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Stereoselectivity of Macrocyclic Ring-Closing Olefin Metathesis

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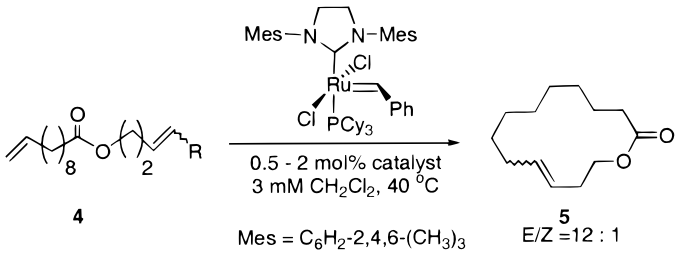
ABSTRACT



4 **5** E/Z =12 : 1

Macrocyclic ring-closing olefin metathesis using ruthenium catalyst 3 was performed to produce a 14-membered lactone. The *E*/*Z* ratio of lactone was high regardless of the R group (auxiliary) or the initial alkene stereochemistry. A kinetic study demonstrates that the high *E*/*Z* ratio is due to secondary metathesis reactions that isomerize the product to the thermodynamic *E*/*Z* ratio.

Increasing attention has been directed toward the synthesis of medium and large rings using metal-catalyzed ring-closing olefin metathesis (RCM).[1] This interest was initiated by the development of well-defined metathesis catalysts, such as $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**)[2] and **2**.[3] While **2** shows higher activity in RCM, the remarkable functional group tolerance in olefin metathesis gives **1** a distinct advantage in the synthesis of organic compounds. In fact, Ru-catalyzed RCM has proven to be highly efficient and is becoming recognized as one of the most straightforward and reliable methods for the synthesis of large (≥9) rings.[4]

We recently reported that the ruthenium-based olefin metathesis catalyst **3**,[5] containing 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene as a ligand, not only exihibited higher activity in RCM and cross metathesis relative to the parent complex **1** but also maintained excellent functional group tolerance.[6] In addition to its enhanced electron-donating nature, N-heterocyclic carbenes possess sterically large

(1) For recent reviews on olefin metathesis, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036−2056. (b) Grubbs, R. H.; Chang, S. *Tetarhedron* **1998**, *54*, 4413−4450. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (d) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211−240.

(2) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

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(4) (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614. (b) Yang, Z.: He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 166−168. (c) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett*. **1997**, *38*, 2601−2604. (d) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136. (e) Meng, D.; Bertinato, P.; Balog, A.; Su, D.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073−10092. (f) Smith, A. B.; III; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423−7424. (g) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648−10649. (h) Dixon, D. J.; Foster, A. C.; Ley, S. V. *Org. Lett.* **2000**, *2*, 123−125. (i) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742−2748. (j) Dvorak, C. A.; Schmitz, W. D.; Poon, D J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem., Int. Ed.* **2000**, *39*, 1664−1666. (k) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984−4985 and also see ref 1.

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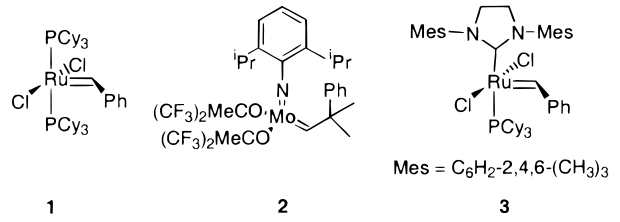
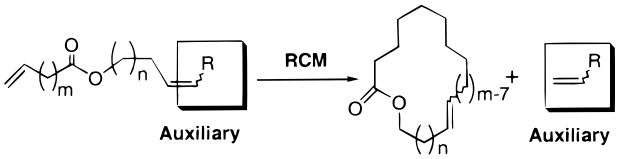
substituents as well. We believe that catalyst **3** becomes an activated species for olefin metathesis by dissociation of the phosphine ligand rather than the carbene ligand.[7]



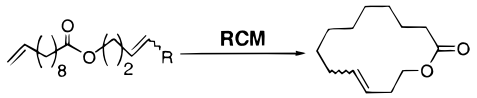
1 **2** **3**

Macrocyclic RCM using catalyst **1** generally provides products as a mixture of *E* and *Z* isomers with low selectivity. Thus, the *E*/*Z* selectivity of the product is often difficult to control or predict in the RCM, since the selectivity changes with ring size and position of the olefin.[8] As demonstrated in a recent RCM study of epothilone, a functionality far from the metathesis reaction site is capable of affecting the *E*/*Z* ratio of the products.[9] If such a remote functionalization could affect the stereoselectivity of olefin metathesis, we expected that positioning an auxiliary in closer proximity to the olefin involved in the RCM might influence the *E*/*Z* selectivity more significantly. Ideally, the auxiliary group will only play a role in affecting the stereochemistry of the product during RCM reaction and can be effectively removed after the reaction is completed. In conjunction with the increased steric bulk of **3**, we also anticipated this new Ru catalyst might afford different stereoselectivity during macro-RCM.



We describe here a study of the stereoselectivity in macrocyclic RCM of 14-membered lactone using catalyst **3**. As summarized in Table 1, catalyst **3** shows enhanced macro-RCM activities compared to its parent catalyst **1**; therefore it was possible to use a lower catalyst loading. For example, compounds **4a** and **4b** were converted within 30−40 min to the corresponding lactone using catalyst **3** (entry 1 and 3), while the same RCM using **1** (entry 2 and 4) needed over 5 h and 5−10 times higher loading of catalyst.

Table 1. Macrocyclic RCM for 14-Membered Lactone Using Catalysts **1** and **3**[a]



4 **5**

no.	substrate	catalyst (mol %)	time	Y (%)[b]	*E*/*Z*[c]
1	**4a**, R = H	**3** (1.0)	40 min	quant	11.5:1 (4.8:1)
2	**4a**, R = H	**1** (5.0)	5 h	97[d]	4.5:1 (3.5:1)
3	**4b**, R = CH_2CH_3(*cis*)	**3** (0.5)	30 min	quant	9.7:1 (3.4:1)
4	**4b**, R = CH_2CH_3(*cis*)	**1** (5.0)	6.5 h	77	4.5:1 (3.4:1)
5	**4c**, R = $(CH_2)_4CH_3$(*cis*)	**3** (0.5)	40 min	quant.	10.8:1 (4.0:1)
6	**4d**, R = CH_2OAc(*trans*)	**3** (2.0)	3 h	80	9.7:1 (3.6:1)
7	**4e**, R = CH_2OH(*trans*)	**3** (2.0)	6 h	23[e]	2.2:1

[a] Reactions in CH_2Cl_2 (3 mM) at reflux temperature. [b] Yields were determined by GC and NMR. [c] *E*/*Z* ratios were determined by GC. Data in parentheses are *E*/*Z* ratios at low conversion (10−30%). *E* and *Z* forms were confirmed by comparison of reported data (see ref 10). [d] Isolated yield. [e] Starting material was not present.

When the reaction was performed at room temperature, intermolecular dimerization competed with ring closure even under high dilution condition (3 mM in CH_2Cl_2). As anticipated, dimerization was suppressed at elevated temperatures. In addition to a distinct shortening of the reaction times, catalyst **3** was sufficiently stable to produce the 14-membered lactone in high yields and *E* selectivities.[10]

In the case of entry 7 (Table 1), it is evident that the free hydroxyl group proximal to the substrate olefin was detrimental to the macro-RCM reaction.[11] The low *E*/*Z* ratio of entry 7 may reflect the low product conversion or an auxiliary effect. At the end of the RCM reaction using catalyst **3** (entries 1, 3, 5, and 6), it is noteworthy that the *E*/*Z* ratios of the 14-membered lactone were high and similar regardless of the presence of auxiliaries or initial alkene stereochemistry.[12] This is an unexpected result if the aforementioned proposed auxiliary effects are considered.

(6) (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784 and also see ref 5.

(7) Ulman, M. Ph.D. Dissertation, California Institute of Technology, Pasadena, CA, 2000. As previously reported for a ruthenium complex combining an imidazolinylidene ligand, the dissociation of the phosphine ligand is suggested. See: Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202−7207.

(8) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942−3943. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792−803. (c) Goldberg, W. P. D.; Hobber, A .S.; Weiler, L. *Tetrahedron Lett.* **1998**, *39*, 4955−4958. Recently, macrocyclic *Z*-alkene compounds have been prepared indirectly using alkyne metathesis. See: (d) Fürstner, A.; Seidel, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1734−1736. (e) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108−11113. (f) Fürstner, A.; Grela, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234−1236.

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(10) The ^{1}H NMR and ^{13}C NMR data of the *E* and *Z* isomers of **5** were reported in ref 8b, allowing the identification of the stereochemistry of RCM product by comparison to these ^{1}H NMR and ^{13}C NMR data. HRMS of **5**: 210.1621 (M^+), calcd for $C_{13}H_{22}O_2$ 210.1620.

(11) We believe that a free hydroxyl group might coordinate to the ruthenium metal center, changing catalyst properties. For other examples of oxygen chelation to olefin metathesis catalyst, see: (a) Johnson, L .K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8130−8145. (b) Johnson, L. K.; Frey, M.; Ulibarri, T. A.; Virgil, S. C.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*. 8167−8177. (c) Maughon, B. R.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 3459−3469. (d) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799.

(12) We also see the similar high *E*/*Z* ratio (*E*/*Z* = 11:1) in the RCM with substrate **4**, R = CH_2OTBS.

This result prompted us to investigate the kinetics of the macro-RCM reactions. As shown in Figure 1, a dramatic

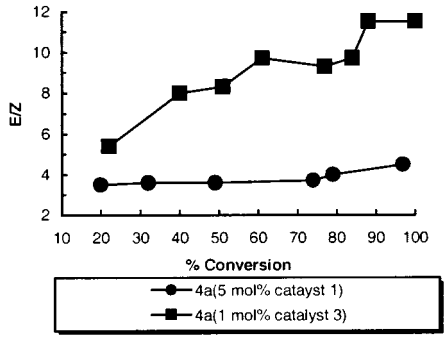

Figure 1. Figure 1. Macrocyclic RCM for 14-membered lactone **5** using catalysts **1** and **3**: plot of the ratio of *E* to *Z* isomers of **5** versus the amount of conversion of starting material **4a** (*E*/*Z* ratio and % conversion were determined by GC.)

change in the product *E*/*Z* ratio using catalyst **3** was observed at 30−70% conversion of substrate **4a**. When **1** was employed as the catalyst, however, the analogous ratio did not significantly change over the entire course of the reaction. The RCM of other substrates (**4b**, **4c**, **4d**) using catalyst **3** revealed similar trends in the progression of initial *E*/*Z* ratio.

This study suggests that the high *E*/*Z* ratio observed with catalyst **3** may be due to secondary metathetical isomerization progressively leading to the ultimate thermodynamic equilibrium ring closure product.[13]

To verify our conclusion, the isomerization of a product **5** mixture (*E*/*Z* = 4:1) was investigated (Figure 2). The lactone maintained the initial *E*/*Z* ratio value in the absence of catalyst over the duration of a typical isomerization reaction. This control experiment showed that the thermal isomerization did not contribute to the results. However, rapid isomerization of **5** to the higher *E*/*Z* ratio (*E*/*Z* = 12:1) was observed in the presence of **3** (1 mol %). Consequently, catalyst **3** is capable of isomerizing the initial lactone product under the reaction conditions. The lower *E* content of the low % conversion products **4b**−**e** compared to **4a** suggests

(13) For the kinetic study of the isomerization in olefin metathesis, see: (a) Bilou, J. L.; Basset, J.; Mutin, R.; Graydon, W. F. *J. Am. Chem. Soc.* **1977**, *99*, 4083−4090. (b) Grubbs, R. H.; Hoppin, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 1499−1508. (c) Couturier, J.; Paillet, C.; Leconte, M.; Basset, J.; Weiss, K. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 628−630.

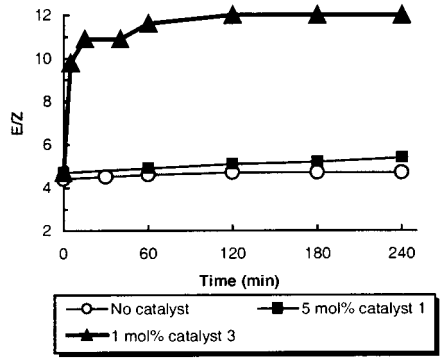

Figure 2. Isomerization of an isolated lactone **5** mixture (*E*/*Z* starting ratio = 4:1): plot of the ratio of *E* to *Z* isomer of **5** versus the reaction time (conditions: no catalyst (60 mM in CH_2Cl_2), catalysts **1** and **3** (3 mM in CH_2Cl_2); *E*/*Z* ratio and % conversion were determined by GC.)

that the auxiliaries may provide a slight decrease in the kinetic preference for the *E* isomer.

The high thermodynamic *E*/*Z* ratio of **5** coincides with the earlier calculated *E*/*Z* ratio (19:1) reported.[14] The same reaction using catalyst **1** (5 mol %) exhibited no significant secondary metathesis isomerization. This kinetic study illustrates the important consequence that RCM using catalyst **3** is capable of isomerizing macro-lactone products to give more their favorable *E*/*Z* ratio.

In conclusion, 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium complex **3** exhibits high olefin metathesis activity in macrocyclic RCM to obtain the 14-membered lactone in high yield and high *E*/*Z* ratio. In addition, the high *trans* preference is in large part due to secondary isomerization of ring-closed product. Further studies regarding stereocontrolled macrocyclic RCM using catalyst **3** are currently under investigation.

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(14) Calculation with MM3*, see ref 8c.