JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Stereoselective Access to *Z* and *E* Macrocycles by Ruthenium-Catalyzed *Z*-Selective Ring-Closing Metathesis and Ethenolysis

Vanessa M. Marx, Myles B. Herbert, Benjamin K. Keitz, and Robert H. Grubbs*

Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

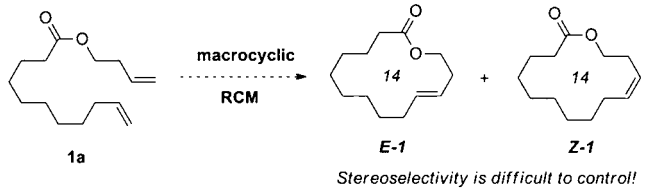
Supporting Information

ABSTRACT: The first report of *Z*-selective macrocyclizations using a ruthenium-based metathesis catalyst is described. The selectivity for *Z* macrocycles is consistently high for a diverse set of substrates with a variety of functional groups and ring sizes. The same catalyst was also employed for the *Z*-selective ethenolysis of a mixture of *E* and *Z* macrocycles, providing the pure *E* isomer. Notably, an ethylene pressure of only 1 atm was required. These methodologies were successfully applied to the construction of several olfactory macrocycles as well as the formal total synthesis of the cytotoxic alkaloid motuporamine C.

The macrocyclic motif is widely prevalent in an abundance of natural products and pharmaceuticals and also provides the backbone for a unique class of olfactory compounds, termed macrocyclic musks. Originally derived from natural sources, macrocyclic musks have been rapidly gaining popularity in the perfume industry as alternatives to synthetic nitroarene and polycyclic musks, which exhibit bioaccumulation and toxicity hazards.[1,2] In general, many biologically and industrially relevant macrocyclic compounds feature an internal olefin. The alkene geometry is instrumental in the resulting biological activity or olfactory properties of the compound of interest, which can be adversely affected by even minute amounts of stereoisomeric impurities. In addition, stereochemically pure macrocyclic olefins are often utilized as platforms to install other functional groups stereospecifically. Although in some cases it might be possible to separate a mixture of *E* and *Z* isomers chromatographically or by crystallization, these methods are by no means general and often require extensive optimization for each individual compound. Furthermore, with respect to macrocyclic musks in particular, certain perfumes often contain a specific mixture of *E* and *Z* olfactory macrocycles.[2] Hence, selective methods for the preparation of both *E*- and *Z*-olefin-containing macrocycles are of paramount importance.

Ring-closing metathesis (RCM) has become a ubiquitous tool for the synthesis of carbo- and heterocylic ring systems and is particularly well-suited for the efficient synthesis of macrocycles.[3] Unfortunately, most metathesis catalysts exhibit minimal kinetic selectivity, and thus, for medium- to large-sized ring systems in which both *E* and *Z* isomers are accessible, the product distribution at high conversion reflects the thermodynamic energetic difference between the two. For ruthenium-based metathesis catalysts bearing N-heterocyclic carbene (NHC) ligands, the *E* isomer is often favored, as in the macrocyclic RCM of diene **1a**, which produces 14-membered lactones ***E*-1** and ***Z*-1** in a ratio of ca. 12:1 (Scheme 1).[4]

Scheme 1. Macrocyclic RCM of Diene 1a to *E*-1 and *Z*-1



However, it can be difficult to predict the thermodynamic product a priori, and the reaction frequently proceeds with minimal selectivity or the inverse of that which was anticipated.[5] This issue has been circumvented indirectly through the implementation of ring-closing alkyne metathesis (RCAM) followed by Lindlar- or Birch-type reductions to generate stereopure *Z* or *E* macrocycles, respectively.[3,6] Fürstner and co-workers have also developed a complementary method for the synthesis of *E* macrocycles from cycloalkynes that employs a hydrosilylation/desilylation sequence.[7] More recently, a report has appeared detailing the use of vinylsiloxanes to promote stereoselective RCM, generating (*E*)-alkenylsiloxanes, which upon desilylation yield *Z* macrocycles.[8]

Accordingly, a considerable effort has been expended in the search for metathesis catalysts exhibiting kinetic selectivity. This has resulted in numerous current reports detailing the successful realization of *Z*-selective homocoupling, cross-metathesis, and ring-opening/cross-metathesis reactions employing tungsten and molybdenum-based catalyst systems.[9] In addition, a single report has emerged detailing the *Z*-selective ethenolysis of straight-chain olefins, resulting in pure *E* olefins from an *E*/*Z* mixture with a molybdenum catalyst.[10] Recently, in an elegant publication, the Schrock and Hoveyda groups disclosed the first example of catalyst systems capable of performing a highly *Z*-selective macrocyclic RCM reaction, utilizing the monoaryloxide−pyrrolide (MAP) catalysts **3a** and **3b** (Figure 1) to generate a 16-membered lactone.[12] They further showcased the utility of these types of complexes in the synthesis of the 16-membered core of epothilone C (85% yield,

Received: November 15, 2012
Published: December 17, 2012

   dx.doi.org/10.1021/ja311241q | *J. Am. Chem. Soc.* 2013, 135, 94−97

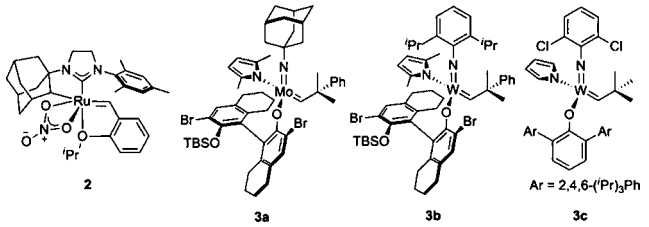


Figure 1. Prominent *Z*-selective metathesis catalysts.

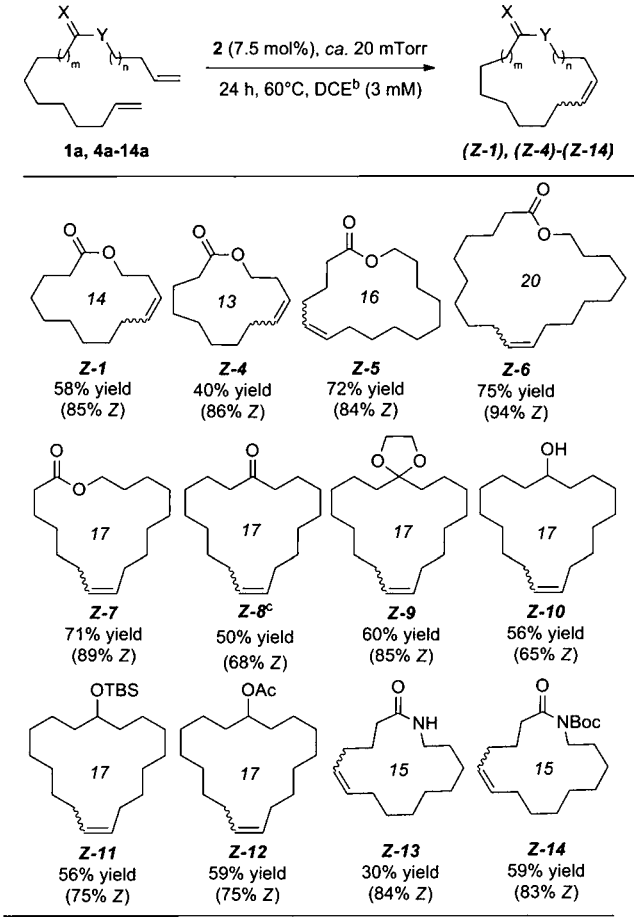
96% *Z*) and the 15-membered core of nakadomarin A (90% yield, 97% *Z*) using tungsten catalyst **3c**.

We recently developed a family of chelated ruthenium-based catalysts that promote highly *Z*-selective homocoupling, cross-metathesis, and ring-opening metathesis polymerization reactions.[13] Herein we disclose the first report of *Z*-selective macrocyclic RCM using a ruthenium-based catalyst system (**2**) that is applicable to a broad range of ring sizes and functional groups. Additionally, we report the first instance of *Z*-selective ethenolysis of macrocycles, resulting in pure *E* macrocycles from an *E*/*Z* mixture, using the same catalyst system. We have successfully applied these strategies to the stereoselective synthesis of a selection of olfactory macrocycles and the formal total synthesis of the cytotoxic alkaloid motuporamine C.

We initiated our studies by optimizing the reaction conditions for the macrocyclic RCM of diene **1a**, producing lactone **Z-1** in 58% yield with 85% *Z* selectivity (Table 1). Although all of the reagents were initially combined in a glovebox using rigorously degassed anhydrous 1,2-dichloroethane (DCE), the reaction could also be conveniently set up on the benchtop using commercial anhydrous DCE directly as received, generating **Z-1** in 49% yield with 86% *Z* selectivity. The main competing process in the macrocyclic RCM to give **Z-1** was oligomerization of diene **1a**,[14] and the amount of **Z-1** produced was dependent upon the ratio of these respective rate constants ($k_{RCM}/k_{oligomer}$) as well as the rate of catalyst decomposition.[15] Macrocyclic ring closure in general is entropically disfavored. In the case of macrocyclic RCM reactions mediated by **2**, the transformation might also suffer from a significant negative enthalpic contribution as a result of steric interactions with the NHC moiety in transition states leading to productive turnovers.[16] Thus, in order to favor ring closure over oligomerization, dilute conditions (3 mM) and elevated temperatures (60 °C) were required. The application of a static vacuum (20 mTorr) was also necessary, as refluxing conditions either under an inert atmosphere or while sparging with argon resulted in increased formation of oligomerization products.[14] An increase in temperature (80 °C) decreased the yield of **Z-1**, likely as a result of catalyst decomposition, and a further increase in dilution (1 mM) resulted in prohibitively long reaction times. An increase in the catalyst loading (10 mol %) or reaction time (48 h) did not increase the conversion to **Z-1**.[17]

A variety of substrates readily underwent macrocyclic RCM with ruthenium catalyst **2** under the single set of standard reaction conditions optimized for lactone **Z-1** (Table 1).[18] In almost all cases, consumption of the diene precursor was high, resulting in ca. 80% conversion to macrocyclic products; unprotected amide **13a** was the sole exception, reaching only ca. 50% conversion to **Z-13**. Protection of **13a** as its *tert*-butyl carbamate derivative **14a** restored the activity and resulted in higher yields of **Z-14**.[19] The larger, 16-, 17-, and 20-membered lactones **Z-5**, **Z-7**, and **Z-6** gave the highest yields (72, 71, and

Table 1. *Z*-Selective Macrocyclizations Employing Ruthenium Catalyst 2[a]



[a]Yields are of isolated products. *E*/*Z* ratios were determined by ^{1}H or ^{13}C NMR spectroscopy.[11] [b]DCE = 1,2-dichloroethane. [c]The reaction was quenched after 8 h.

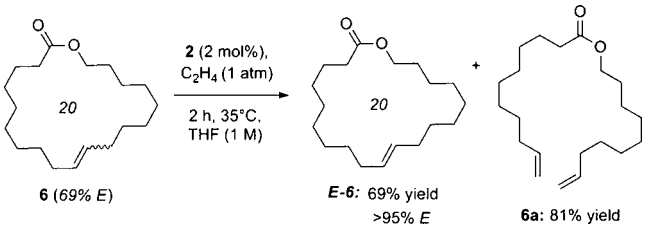
75%, respectively),[20] whereas the reaction was less efficient for the smaller 13-membered lactone **Z-4** (40% yield). In general, the *Z* selectivity was high for all of the macrocyclizations (75–94%), although it was necessary to mask ketone (**Z-8**) and alcohol (**Z-10**) functionality in order to maintain high *Z* selectivity.[21] The origin of the considerable bias exhibited by **2** for the production of *Z* olefins is attributed to the strong preference for the formation of side-bound metallocyclobutanes in these systems, in which transition states leading to *E* olefins are strongly disfavored as a result of unfavorable steric interactions with the mesityl ring of the NHC ligand.[16]

It is noteworthy that macrolides **Z-4**, **Z-7**, and **Z-8** are currently in demand by the perfume industry (marketed as yuzu lactone, ambrettolide, and civetone respectively).[2] Fürstner and co-workers had previously accessed these compounds by RCAM/Lindlar hydrogenation,[22] as RCM strategies had failed to proceed with adequate *Z* selectivities for these types of ring systems.[23] Macrocyclic lactam **Z-13** is also an intermediate in Goldring and Weiler's total synthesis of the cytotoxic alkaloid motuporamine C.[24,25] In this case, **Z-13** was obtained following RCM and purification from a mixture with its *E* isomer (only 44% *Z*), using radial chromatography. Fürstner and co-workers had also previously employed a RCAM/Lindlar hydrogenation sequence to access motuporamine C stereospecifically.[26]

dx.doi.org/10.1021/ja311241q | J. Am. Chem. Soc. 2013, 135, 94–97

In an approach complementary to the synthesis of the *Z* macrocycles shown above in Table 1, we were also able to exploit catalyst **2** further for the isolation of pure *E* macrocycles through selective degradation of the *Z* isomers in the corresponding *E*-dominant mixtures (Scheme 2).[27] Ring

Scheme 2. *Z*-Selective Ethenolysis of an *E*/*Z* Mixture of 6[a]

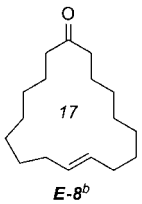
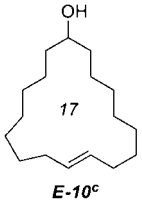
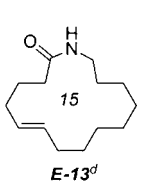


[a]Isolated yields based on the theoretical amount of pure *E* isomer are shown.

opening via ethenolysis is simply the reverse of the macrocyclic RCM reaction. Thus, as high *Z* selectivity was evidenced in the forward reaction (cf. Table 1), it was expected that the reverse reaction would also display high selectivity for *Z* olefins.[28] Indeed, exposure of an *E*/*Z* mixture of lactone **6** (69% *E*) to ethylene (1 atm) in the presence of catalyst **2** (2 mol %) led to the complete degradation of ***Z*-6** after only 2 h at 35 °C (Scheme 2). Notably, an ethylene pressure of only 1 atm was necessary.[29] It is also significant to mention that the corresponding ring-opened diene was also recovered and thus could subsequently be recyclized in subsequent macrocyclic RCM reactions if desired.

We were able to apply similar reaction conditions to macrocycles containing ketone (**8**), alcohol (**10**), and amide (**13**) functionality (Table 2). In general, complete consumption of the *Z* macrocycle occurred within 2 h, affording the pure *E* macrocycle in good yield. The lower yield of ketone-containing product ***E*-8** is likely a result of the elevated temperature required to form the *E* isomer exclusively, which might also be expected to accelerate undesired degradation of the *E* macrocycle. Additionally, an increase in oligomerization was also observed in this case, thus reducing the yield of the recovered diene **8a**.

Table 2. *Z*-Selective Ethenolysis of *E*-Dominant Mixtures of Macrocycles[a]

Compound	 ***E*-8**[b]	 ***E*-10**[c]	 ***E*-13**[d]
Initial *E* (%)	80	80	55
Final *E* (%)[e]	>95	>95	>95
Yield (%)[f]	***E*-8**: 40[g]	***E*-10**: 78[g]	***E*-13**: 75[g]
	8a: 46[h]	**10a**: 79[h]	**13a**: 86[h]

[a]Reaction conditions: **2** (2 mol %), C_2H_4 (1 atm), THF (1 M), 2 h. [b]The reaction was run at 75 °C. [c]The reaction was run at 35 °C. [d]The reaction was run at 40 °C. [e]The product was entirely *E* on the basis of ^1H or ^{13}C NMR analysis. [f]Isolated yields. [g]Based on the initial amount of the *E* isomer. [h]Based on the initial amount of the *Z* isomer.

In summary, we have demonstrated the first example of a ruthenium metathesis catalyst that is capable of promoting *Z*-selective macrocyclic RCM. This represents the first systematic study of the scope of *Z*-selective macrocyclic RCM with respect to a broad range of ring sizes. The transformation is amenable to a variety of functional groups and proved applicable in the synthesis of a number of olfactory macrocycles as well as the formal total synthesis of motuporamine C. In addition, it has been shown that the same catalyst system can promote *Z*-selective ethenolysis of macrocyclic compounds that are present in *E*/*Z* mixtures, providing pure *E* macrocycles. It is anticipated that both methods will realize extensive use in the synthesis of natural products and pharmaceuticals as well as in the perfume industry. The ability to utilize ethylene at 1 atm pressure for *Z*-selective ethenolysis should enable the widespread use of this application in particular, on both benchtop and industrial scales, as an effective method for the isolation of pure *E* macrocycles without advanced chromatography or alternative purification techniques. Therefore, as improved *Z*-selective catalysts based on ruthenium are discovered, the utility of these complementary methodologies will only increase. As in the past, organic chemists will find these ruthenium-based systems to have broad applicability.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

rhg@caltech.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dr. David VanderVelde is thanked for assistance with NMR experimentation and analysis. This work was financially supported by the NIH (R01-GM031332), the NSF (CHE-1212767), and the NSERC of Canada (fellowship to V.M.M.). Instrumentation on which this work was carried out was supported by the NIH (NMR spectrometer, RR027690). Materia, Inc. is thanked for its donation of metathesis catalyst **2**.

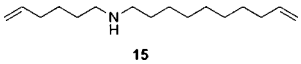
■ REFERENCES

(1) Rimkus, G. G. *The Handbook of Environmental Chemistry*; Springer: Berlin, 2004; Vol. 3*X*.

(2) (a) Rowe, D. J. *Chemistry and Technology of Flavors and Fragrances*; Blackwell: Oxford, U.K., 2005. (b) Ohloff, G.; Pickenhagen, W.; Kraft, P. *Scent and Chemistry: The Molecular World of Odors*; Verlag Helvectica Acta: Zürich, 2011.

(3) (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH:Weinheim, Germany, 2003; Vol. 2. (b) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086−6101. (c) Majumdar, K. C.; Rahaman, H.; Roy, B. *Curr. Org. Chem.* **2007**, *11*, 1339−1365. (d) Diederich, F.; Stang, P. J.; Tykwinski, R. R. *Modern Supramolecular Chemistry: Strategies for Macrocycle Synthesis*; Wiley-VCH: Weinheim,

Germany, 2008. (e) Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis*; Wiley-VCH: Weinheim, Germany, 2010.
(4) Lee, C.-W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147.
(5) Rivkin, A.; Cho, Y. S.; Gabarda, A. E.; Yoshimura, F.; Danishefsky, S. J. *J. Nat. Prod.* **2004**, *67*, 139−143.
(6) (a) Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307−2320. (b) Zhang, W.; Moore, J. S. *Adv. Synth. Catal.* **2007**, *349*, 93−120.
(7) (a) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2002**, 2182−2183. (b) Lacomber, F.; Radkowski, K.; Seidel, G.; Fürstner, A. *Tetrahedron* **2004**, *60*, 7315−7324.
(8) Wang, Y.; Jimenez, M.; Hansen, A. S.; Raiber, E.-A.; Schreiber, S. L.; Young, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 9196−9199.
(9) (a) Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844−3845. (b) Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16630−16631. (c) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461−466. (d) Peryshkov, D. V.; Schrock, R. R.; Takase, M. K.; Muller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 20754−20757. (e) Marinescu, S. C.; Schrock, R. R.; Muller, P.; Takase, M. K.; Hoveyda, A. H. *Organometallics* **2011**, *30*, 1780−1782. (f) Yu, M.; Ibrahem, I.; Hasegawa, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 2788−2799.
(10) Marinescu, S. C.; Levine, D. S.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 11512−11514.
(11) *E* and *Z* macrocycles can be readily differentiated through careful analysis of their ^{1}H, ^{13}C, and HSQC NMR spectra, as the carbon atoms α to the olefin moiety in the *E* isomer are located significantly more downfield than the corresponding carbon atoms in the *Z* isomer. See: Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy: High-Resolution Methods and Applications in Organic Chemistry and Biochemistry*; Verlag Chemie: Weinheim, Germany, 1987.
(12) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88−93.
(13) (a) Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 8525−8527. (b) Keitz, B. K.; Endo, K.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9686−9688. (c) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 693−699. (d) Herbert, M. B.; Marx, V. M.; Pederson, R. L.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2012**, DOI: 10.1002/anie.201206079.
(14) This was determined by inspection of the ^{1}H NMR spectra of the crude reaction mixtures. Additionally, no competing olefin isomerization events were observed.
(15) For a detailed study of decomposition pathways of catalysts resembling **2**, see: Herbert, M. B.; Lan, Y.; Keitz, B. K.; Liu, P.; Endo, K.; Day, M. W.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 7861−7866.
(16) Liu, P.; Xu, X.; Dong, X.; Keitz, B. K.; Herbert, M. B.; Grubbs, R. H.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 1464−1467.
(17) When tetrahydrofuran (THF) was used in place of DCE, a significant increase in oligomerization products was observed; chloroform resulted in decomposition of **2**, and multiple byproducts were formed when toluene or methanol was used.
(18) This is in contrast to the report by Yu et al.,[12] in which a separate optimization event was required for each individual substrate.
(19) Macrocyclic RCM was also attempted with aminodiene **15**, but <5% conversion resulted. Similar results were obtained with the hydrochloride salt derived from **15**.



15

(20) This is comparable to the results obtained by Yu et al.[12] for the macrocyclization of **5a**, which generated lactone **Z-5** in 56% yield (92% *Z*) using Mo-based catalyst **3a** and 62% yield (91% *Z*) using W-based catalyst **3b**.
(21) Ketone (**8**) and alcohol (**10**) were protected as their corresponding ethylene glycol (**9**) and *tert*-butyldimethylsilyl (**11**) or acetate (**12**) derivatives, respectively.
(22) (a) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108−11113. (b) Fürstner, A.; Siedel, G. *J. Organomet. Chem.* **2000**, *606*, 75−78.
(23) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792−803.
(24) Goldring, W. P. D.; Weiler, L. *Org. Lett.* **1999**, *1*, 1471−1473.
(25) For the isolation of motuporamine C, see: Williams, D. E.; Lassota, P.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 4838−4841.
(26) Fürstner, A.; Rumbo, A. *J. Org. Chem.* **2000**, *65*, 2608−2611.
(27) See the Supporting Information for details regarding the synthesis of the *E*-dominant mixtures of macrocycles.
(28) A more detailed study involving the *Z*-selective ethenolysis of linear olefins using catalyst **2** is currently underway and will be reported in due course.
(29) This can be compared with the molybdenum-based system, which requires higher ethylene pressures (4−20 atm).[10]