A Highly Efficient Synthesis of *Z*-Macrocycles using Stereoretentive, Ruthenium-Based Metathesis Catalysts

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Abstract

A highly efficient, *Z*-selective ring-closing metathesis system for the formation of macrocycles using a stereoretentive, ruthenium-based catalyst supported by a dithiolate ligand is reported. This catalyst is demonstrated to be remarkably active as observed in initiation experiments showing complete catalyst initiation at –20 °C within 10 min. Macrocyclization reactions generated *Z*-products from easily accessible diene starting materials bearing a *Z*-olefin moiety. This stereoretentive approach provides a more efficient and selective route to *Z*-macrocyles than in previously reported systems. Reactions were completed in appreciably shorter reaction times, and turnover numbers of up to 100 could be achieved. Macrocyclic lactones ranging in size from twelve-membered to seventeen-membered rings are synthesized in moderate to high yields (68 – 79% yield) with excellent *Z*-selectivity (95% – 99% *Z*).

Graphical abstract
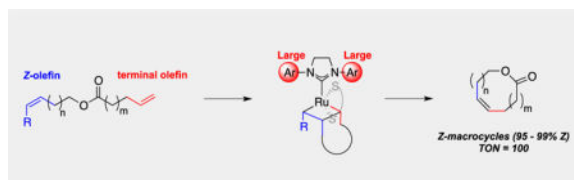
Keywords

macrocycle; metathesis; *Z*-selective; stereoretentive; ruthenium

Transition-metal catalyzed ring-closing metathesis (RCM) has become a powerful method for generating cyclic molecules.[1] It is widely used in the synthesis of pharmaceuticals as well as in the production of pheromones and musks as replacements for toxic, synthetic polycyclic and nitroarene musks.[2] The stereochemistry of the alkene, *E* or *Z*, in these cyclic structures is often crucial to the biological activity of a molecule or its olfactory characteristics, and small amounts of impurity of the other stereoisomer in chemical

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Experimental Section

Experimental details are provided in supporting information.

mixtures can drastically decrease their potency. It is often particularly difficult to separate *E*- and *Z*-isomers as techniques for their separation are not general. As such, methods for producing stereochemically pure cyclic compounds are of paramount importance.

Controlling olefin stereochemistry in RCM reactions can be difficult. When using common non-selective metathesis catalysts, selectivity is controlled by the thermodynamic stability of the olefin products and can vary depending on ring size and double bond position.[3] Because of the dilute conditions required to prevent oligomerization, high catalyst loadings are often needed for macrocyclization reactions using RCM, but removing residual metals can be challenging. For some applications, this requires further purification with lead or phosphine additives or with multiple chromatographic columns followed by treatment with charcoal.[4] Reducing catalyst loadings required for these reactions is thus an important goal.

One established method for stereoselectively generating *Z*-macrocycles is ring-closing alkyne metathesis followed by Lindlar hydrogenation.[5] *Z*-macrocycles have also been synthesized by reaction of terminal olefins with internal vinyl silanes followed by protodesilylation.[6] However, these approaches require multiple steps to synthesize the desired product, and thus more direct methods using olefin metathesis are desirable. In 2011, the first report of *Z*-selective RCM was disclosed. Mo- and W-based catalysts **1**–**3** were used to synthesize a 16-membered macrocyclic lactone (91 – 95% *Z*), nakadomarin A (90 – 97% *Z*), and epothilone C (69 – 97% *Z*).[3e] While these catalysts afforded exceptional selectivity, they required catalyst loadings of 5 to 6 mol %. One year later, *Z*-selective cyclometallated ruthenium-based catalyst **4** (7.5 mol %) was reported to generate macrocyclic lactones, lactams, and ketones (75 – 94% *Z*) with the purpose of synthesizing pheromones and fragrances.[2f] This method was limited by long reaction times, required the use of high boiling solvents and elevated temperatures, and delivered most products with ca. 85% *Z*-selectivity.

In 2015, Hoveyda reported cross metathesis of *Z*-olefins and terminal olefins to generate highly *Z*-products (>96% *Z*) using Ru-based complexes supported by dithiolate ligands.[7] Additional studies of these catalysts in 2016 demonstrated that they were highly stereoretentive, also capable of cross metathesis between two *E*-olefins or between an *E*-olefin and a terminal olefin to deliver products with kinetic *E*-selectivity (>98% *E*).[8] The proposed model for *Z*-selectivity using these catalysts is based on a proposed side-bound metallacyclobutane intermediate in which stereoselectivity arises from the α-substituents of the metallacyclobutane favorably positioned away from the large *N*-aryl groups of the *N*-heterocyclic carbene (NHC) ligand (Figure 2). Given that the reacting olefin has *Z*-stereochemistry, the β-substituent points down in the favored proposed intermediate. Subsequent cycloreversion of this metallocyclobutane intermediate leads to the formation of the *Z*-product.

Based on this model for selectivity, it was expected that highly *Z*-selective RCM to generate *Z*-macrocycles could be possible from diene substrates containing a *Z*-olefin and a terminal olefin using these catalysts (Figure 3a). These substrates are easily synthesized in high yield by reaction of commercially available *Z*-hydroxy olefins with alkenoyl chlorides (Figure 3b). Substrates were designed such that RCM of these substrates would give the desired

product as well as a gaseous byproduct, propylene or 1-butene, which could be readily removed from the reaction mixture under static vacuum.

For these reactions, catalyst **5**, bearing an NHC with *N*-2,6-diisopropylphenyl groups, was chosen due to its remarkable activity in cross metathesis reactions of *Z*-olefins.[7] To compare the initiation rates of **4** and **5**, the reactions of butyl vinyl ether with each catalyst were monitored by ^{1}H NMR (Figure 4). Under standard conditions at 30 °C,[9] catalyst **5** had already fully initiated within the 15 s required to acquire the first spectrum, and thus a rate constant could not be determined. The reaction was then monitored at 0 °C and was completed within 2 min with **5** while **4** required 1.5 h. Values of k_{init} for **4** and **5** at this temperature were determined to be 1.00×10^{-3} s^{-1} and 2.42×10^{-2} s^{-1}, respectively. Thus, there is an order of magnitude of difference in the initiation rates of these catalysts, $k_{rel} = k_{init5}/k_{init4} = 24.2$. Furthermore, full initiation of **5** was remarkably complete at −20 °C within 10 min with $k_{init} = 6.14 \times 10^{-3}$ s^{-1}.[10] Negligible Fischer carbene formation could be observed using **4** at −20 °C. This stark difference in initiation rate is a direct reflection of the significantly greater activity of **5** compared to **4**.

RCM was then attempted using **5** and was shown to be possible using a variety of substrates, **6** – **12** (Table 1). Using a standard catalyst loading of 6 mol % often used in macrocylization reactions, reactions were completed within 1 h in dichloromethane under static vacuum at 40 °C. Twelve- to seventeen-membered rings were all synthesized with high *Z*-selectivity (95 – 99% *Z*) in moderate to high yields (68 – 79% isolated yield). Yuzu lactone, **Z-7**, is in high demand by the perfume industry and can be synthesized more rapidly and selectively using **5** than in previous reports.[2f,11] Larger macrocyclic lactones, fifteen-membered to seventeen-membered rings, were synthesized in slightly higher yields than with smaller twelve- to fourteen-membered rings.

Given the exceptional activity exhibited by **5** in initiation experiments and its high activity in macrocyclic RCM (turnover numbers, TON, of 11–13 were achieved using 6 mol % catalyst loading), the limit for the catalyst loading required for reaction was examined. Using 0.5 mol % **5**, 50% conversion (TON of 100) was attained in the macrocyclization of **8** within 1 h as determined by observation of aliquots of the reaction by ^{1}H NMR. With 1 mol % **5**, complete conversion of the starting material to the macrocyclic product and a small amount of unidentified byproduct, possibly an oligomer of the starting material, was observed. This is significantly lower than reported catalyst loadings used for achieving high conversion in previously reported *Z*-selective macrocyclizations.

In summary, highly active, stereoretentive Ru-based catalyst **5** was used for generating highly *Z*-macrocycles (95 – 99% *Z*) from easily available diene substrates with a *Z*-olefin moiety. The exceptional activity exhibited by this catalyst was determined through initiation studies and showed that full catalyst initiation could be achieved at −20 °C within minutes. Twelve- to seventeen-membered macrocycles, including yuzu lactone, were synthesized using this method in moderate to high yields (67 – 79% yield). These reactions were completed in significantly shorter times, and the use of lower catalyst loadings than in previously reported *Z*-selective systems was shown to be possible with TON of up to 100. Further studies using stereoretention for *E*-selective macrocyclization are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Grubbs, RH.Wenzel, AG.O'Leary, DJ., Khosravi, E., editors. Handbook of Metathesis. Wiley–VCH; Weinheim: 2015.

2. (a) Michrowska A, Wawrzyniak P, Grela K. Eur J Org Chem. 2004:2053.(b) Rimkus, GG. The Handbook of Environmental Chemistry. Vol. 3X. Springer: Berlin; 2004. (c) Rowe, DJ. Chemistry and Technology of Flavors and Fragrances. Blackwell; Oxford, U.K: 2005. (d) Gradillas A, Perez-Castells J. Angew Chem, Int Ed. 2006; 45:6086.(e) Ohloff, G., Pickenhagen, W., Kraft, P. Scent and Chemistry: The Molecular World of Odors. Verlag Helvetica Acta; Zürich: 2011. (f) Marx VM, Herbert MB, Keitz BK, Grubbs RH. J Am Chem Soc. 2013; 135:94. [PubMed: 23244210] (g) Higman CS, Lummiss JAM, Fogg DE. Angew Chem Int Ed. 2016; 55:3552.

3. (a) Fürstner A, Langemann K. J Org Chem. 1996; 61:3942. [PubMed: 11667264] (b) Fürstner A, Langemann K. Synthesis. 1997:792.(c) Goldberg WPD, Hobber AS, Weiler L. Tetrahedron Lett. 1998; 39:4955.(d) Lee CW, Grubbs RH. Org Lett. 2000; 2(14):2145. [PubMed: 10891252] (e) Yu M, Wang C, Kyle AF, Jakubec P, Dixon DJ, Schrock RR, Hoveyda AH. Nature. 2011; 479:88. [PubMed: 22051677]

4. (a) Paquette LA, Schloss JD, Efremov I, Fabris F, Gallou F, Mendez-Andino J, Yang J. Org Lett. 2000; 2:1259. [PubMed: 10810722] (b) Maynard H, Grubbs RH. Tetrahedron Lett. 1999; 40:4137.

5. (a) Fürstner A, Mathes C, Lehmann CW. Chem Eur J. 2001; 7:5299. [PubMed: 11822430] (b) Nilson MG, Funk RL. Org Lett. 2010; 12:4912. [PubMed: 20932022] (c) Fürstner A. Angew Chem Int Ed. 2013; 52:2794.(d) Fürstner A. Science. 2013; 341:1229713. [PubMed: 24052310]

6. Wang Y, Jimenez M, Hansen AS, Raiber EA, Schreiber SL, Young DW. J Am Chem Soc. 2011; 133:9196. [PubMed: 21557625]

7. Koh MJ, Khan RKM, Torker S, Yu M, Mikus MS, Hoveyda AH. Nature. 2015; 517:181. [PubMed: 25567284]

8. (a) Johns AM, Ahmed TS, Jackson BW, Grubbs RH, Pederson RL. Org Lett. 2016; 18(4):772. [PubMed: 26840878] (b) Ahmed TS, Grubbs RH. J Am Chem Soc. 2017; 139(4):1532. [PubMed: 28107003] Stereoretention has been seen in metathesis previouslyBilhou JL, Basset JM, Graydon WF. J Am Chem Soc. 1977; 99(12):4083.

9. Keitz BK, Endo K, Patel PR, Herbert MB, Grubbs RH. J Am Chem Soc. 2012; 134(1):693. [PubMed: 22097946]

10. Substantial initiation of catalysts at low temperatures is often difficult using common metathesis catalystsRomero PE, Piers WE, Mcdonald R. Angew Chem, Int Ed. 2004; 43(41):6161.

11. Alternative synthesis of yuzu lactone using alkyne metathesisFürstner A, Guth O, Rumbo A, Seidel G. J Am Chem Soc. 1999; 121(48):11108.
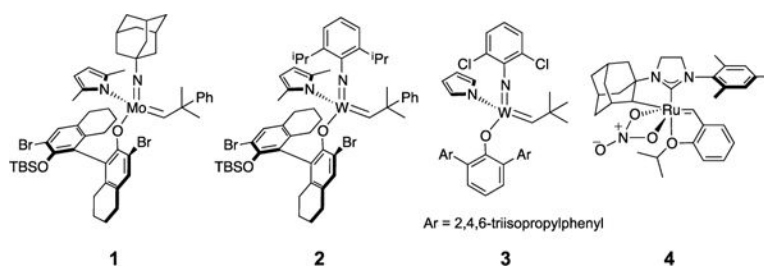
Figure 1.
Catalysts used previously to selectively generate highly *Z*-macrocycles.
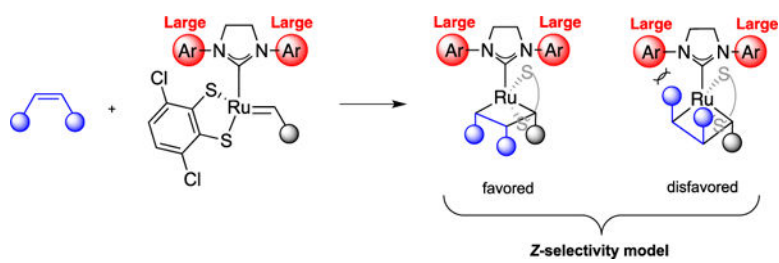
Figure 2.
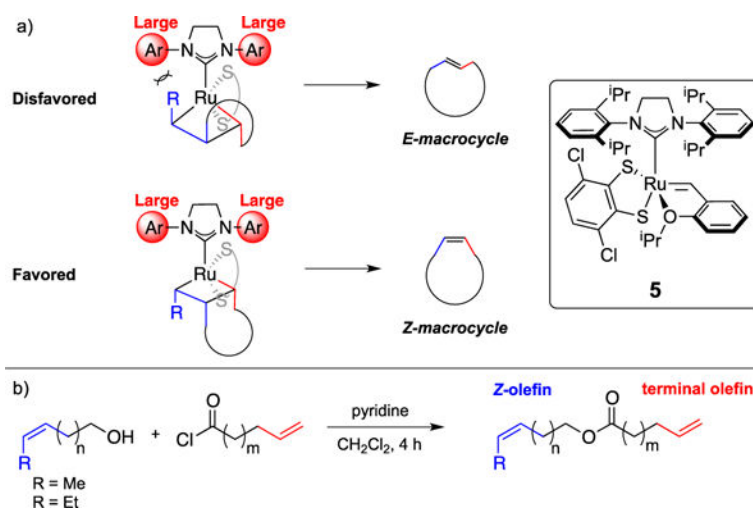Model for *Z*-selectivity using stereoretentive metathesis catalysts in cross metathesis.

Figure 3.
(a) Proposed disfavored and favored metallacyclobutane intermediates in macrocylization reactions implementing stereoretentive catalyst **5** (b) Synthesis of diene substrates from acyl chlorides and *Z*-hydroxy olefins.
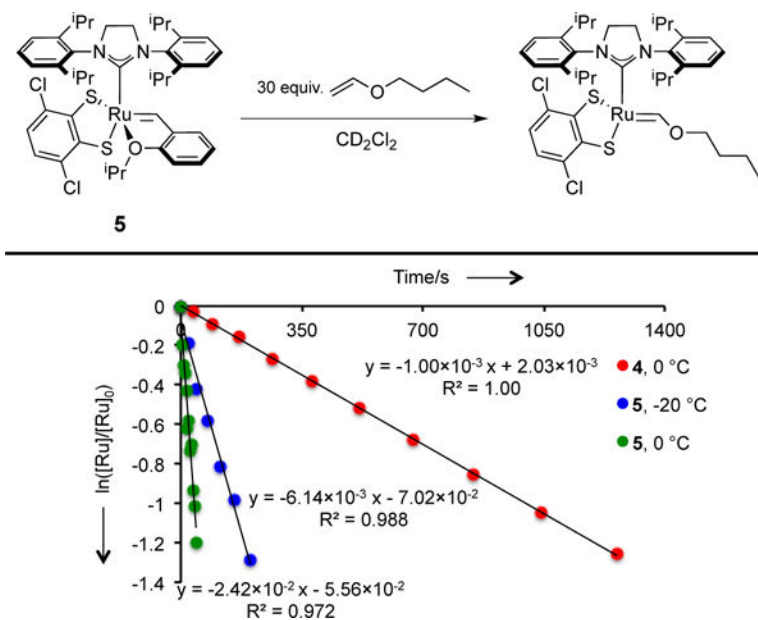
Figure 4.

Plot of $\ln([Ru]/[Ru]_0)$ versus time for initiation experiments conducted with catalysts **4** and **5** at 0 °C and −20 °C monitored by disappearance of the benzylidene signal by ^{1}H NMR. Plots remain approximately linear for three half-lives of the reaction.

Table 1

Synthesis of macrocyles using **5**.

Entry	Substrate	Product	Yield[a]	Z/E[b]
1	6	Z-6 (12)	70% yield	>99/1
2	7	Z-7 (13)	68% yield	95/5
3	8	Z-8 (14)	67% yield (60% yield)[c]	95/5 (98/2)
4	9	Z-9 (14)	72% yield	98/2
5	10	Z-10 (15)	74% yield	99/1
6	11	Z-11 (16)	79% yield	95/5
7	12	Z-12 (17)	75% yield	95/5

[a] Yields shown are isolated yields.

[b] Selectivity determined by gas chromatography. Selectivity of **Z-7** and **Z-8** can be determined by ^{1}H NMR.

[c] Reaction was run on a preparative scale.