Ruthenium-Promoted Ring-Closing Metathesis of Ene-Dienes. Competitive Intramolecular Regioselection as a Function of Chain Length

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Abstract: The course of ring-closing metathesis of a series of ene-dienes has been examined for its regio- and stereoselectivity. Each example studied gave rise predominantly or exclusively to a cyclization product of a specific structural type. Each of the four possible mechanistic pathways are represented. Thus, **11a** furnished the (*Z*)-monoene **12** in good yield without any evidence for formation of a 10-membered ring diene. For **11b**, the kinetic preference lies very much in favor of producing the (*E,Z*)-diene **13**. Systematic chain extension to the level of **11c** is met with a return to preferred cycloalkene production, but now *E*-configured. As concerns **11d**, the longest-chain homologue examined, ring-size effects are less distinctive and both monoene **15** and diene **16** are formed, the latter being favored by a factor of 4:1. These experimental results indicate that chain length significantly influences the regiochemical and stereochemical course of intramolecularly competitive metathesis reactions.

Keywords: cyclization; ene-dienes; metathesis; regioselectivity

As the level of attention directed to the deployment of metal-catalyzed ring-closing metathesis (RCM) continues to expand, more probing aspects of this powerful synthetic transformation come under investigation. The distinct advantages of catalyst design have been extensively demonstrated.[1,2] Substitutions directly on the double bonds[3] and at the somewhat more remote allylic sites[4] have been evaluated to some degree. Ring-size influences[5] and the *E/Z* stereoselectivity of these cyclizations[6] have come under rather intense scrutiny. At the present time, catalytic asymmetric olefin metathesis is becoming established as highly utilitarian,[7] and tandem catalysis applications have just surfaced.[8]

As an extension of our work directed toward useful synthetic applications of the RCM process,[4b,9] we initiated a systematic study designed to explore the intramolecularly competitive cyclization of ene-dienes as a function of chain length. Our purpose for entering into this investigation was to gain a greater appreciation of the kinetically more favored reaction pathway that operates when the ruthenium catalyst has the intrinsic capacity to follow several cyclization alternatives. Three conceptually related reports have appeared. The Mioskowski group discovered that when C- and O-membered ring cyclizations are possible, formation of the heterocycle is favored over the carbocycle.[10] In their quest for macrolide analogues of the sanglifehrins, Wagner et al. noted that different ring-sized products were formed as a function of the metathesis catalyst.[11] The route devised by Danishefsky to synthesize radicicol and monocillin I involved intramolecular ring closure of a pair of ene-dienes.[12] Only the most active ruthenium catalyst[2] promoted reaction to give (*Z,E*)-14-membered lactones.

In the specific case of an ene-diene substrate, the catalyst can react with the isolated double bond to generate a species of type **2**. This reactive intermediate may then capture the more proximal or the more distal electron-rich conjugated double bond and generate one or more members of the stereoisomeric ruthenacyclobutane pairs **3**/**4** or **5**/**6** (Scheme 1).

Since each olefinic segment of the diene is disubstituted and of *E* geometry, differences in reactivity stemming from steric and electronic differences within these sectors were expected to be minimal. On the other hand, incremental increases in the length of the upper side chain, as determined by the value of *n*, were certain to play more than a bystander role. The consequences of ring strain on the ease of cyclization of bifunctional chain molecules has been a topic of long-standing interest.[13] Notwithstanding, the mechanistic details associated with Scheme 1 differ fundamentally from those associated with the many ring closures examined heretofore. Thus, it was anticipated that the regio- and

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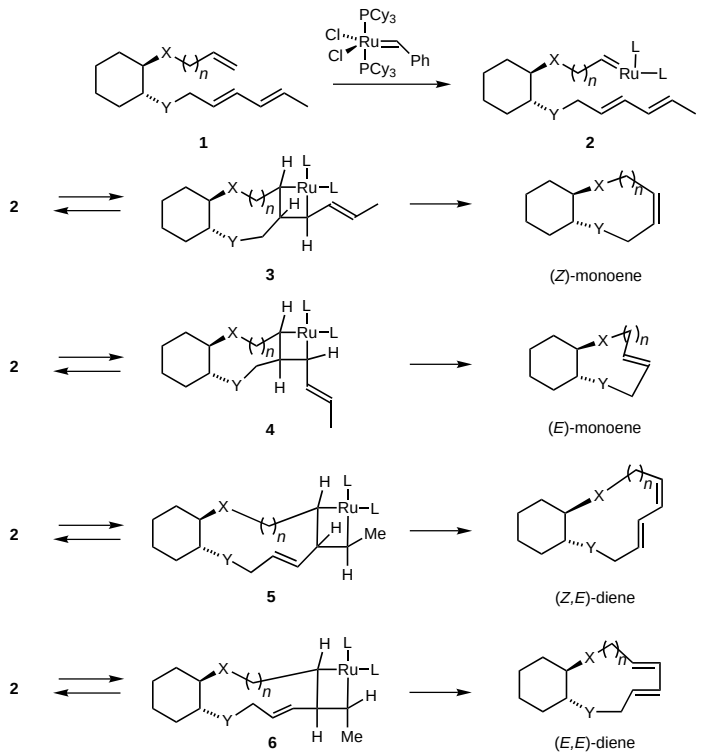


Scheme 1.

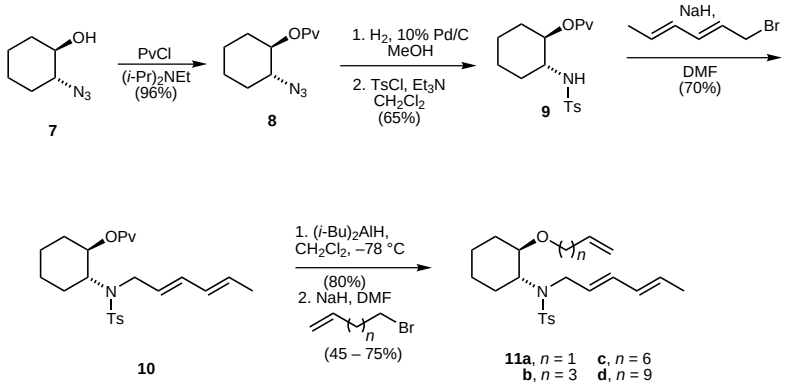
stereoselective course of the RCM reactions to be examined, as revealed by product composition, would show the extent to which competitive metal-promoted cyclizations are affected by chain length. The possibility of reversible involvement of the monoene and diene products in metathesis is not considered here.

The requisite substrates were prepared as outlined in Scheme 2. Reaction of cyclohexene oxide with sodium azide in refluxing aqueous ethanol according to an established protocol[14] resulted in conversion to the azido carbinol **7**. Subjection of this substrate in turn to chemoselective *O*-pivaloylation, catalytic hydrogenation, and *N*-tosylation[15] delivered the generic intermediate **9**. Addition of (*E,E*)-1-bromo-2,4-hexadiene[16] to the sodium salt of **9** gave rise to the desired **10** in good yield. Following Dibal-H reduction to unmask the hydroxyl group,[17] arrival at **11** was brought about by coupling to the appropriate ω-alkenyl bromide in the presence of sodium hydride with DMF as solvent.[18]

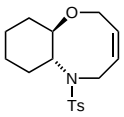
All of the RCM reactions were performed identically at a substrate concentration of 0.003 M in the presence of 20 mol percent bis(tricyclohexylphosphine)benzylidene-ruthenium(IV) chloride. A solution of each ene-diene was introduced into a refluxing solution of the catalyst in CH_2Cl_2 during 12 h via a syringe pump and under a nitrogen atmosphere. Removal of the spent ruthenium was achieved by exposure of the reaction mixtures to lead tetraacetate[9d] prior to chromatographic purification.

Under these conditions, **11a** was cleanly converted into the (*Z*)-monoene **12** (71% isolated yield). No unreacted starting material was seen, and the balance of the product is therefore considered to be oligomeric. The *cis* geometry of the lone double bond in **12** was readily apparent from its ^{1}H NMR spectrum. Its two olefin protons appear as two widely spaced multiplets centered upfield and downfield of 5.5 ppm. The *trans* isomer would be characterized by a narrow multiplet of area 2 in the center of this region.[9a,19]

The presence of two additional methylene groups as in **11b** already exerts a striking influence on the course of cyclization. This homologue is less reactive than **11a**, as judged by the recovery of 20% of unchanged ene-diene. As before, only one monomeric product was isolated, the (*Z,E*)-diene **13** (33%). Accordingly, oligomer production had now advanced to the 47% level. The ^{1}H NMR spectrum of **13** features three relevant multiplets. Two of these, each of unit area 1, are positioned at $\delta = 7.12 - 6.98$ and $6.24 - 6.17$, and are attributable to the central olefinic protons of the diene. Twice as intense is the third multiplet positioned at $\delta = 5.51 - 5.36$, which originates from the remaining vinylic hydrogens. Irradiation at $\delta = 6.2$ caused the downfield signal to collapse to a doublet ($J = 15.5$ Hz) and the reciprocal experiment



Scheme 2.



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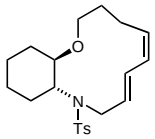

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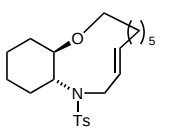
at $\delta = 7.0$ left a doublet ($J = 9.9$ Hz) at $\delta = 6.24$. These features unequivocally define the (*E,Z*)-geometry.[20]

The behavior of **11c**, the example featuring an *n* value of 6, has been an equally useful probe of the mechanistic diversity open to these systems. Like **11b**, complete consumption of the starting ene-diene did not materialize (29% recovered) and appreciable quantities of oligomer (40%) resulted. The key experimental finding was the fact that the (*E*) monoene **14** was the sole monomeric product (31% isolated). The preference for cyclization to deliver the 13-membered heterocycle to the exclusion of either 15-membered alternative appears to be wholesale.

The identical processing of **11d** led to the formation of two products in addition to oligomer (38%). These were readily separated and identified as **15** (8%) and **16** (33%). The level of unreacted **11d** recovered was 21%. The 500 MHz NMR spectrum of the (*E,E*)-diene **16** consists of four distinctively separated downfield multiplets. The *trans, trans* nature of its double bonds was elucidated by irradiation of the multiplets at $\delta = 6.06$ and 5.91. In the first instance, the $\delta = 5.91$ signal was simplified to a doublet with $J = 15.0$ Hz. The complementary experiment caused the $\delta = 6.06$ signal to collapse as well to a doublet with $J = 14.2$ Hz.

The present results have demonstrated a direct link between ring size and the regioselectivity of ring-closing metathesis. When the option is 8- versus 10-membered product formation, a strong bias in favor of the smaller, medium-sized alternative is seen. A parallel preference dominates the cyclization of **11c** where the competition involves the generation of 13- and 15-membered rings. Interestingly, the experimental data for **11b** reveal that the kinetic barriers associated with the generation of 10- or 12-membered cycles are better accommodated by that reaction trajectory leading to the larger ring. The same is true for **11d**, although a closer energetic balance between 16- and 18-membered products is clearly in place.

Beyond this, all four pathways defined in Scheme 1 are represented in the collective results. The factors associated with the control of stereoselectivity are subtle and may in some cases manifest themselves only after ring closure. Notwithstanding, the described chemistry opens up expectations that useful applications to synthesis are indeed possible and perhaps extensive.



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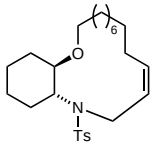

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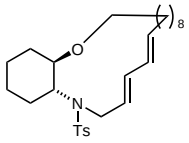

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Experimental Section

General RCM Procedure

All reactions were performed such as to arrive at a final concentration of 0.003 M. The ruthenium catalyst (20 mol %) was carefully weighed in a dry box and placed in a flame-dried flask inside the dry box. A 0.03 M stock solution of **11** in CH_2Cl_2 was prepared earlier. The remainder of the required solvent volume was added to the catalyst, and the proper volume of the substrate solution was introduced by syringe pump over 12 h while stirring was maintained at 50 °C. The reaction mixture was agitated at this temperature for an additional 12 h, cooled to room temperature, quenched with lead tetraacetate (1.5 equiv. relative to Ru catalyst) and stirred overnight under N_2. The products were purified by column chromatography.

Supporting Information Available

Spectral data for **11a – d** and **12 – 16**.

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