	1.923
Mo–N (pyrrolide)	2.018	2.037	2.028	2.048

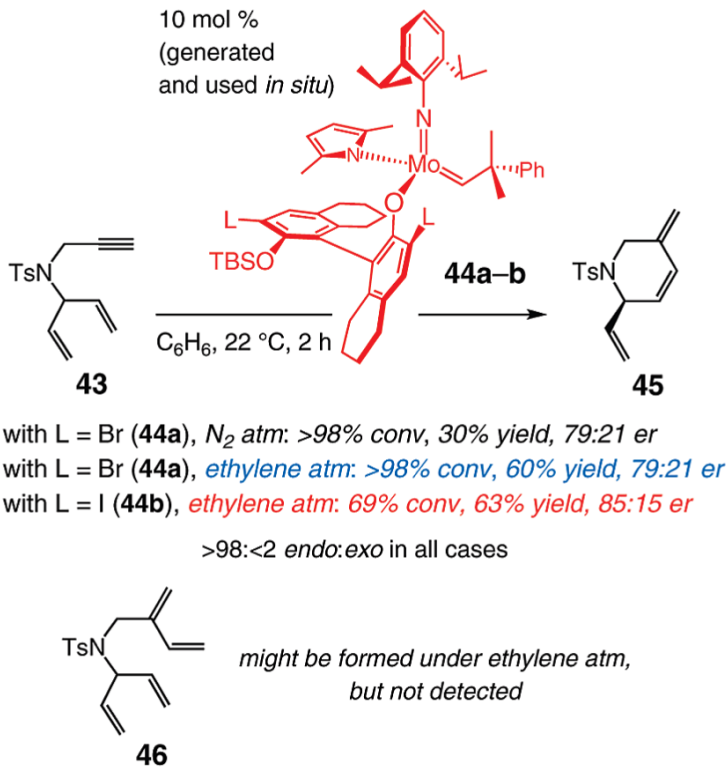
Bond Angles

	5 (°)	28 (°)	38a (°)	38b (°)
Mo–N–C (imido)	175.33	172.57	168.54	172.34
Mo–O–C	151.32	143.58	138.51	157.23
Mo–C–C	146.33	139.48	147.85	145.34
Mo–N–C (pyrrolide)	137.23	135.28	137.40	135.74
C–Mo–O	108.72	108.85	106.35	115.03

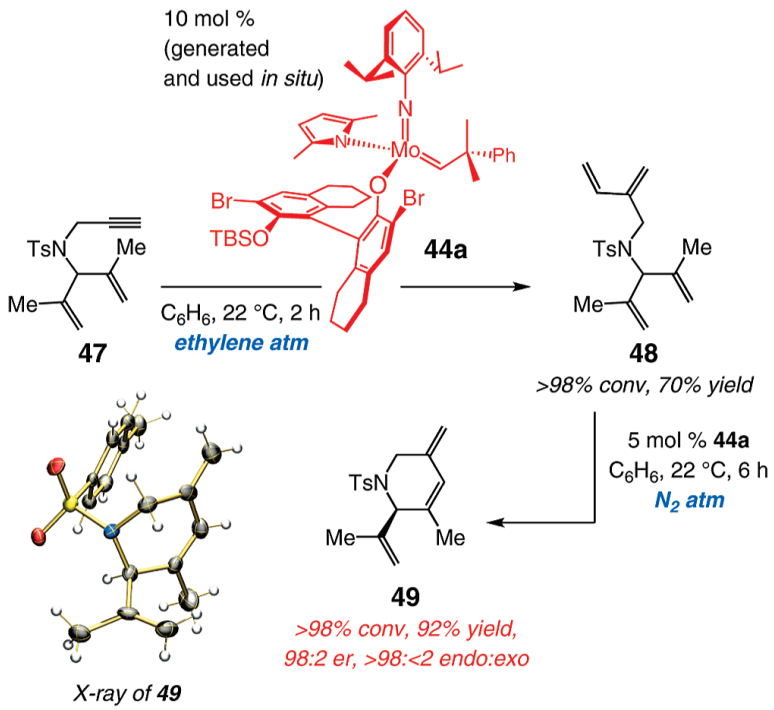
Scheme 6.

X-ray Structures and Select Physical Properties of Mo-Based Monopyrrolides[a]

[a] See the Supporting Information for details regarding the X-ray structures of complexes **5**, **38a**, and **38b**.

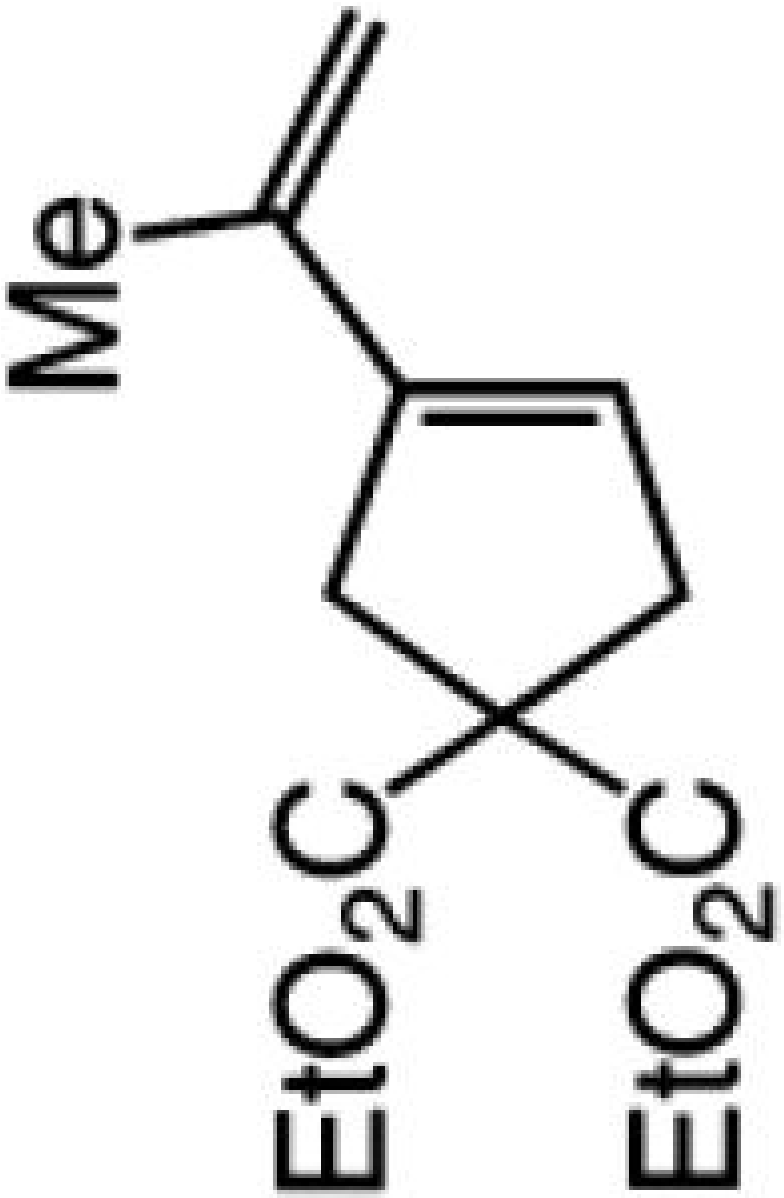


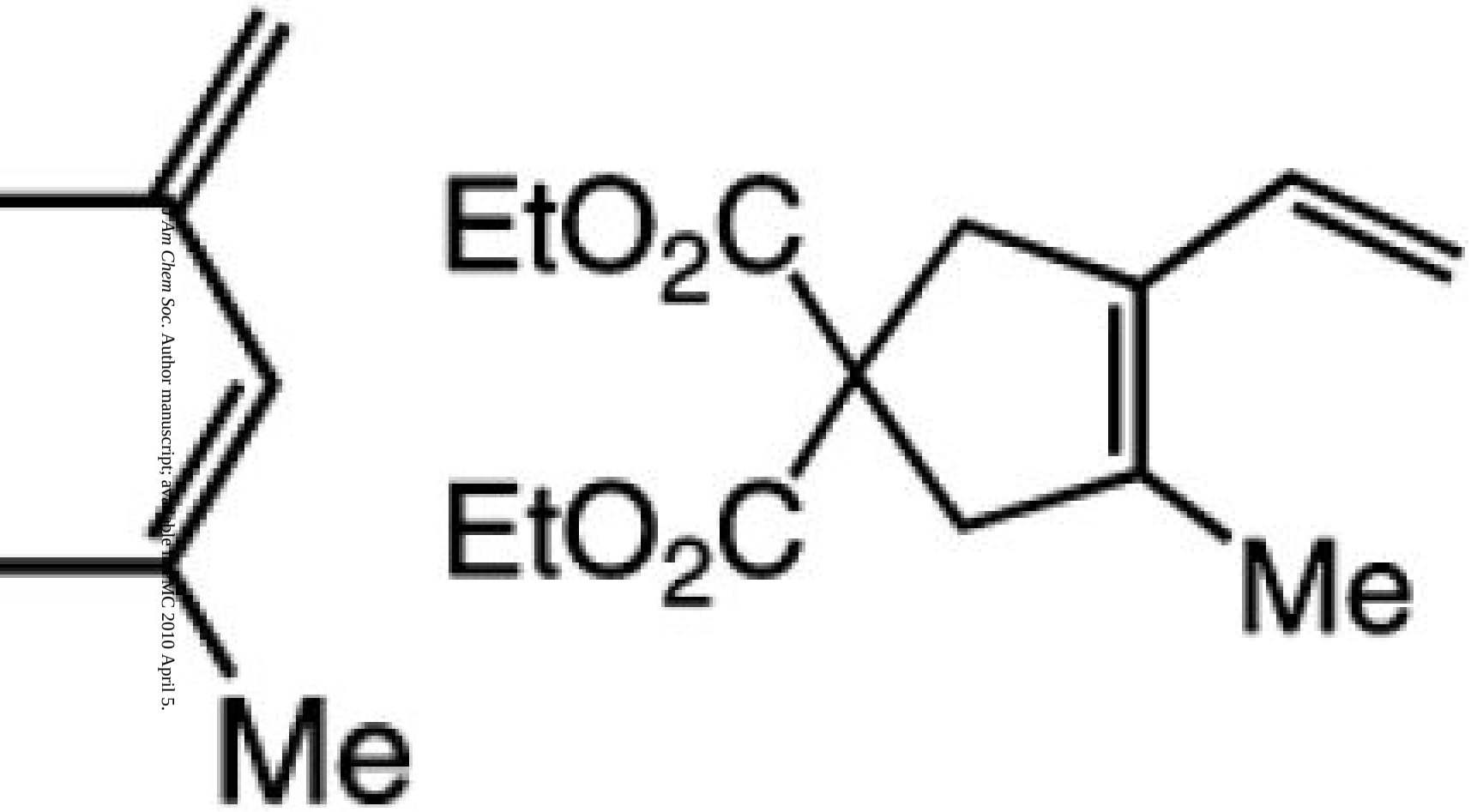
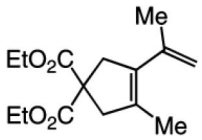
Scheme 7.
Mo-Catalyzed Enantioselective RCM of a Dienyne



Scheme 8.
Effect of Ethylene on Catalytic Cross-Metathesis/Enantioselective RCM of a Dienyne

exo product	*endo*:*exo*[b]	yield (%)[c]
	>98:<2	70

exo product	*endo*:*exo*[b]	yield (%)[c]
	75:25	80[d]

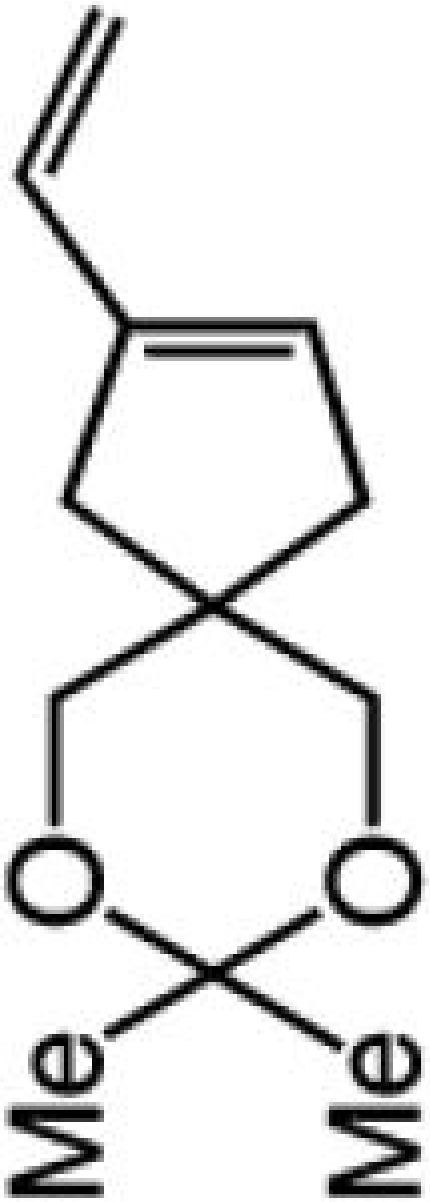
	exo product	*endo*:*exo*[b]	yield (%)[c]
		>98:<2	82
		>98:<2	75

[b] Ratios were determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures prior to purification.

[c] Yield of isolated products after purification.

[d] Combined yields of the product mixture.

[e] Reaction performed with 20 mol % **5**.

exo product	*endo*:*exo*[b]	yield (%)[c]
	>98:<2	81

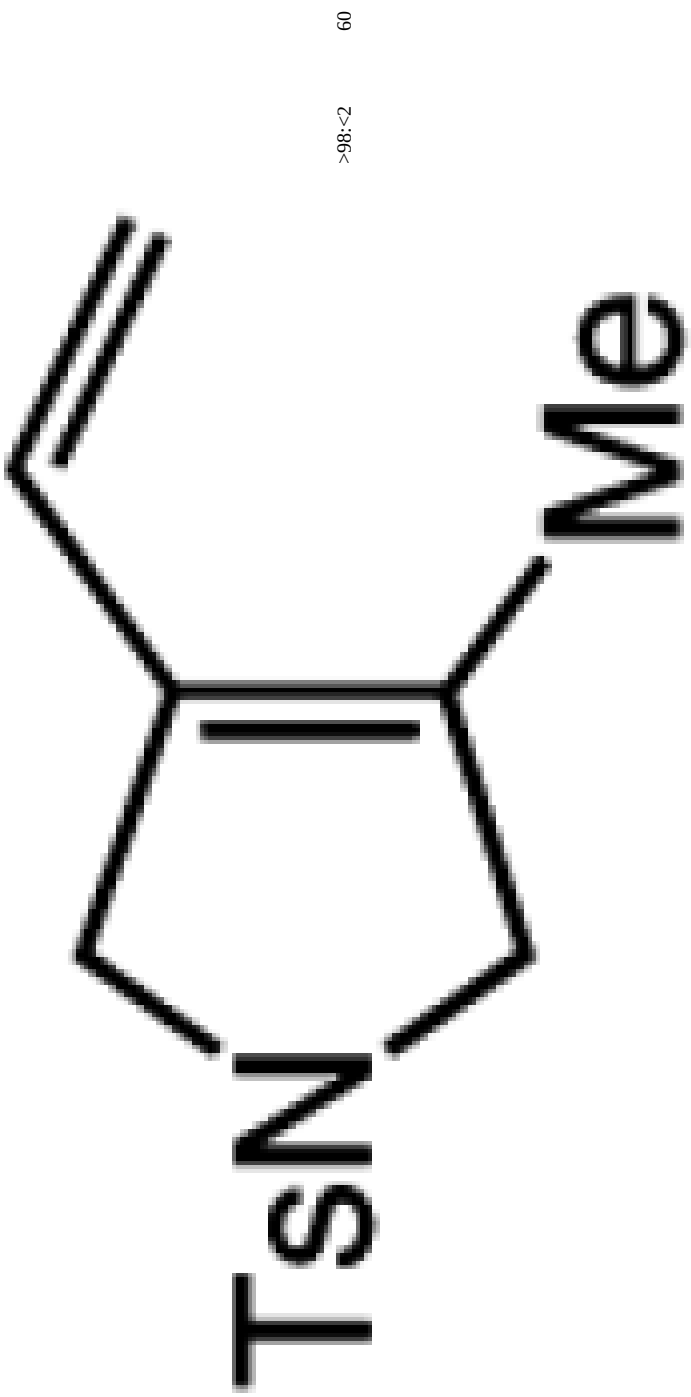
exo product	*endo*:*exo*[b]	yield (%)[c]
	75:25	75[d]

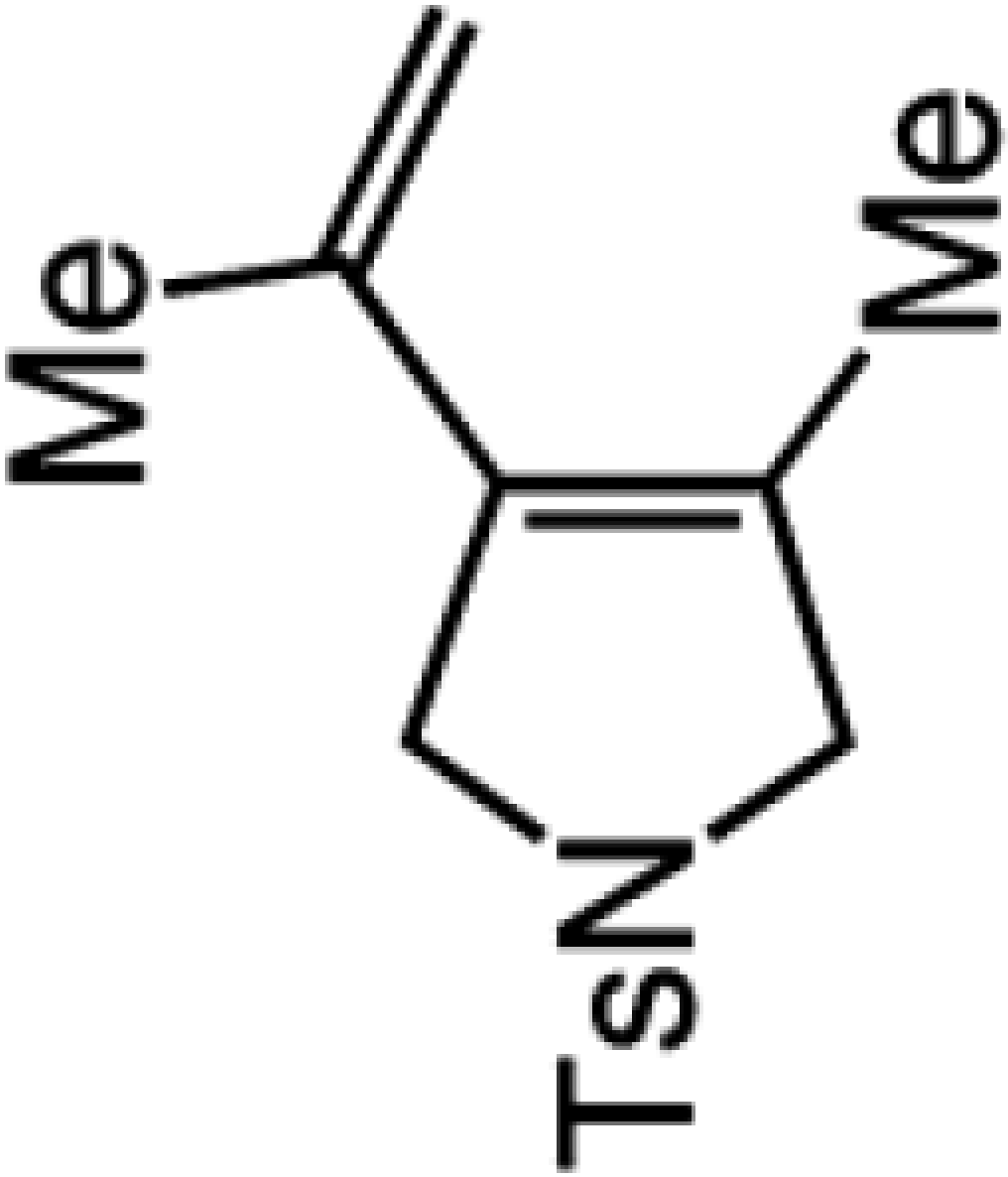
exo product	*endo*:*exo*[b]	yield (%)[c]
	66:33	72[d]
	>98:<2	81

[c] Yield of isolated products after purification.

[d] Combined yields of the product mixture.

exo product	*endo*:*exo*[b]	yield (%)[c]
	>98:<2	80
	84:16	90[d]

exo product	*endo*:*exo*[b]	yield (%)[c]
	>98:<2	60

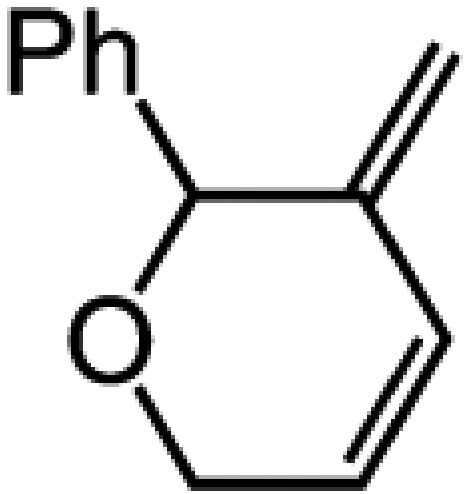
exo product	*endo*:*exo*[b]	yield (%)[c]
	>98:<2	77

[c] Yield of isolated products after purification.

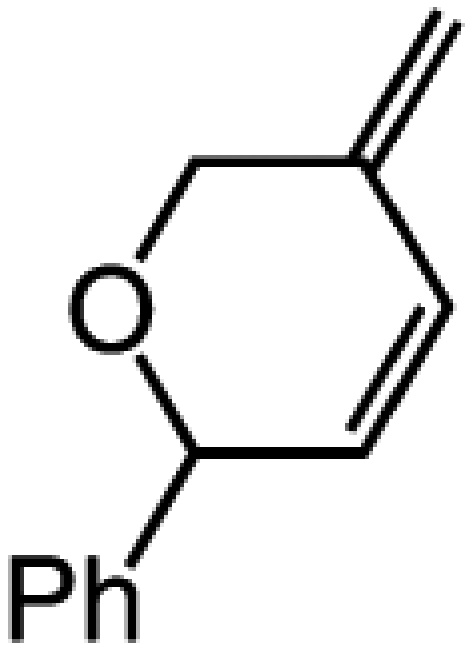
[d] Combined yields of the product mixture.

Table 4

Solvent Effect in Mo-Catalyzed RCM of *O*-Containing Enynes Promoted by Mo–Monoalkoxide Complex **5**[a,b]

entry	*endo* product	solvent	time (h)	*endo*:*exo*[b]	conv (%);[b] yield (%)[c]
1		Et_2O	12	>98:<2	40; nd
2		THF	12	>98:<2	76; 75
3		2-MeTHF	10	>98:<2	55; nd
4		2,5-Me_2THF	10	>98:<2	48; nd

32

entry	*endo* product	solvent	time (h)	*endo*:*exo*[b]	conv (%);[b] yield (%)[c]
5		Et_2O	4	>98:<2	21; nd
6		THF	6	>98:<2	46; 44
7		2-MeTHF	3	>98:<2	31; nd
8		2,5-Me_2THF	3	>98:<2	29; nd

35

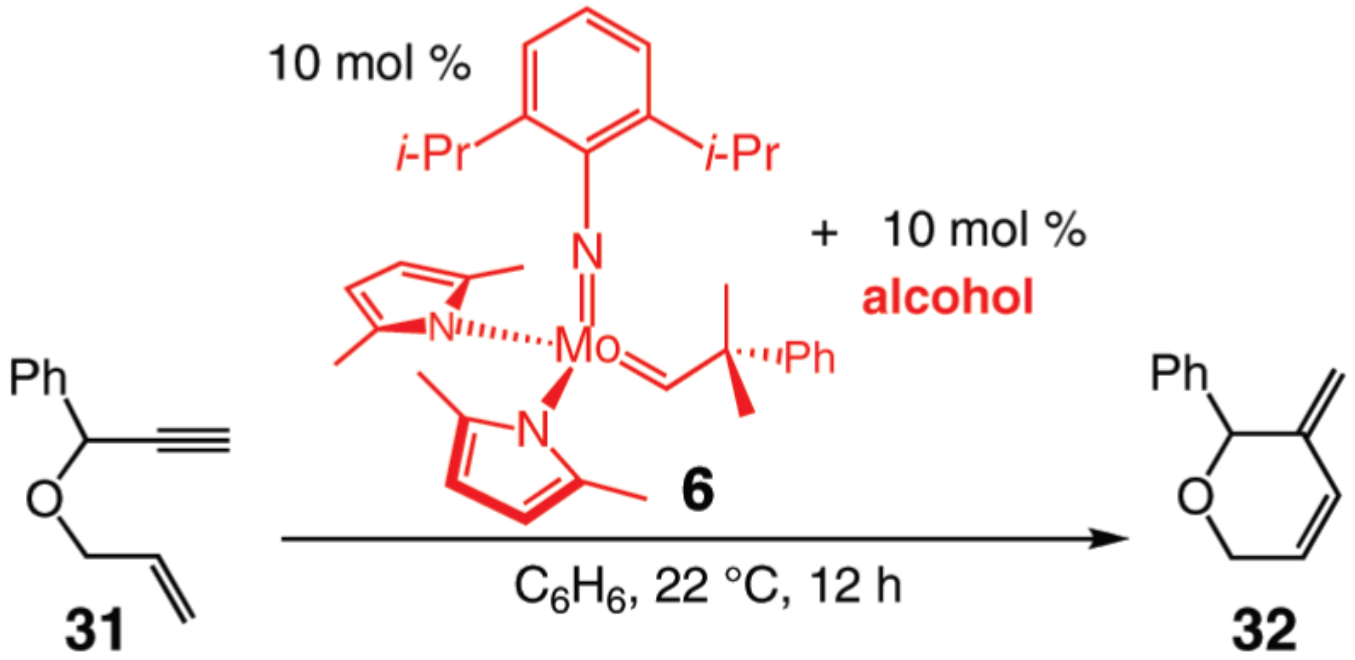
[a] Reactions were performed under N_2 atmosphere with 5 mol % **5** for 30 min in C_6H_6 at 22 °C.

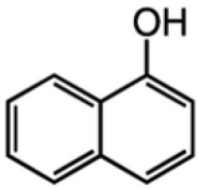
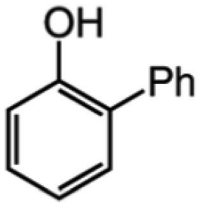
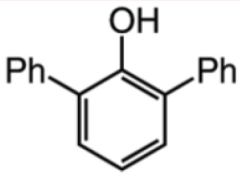
[b] Ratios were determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures prior to purification.

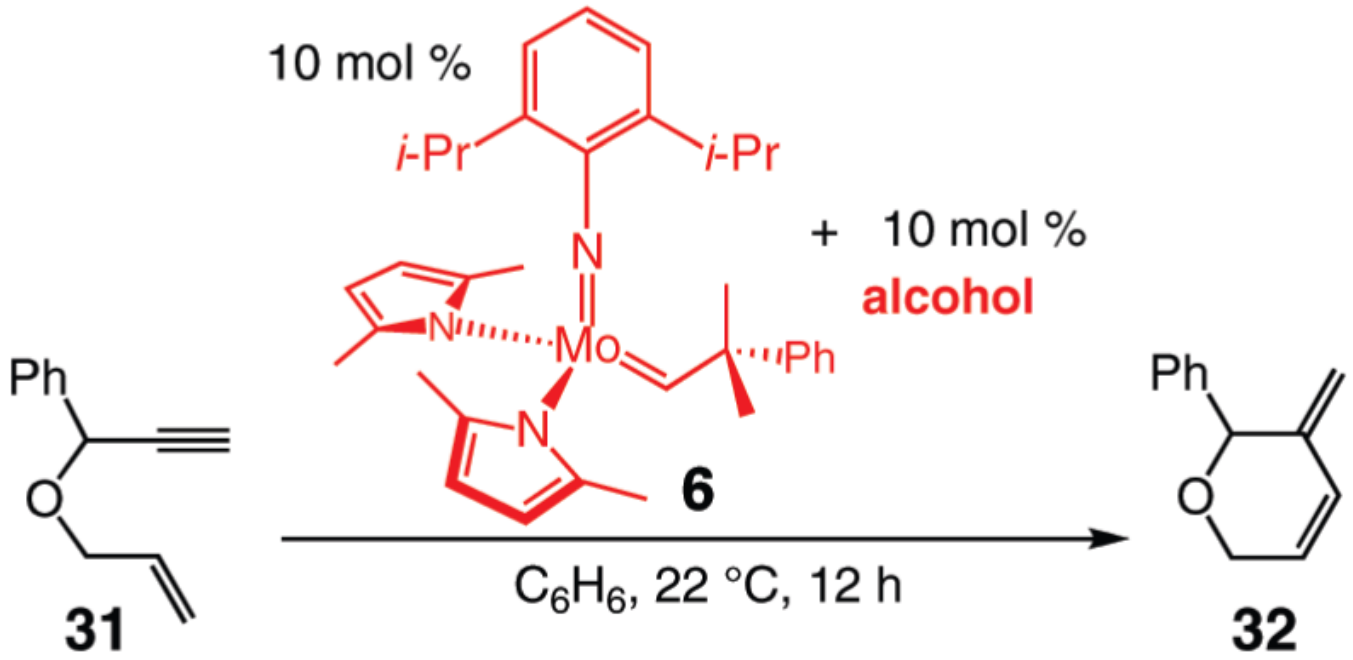
[c] Yields of purified *endo* products; >98% substrate consumption in all cases (400 MHz ^{1}H NMR analysis). nd = not determined.

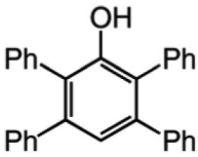
Table 5

Effect of Aryloxide on Efficiency of Catalytic RCM of **31**[a-c]



entry	alcohol	conv (%)[b]	yield (%)[c]
1		12	nd
2		>98	43
3		>98	62



entry	alcohol	conv (%)[b]	yield (%)[c]
4		55	32

[a] Reactions were performed under N_2 atmosphere with 5 mol % **5** for 30 min in C_6H_6 at 22 °C.

[b] Ratios were determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures prior to purification.

[c] Yield of isolated products after purification.

Table 6

substrate	*endo* product	Mo complex; mol (%)	conv (%);[b] time (h)	*endo:exo*[b]	yield (%)[c]
31	**32**	**38a**; 10	>98; 12	>98:<2	62
		38b; 10	55; 12	>98:<2	32

substrate	*endo* product	Mo complex; mol (%)	conv (%);[b] time (h)	*endo:exo*[b]	yield (%)[c]
	35	**38a**; 5	>98; 3	>98:<2	43
		38b; 5	>98; 3	>98:<2	67

substrate	*endo* product	Mo complex; mol (%)	conv (%);[b] time (h)	*endo*:*exo*[b]	yield (%)[c]
39	**40**	**38a**; 5	>98; 1	>98:<2	75
		38b; 5	>98; 1	>98:<2	85

substrate	*endo* product	Mo complex; mol (%)	conv (%);[b] time (h)	*endo*:*exo*[b]	yield (%)[c]
41	**42**	**38a**; 5	>98; 3	>98:<2	67[d]
		38b; 5	>98; 6	>98:<2	61[d]

[a] Reactions were performed under N_2 atmosphere with 5 mol % **5** for 30 min in C_6H_6 at 22 °C.

[b] Ratios were determined by analysis of 400 MHz ^1H NMR spectra of unpurified mixtures prior to purification.

[c] Yield of isolated products after purification.

[d] Mixture of diastereomers (~60:40; stereogenic at Si).