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Synthesis of Unsaturated Macrocycles by Ru-Catalyzed Ring-Closing Metathesis: A Comparative Study

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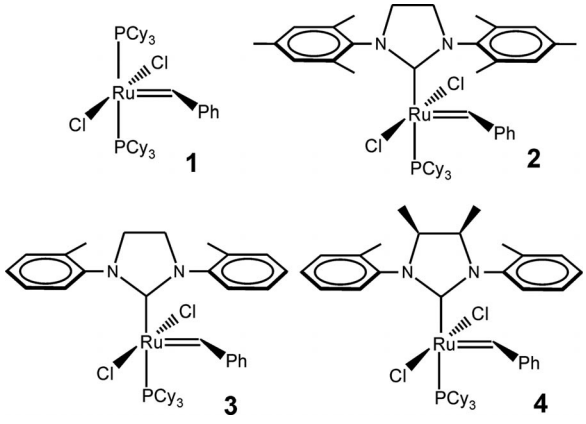
The activity and stereoselectivity of phosphane- and N-heterocyclic carbene (NHC)-containing ruthenium benzylidene complexes have been evaluated in macrocyclic ring-closing olefin metathesis to produce unsaturated lactones and lactams. The success of the macrocyclization depends on the nature of the ligand (phosphane or N-heterocyclic carbene) on the ruthenium center and on the NHC properties. As for stereoselectivity, *E*/*Z* ratios seem to be influenced not only by the nature of the ruthenium catalyst but also by the thermodynamic stabilities of the resulting unsaturated macrocycles, as confirmed by theoretical results.

Introduction

The discovery of well-defined catalysts for olefin metathesis has had a tremendous impact on organic synthesis and polymer chemistry.[1] Among them, Ru-based complexes developed by Grubbs et al. are of special interest because of their ease of handling and their remarkable tolerance towards a wide range of functional groups (e.g., **1**–**3** in Scheme 1).[2] They show excellent application profiles in a variety of metathesis reactions such as ring-closing metathesis (RCM), cross metathesis (CM), ring-opening metathesis polymerization (ROMP), ring-opening cross metathesis (ROCM), acyclic diene metathesis polymerization (ADMET), and enyne metathesis.[1,2]

Catalytic RCM of alkenes allows the synthesis of cyclic compounds containing five- or six-membered and even higher-membered rings. A ring architecture of 12 or more atoms is frequent in a large number of natural and unnatural macrocyclic lactones, lactams, ethers, and ketones, some of which exhibit important biological properties, such as antitumor, antibiotic, and antifungal activities; these compounds are also used as perfumery ingredients.[1j,3]

Various studies on macrocyclization reactions by RCM have been conducted to find appropriate conditions for the success of the reactions, but there is no clear rule to follow. Indeed, numerous factors, such as catalyst, steric demand of the substrate, presence of coordinating heteroatoms, ring size to be formed, solvent, concentration, temperature, and reaction time, have to be taken into account for synthetic RCM approaches to macrocyclic compounds.[3k,4]



Scheme 1.

Our recent interest in the synthesis of Ru-based complexes as active catalysts for olefin metathesis has led to the identification of a class of Ru catalysts containing N-heterocyclic carbene ligands with methyl groups on the NHC backbone in a *syn* and *anti* orientation.[5,6] Among them, complexes with aryl N-substituents of different bulkiness (*o*-tolyl or *o*-isopropylphenyl) revealed high efficiency in RCM reactions. In particular, *syn* complex **4**[6a] with *o*-tolyl N-substituents (Scheme 1) emerges among the most efficient catalysts in the formation of hindered olefins through RCM.

To further explore the catalytic potential of this latter catalyst in RCM reactions, herein we describe a systematic study on the macrocyclic RCM of unsaturated 14- and 15-

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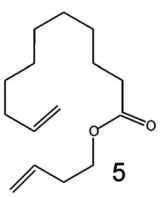
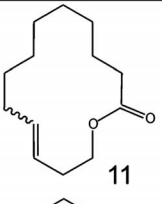
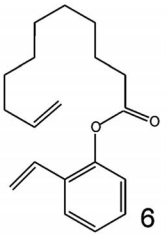
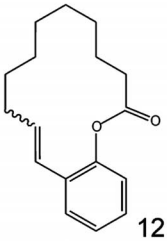
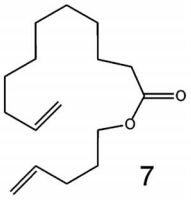
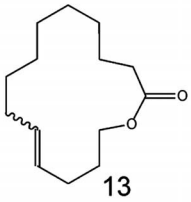
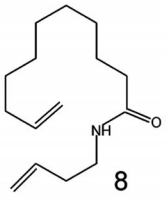
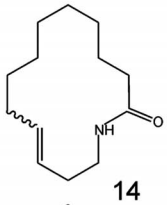
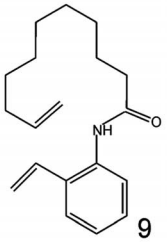
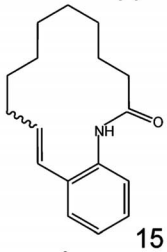
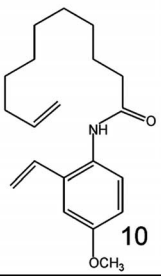
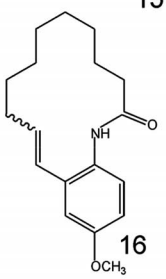
membered lactones and 14-membered lactams. The catalytic behavior of complex **4** in the formation of these macrocyclic frameworks is compared to that of commercial benchmark catalysts **1**,[7] **2**,[8] and **3**[9] (Scheme 1), in an attempt to find a trend in the reactivity and stereoselectivity of the different precatalysts.

Results and Discussion

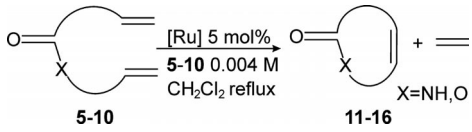
Ring-closure substrates **5**–**10** are depicted in Table 1. Compounds **5**, **7**, and **8** were easily prepared by acylation[10] of the corresponding commercially available alcohol or amine with 10-undecenoyl chloride. Diene ester **6** was ob-

Table 1. Synthesis of macrocyclic lactones and lactams by RCM of dienes **5**–**10** with catalysts **1**–**4**.[a]

Entry	Substrate	Product	Catalyst	Time [h]	Conv. [%][b]	*E*/*Z*[c]	*E*/*Z* calcd.[d]
1	 5	 11	**1**	4	97	83:17	
2			**2**	2	97	94:6	
3			**3**	4	54	94:6	96.5:3.5
4			**3**	24	54	94:6	
5			**4**	4	73	94:6	
6			**4**	24	73	94:6	
7	 6	 12	**1**	4	9	76:24	
8			**1**	24	26	94:6	
9			**2**	1	>99	>99:1	99.8:0.2
10			**3**	2	75	98:2	
11			**3**	24	77	99:1	
12			**4**	2	>99	>99:1	
13	 7	 13	**1**	4	97	40:60	
14			**2**	2	64	46:54	
15			**2**	24	70	46:54	
16			**3**	4	7	44:56	38.3:61.7
17			**3**	24	7	44:56	
18			**4**	4	13	44:56	
19			**4**	24	13	44:56	
20	 8	 14	**1**	4	20	80:20	
21			**1**	24	28	80:20	
22			**2**	2	76	92:8	
23			**2**	24	84	92:8	96.7:3.3
24			**3**	2	13	90:10	
25			**3**	24	14	90:10	
26			**4**	2	47	90:10	
27			**4**	24	47	90:10	
28	 9	 15	**1**	4	2	>99:1	
29			**1**	24	3	>99:1	
30			**2**	2	40	>99:1	
31			**2**	20	99	>99:1	95.8:4.2
32			**3**	4	9	>99:1	
33			**3**	24	18	>99:1	
34			**4**	2	12	>99:1	
35			**4**	24	50	>99:1	
36	 10	 16	**1**	4	1	>99:1	
37			**1**	24	5	>99:1	
38			**2**	2	49	>99:1	
39			**2**	24	97	>99:1	95.2:4.8
40			**3**	2	10	>99:1	
41			**3**	24	21	>99:1	
42			**4**	2	16	>99:1	
43			**4**	24	40	>99:1	

[a] Reactions in CH_2Cl_2 (4 mM) at reflux temperature. [b] Determined by GC and NMR spectroscopy. [c] *E*/*Z* ratios were determined by GC. [d] *E*/*Z* ratios obtained from DFT calculated energies in CH_2Cl_2 (for computational details see the Experimental Section).

tained by esterification of 2-hydroxystyrene[11] with undecen-10-enoic acid; diene amides **9** and **10** were prepared by condensation[12] of undecen-10-enoic acid with 2-vinylaniline[13] and 4-metoxy-2-vinylaniline,[14] respectively. Substrates **5**–**10** were subjected to the macrocyclic RCM reaction with the catalyst (5 mol-%) in refluxing CH_2Cl_2, under high-dilution conditions (0.004 M), as described in Scheme 2. The formation of corresponding unsaturated lactones and lactams **11**–**16** was monitored by GC analysis over a period of 24 h, and the most relevant results are summarized in Table 1. All reactions were performed at least in duplicate to confirm reproducibility.



Scheme 2.

The ring closure of diene ester **5** was successfully carried out by using catalysts **1** and **2** (Table 1, entries 1 and 2); Grubbs 2nd generation catalyst **2** performed slightly better than Grubbs 1st generation catalyst **1**. This is in line with previously reported results that show enhanced activities in the macrocyclic RCM of a 14-membered lactone with a Ru complex bearing an NHC (1,3-dimesytil-4,5-dihydroimidazol-2-ylidene) ligand (i.e., **2**) with respect to its parent diphosphane complex (i.e., **1**).[15] Conversions were lower with catalysts **3** and **4** (Table 1, entries 3–6), and the maximum value was reached within 4 h of reaction, suggesting that the replacement of the mesityl groups with less bulky *o*-tolyl groups on the nitrogen atoms of the NHC ligand has a detrimental effect on the efficiency of the Ru complexes. This can be explained by considering that Ru catalysts bearing NHCs with reduced bulk at the *ortho* positions of N-aromatic substituents are rather unstable and are susceptible to decomposition through C–H activation processes of the N-aryl groups on the NHC ligand.[16] Very likely, the different macro-RCM reactivities observed for **3** and **4** are related to the different substitution patterns of the NHC backbone. As already reported, the presence of methyl groups on the NHC backbone improves catalyst stability, because restriction of the rotation of the N-aryl group hinders the necessary proximity of an aryl C–H bond and the ruthenium center to promote degradation pathways.[6,17]

In this RCM reaction, catalysts **2**–**4** displayed identical stereoselectivity, furnishing macrocyclic product **11** with very high *E*/*Z* ratios (94:6) regardless of the structure of the RCM initiator. When **1** was employed as the catalyst, a lower *E*/*Z* ratio (83:17) was observed. The results obtained for the formation of macrolactone **11** with **1** and **2** are consistent with literature data, both in yield and *E*/*Z* selectivity.[12,18] It is worth to note that the stereochemical outcome of the RCM reaction to produce macrocycles is not easy to predict and control, and in principle, the *E*/*Z* selectivity of the olefin product reflects the thermodynamic stabilities of both geometrical isomers. Although the effect of catalyst on the geometric ratios of products formed by RCM reactions must be examined on a case-by-case basis, 1st generation catalysts are, in general, prone to produce macrocyclic compounds with a relatively kinetic *E*/*Z* ratios, whereas 2nd generation catalysts are likely to give products under thermodynamic control.[1e,3h,3k,3l]

To afford further information on catalyst behavior, thermodynamic stabilities of the *E* and *Z* isomers of **11** were evaluated by DFT calculations. Minimum-energy structures and energies of **11**-*E* and **11**-*Z* are reported in Figure 1, whereas the relative calculated populations of the two isomers in equilibrium are shown in Table 1. Isomer **11**-*E* is favored by 2.1 kcal mol^{-1} over **11**-*Z*, not only due to the intrinsic stability of the *trans* double bond, but also as a consequence of the higher energy of **11**-*E*, which results from two instances of eclipsing C–C atoms arising from nearly gauche(+)–gauche(–) conformations. The distances of the eclipsed C atoms, which are shorter than van der Waals distances, are indicated in Figure 1. The calculated *E*/*Z* populations are very close to the experimental ratio found for products obtained in the presence of catalysts **2**–**4**, confirming the tendency of these catalysts to give thermodynamic control.

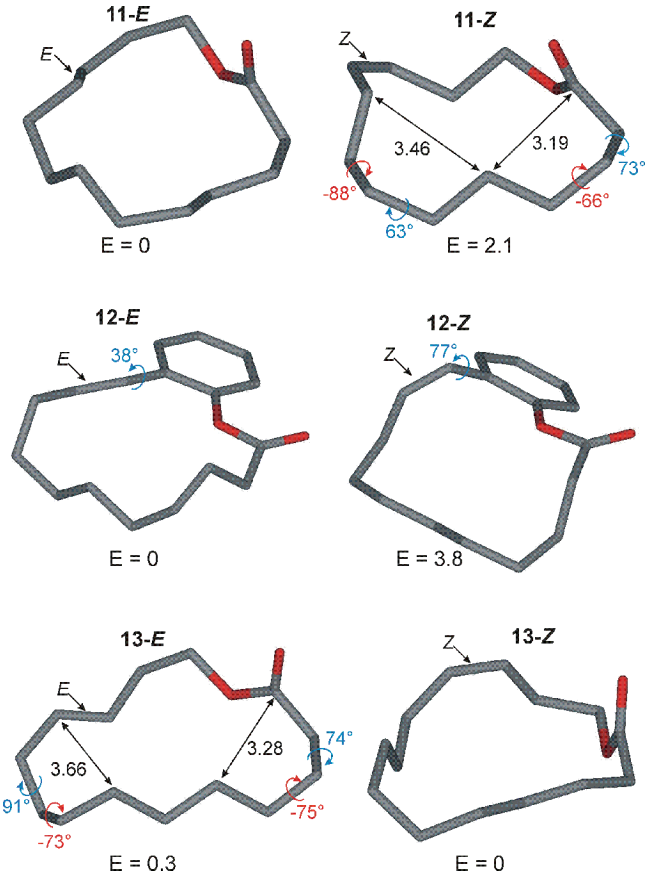


Figure 1. Structures and internal energies of the *E* and *Z* isomers of compounds **11**–**13** calculated in CH_2Cl_2. Energies are in kcal mol^{-1}, distances are in Å.

Initiators **1**–**4** were then investigated in the macrocyclic RCM of **6** to give 14-membered lactone **12**. This substrate is characterized by the same double bond position within the macrocyclic ring as **1** but differs from the latter for the presence of an aromatic ring located between the ester and the olefinic functionalities. The aromatic ring was installed on the macrocyclization precursor as conformational constraint to facilitate metathesis ring-closure reactions.[4]

From the analysis of the data reported in Table 1, macrocyclic RCM of **6** performed with diphosphane catalyst **1** gave very poor yields (Table 1, entries 7 and 8), and the *E*/*Z* ratio slightly changed during the course of the reaction to approach the thermodynamic value, as a consequence of secondary metathesis reactions that can cause isomerization. The decreased efficiency of **1** in the formation of **12** is not surprising. Indeed, it was found to be totally ineffective in the synthesis of a very similar macrolactone, the macrolide (*S*)-zearalenone, for attempted cyclizations of the required styrenyl precursor.[19] On the other hand, the presence of a cyclic conformational constraint in substrate **6** has proven to have a beneficial effect on the same macro-RCM reaction carried out with monophosphane catalysts **2** and **4** (Table 1, entries 9 and 12), which gave the only *E*-configured product in quantitative yield. As previously observed, for **3**, conversions were slightly lower than those for **4**, indicating also in this case an appreciable influence of the substitution pattern of the backbone of the NHC on the activity of the catalyst, whereas no difference in the stereochemical outcome of the reaction was detected. It is worth underlining that *E*-alkene units are frequently found in macrocyclic natural products, but the synthesis of large rings containing *E*-alkenes still represents a challenge.[31] The stereoselective course of this reaction is probably due to the presence of the phenyl ring as a conformational constraint in **6**, which favorably predisposes the reacting sites of dienes during the metathesis ring closure. The excellent *E*/*Z* selectivity observed is consistent with the calculated *E*/*Z* ratio (99.8:0.2 in Table 1). Indeed, as shown in Figure 1, the stability of the *E* isomer with respect to the *Z* isomer for macrocycle **12** is very significant (ΔE = 3.8 kcal mol^{-1}). As for **12**-*Z*, the lack of conjugation of the double bond with the close aromatic ring, as indicated by the 77° torsion angle reported in Figure 1, plays the main role in decreasing the stability of the *Z* isomer.

Treatment of diene **7** (Table 1, entries 13–15) with catalysts **1** and **2** furnished the corresponding 15-membered macrolactone **13** in good yields, whereas unsatisfactory results were obtained with catalysts **3** and **4** (Table 1, entries 16–19). The presence of one more carbon atom than that in substrate **5** renders the cyclization reaction more difficult for monophosphane catalysts **3** and **4**. Indeed, they lose activity within 2 h from the beginning of the reaction, which means, once again, a major tendency of these complexes to decompose. From analysis of the *E*/*Z* ratios, in this RCM reaction, the *Z* isomer of **13** was preferentially formed. A very similar *Z*-selectivity was observed for catalysts **1**–**4** (Table 1, entries 13–19). Once again, the calculated *E*/*Z* populations (38.3:61.7) well reproduced the experimentally observed *E*/*Z* ratios, indicating a mainly thermodynamically controlled RCM in the formation of **13**, for all catalysts. As reported in Figure 1, internal energies of the minimum-energy structures of the *E* and *Z* isomers of **13** are very close; **13**-*E* is less stable than **13**-*Z* by 0.3 kcal mol^{-1}. In the case of 15-membered rings, the lower stability of the *E* isomer is due to the presence of two instances of eclipsing C–C atoms arising from a gauche(+)–gauche(–) conformation. This unfavorable conformation is only partially compensated by the intrinsic stability of the *trans* double bond.

We next examined the efficiency of catalysts **1**–**4** in the RCM of amide dienes **8**–**10** to form macrolactams **14**–**16**. These latter RCM products present the same ring size and the same double bond position within the macrocyclic ring as macrolactones **5** and **6**. As widely described in the literature, the nature of the heteroatoms influences the cyclization reaction leading to a variety of results.[20] The effect of the heteroatom appears evident in the ring closure of **8** with catalyst **1** (Table 1, entries 20 and 21), which proceeded in lower yield (28% in 24 h) with respect to the analogous reaction (Table 1, entry 1) to form macrolactone **11** (97% in 4 h). For catalysts **2**–**4** (Table 1, entries 22–27), the general trend in yield is in alignment with that of previous RCM reactions (Table 1, entries 2–6), but also in this case the

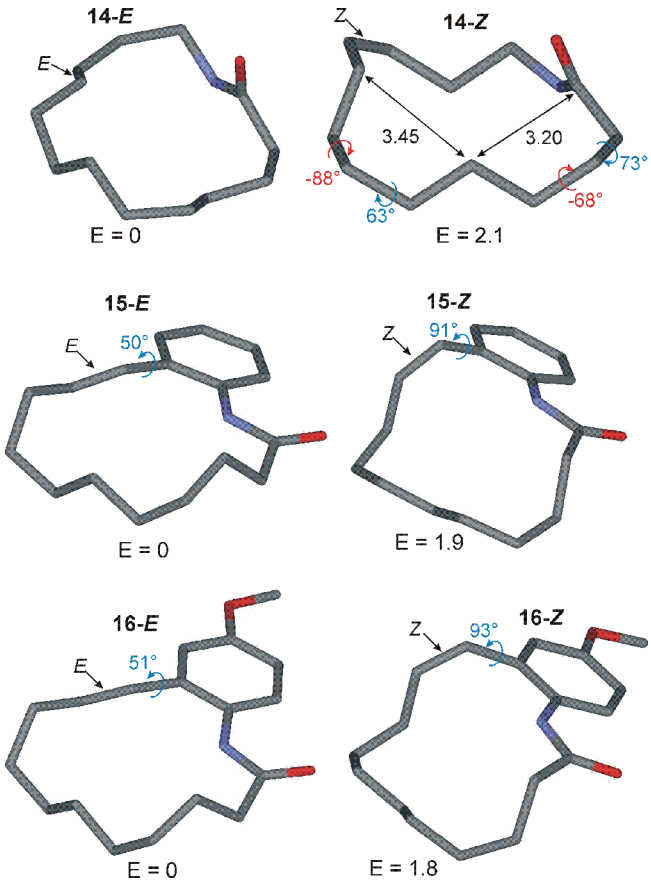


Figure 2. Structures and internal energies of the *E* and *Z* isomers of compounds **14**–**16** calculated in CH_2Cl_2. Energies are in kcal mol^{-1}, distances are in Å.

presence of nitrogen led to less satisfactory results.[21] Comparison of results for ring closures of **9** and **10** shows that the introduction of a methoxy substituent on the aromatic ring does not affect the cyclization reactions (Table 1, entries 28–35, 36–43). As for the *E*/*Z* selectivity, it appears to be clear that the stereochemical outcome of the examined RCM reactions is not influenced by the nature of the heteroatom.

Calculated minimum-energy structures for the *E* and *Z* isomers of compounds **14**–**16** are reported in Figure 2. The replacement of oxygen with –NH– in the macrocyclic ring produces only slight conformational differences between the lactones and the corresponding lactams. Indeed, for macrocycles **14**–**16**, the *E* isomer was found to be about 2 kcal mol^{-1} more stable than the corresponding *Z* isomer, indicating that under thermodynamic control the *E* isomer would prevail >95% in solution.

Conclusions

In this report, we have carried out a comparative study on the synthesis of 14- and 15-membered lactones and lactams (i.e., **11**–**16**) by RCM of the corresponding dienes (i.e., **5**–**10**) with phosphane (i.e., **1**) and NHC-containing catalysts (i.e., **2**–**4**). Much attention was focused on the influence of the N-aryl group and the substitution of the backbone of the NHC ligands in controlling the macrocyclization outcome. Catalyst **1** was found to be highly efficient in the formation of macrolactones **11** and **13**, whereas it was poorly active in the macrocyclic RCM of **12** and **14**. The synthesis of macrolactams **15** and **16** could not be achieved with this catalyst. Catalyst **2** afforded macrocyclic compounds **11**–**16** in good to excellent yields, whereas catalysts **3** and **4** with different NHC bulkiness showed a marked dependence on the nature of the substrate in terms of activity. The higher macro-RCM reactivity displayed by catalyst **4** compared to **3** can be related to the increased stability of catalyst **4**, which is less susceptible to degradation as a result of the presence of methyl groups on the NHC backbone. Interestingly, the general trend in yield with monophosphane catalysts **2**–**4** highlights that small variations in the NHC aryl N-substituents and/or substitution of the backbone lead to different catalyst behavior in RCM reactions. More in detail, catalyst **2** with N-mesityl groups is more efficient than catalysts **3** and **4** bearing N-*o*-tolyl groups, whereas backbone-substituted catalyst **4** is more active than catalyst **3** without backbone substitution. These results are consistent with the notion that metathesis catalysts need to be screened to determine the best catalyst for a reaction and that no single catalyst is the most efficient for all substrates.

As for stereoselectivity, the *E*/*Z* ratios seem to be influenced by the nature of the ligand (phosphane or N-heterocyclic carbene) on the ruthenium center as well as by the thermodynamic stabilities of the resulting unsaturated macrocycles. The presence of an aromatic ring system as conformational control element (substrates **6**, **9**, and **10**) favored *E* selectivity in the presence of all tested catalysts and improved cyclization promoted by catalysts **3** and **4**. Molecular modeling studies, performed to compare the relative stabilities of the *E* and *Z* isomers of compounds **11**–**16**, indicate that for all compounds except **13** the favored thermodynamic product is the *E* isomer. In fact, calculated *E*/*Z* ratios for **11**, **12**, **14**, **15**, and **16** are >95:5, which reflects well the thermodynamic control of macrocycle RCM in the presence of catalysts **2**–**4**. This observation is furthermore confirmed by the calculated *E*/*Z* population for 15-membered ring **13**, which shows a slight prevalence of the *Z* isomer (about 40:60), reproducing experimental *E*/*Z* ratio obtained with all catalysts.

Experimental Section

Experimental Details: All reactions involving metal complexes were conducted in oven-dried glassware under a nitrogen atmosphere with anhydrous solvents by using standard Schlenk techniques and glove box techniques. Toluene and THF were distilled from sodium/benzophenone. CH_2Cl_2 was dried with CaH_2 and freshly distilled before use. All chemical products were purchased from Sigma–Aldrich and were reagent quality. These products were used without further purification. The syntheses of substrates **5**, **7**, and **8** were carried out according to published procedures.[10] Ru catalyst **4** was prepared as previously reported.[6a] Macrocycles **11**,[22] **13**,[23] and **14**[18] were already known. Flash column chromatography of organic compounds was performed by using silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed by using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization of the TLC plate was performed by UV light or by using $KMnO_4$ or I_2 stains. NMR spectra were recorded with a Bruker AM300 and Bruker Avance 400 instruments operating at 300 and 400 MHz for ^{1}H, respectively. The ^{1}H and ^{13}C chemical shifts are referenced to $SiMe_4$ (δ = 0 ppm) by using the residual protio impurities of the deuterated solvents as internal standard. GC analysis were performed by using a Thermo Finnigan gas chromatograph equipped with a FAMEWAX (Crossbond polyethylene glycol) capillary column for compound **8** and an OPTIMA 5 (5% phenyl/95% dimethylpolysiloxane) capillary column for all the other substrates.

General Procedures for the Synthesis of Substrates 6, 9, and 10:[12] To a solution of 10-undecenoic acid (1.0 equiv.) in dichloromethane was added triethylamine (4.0 equiv.) and 1-propylphosphonic acid cyclic anhydride (1.2 equiv.) whilst stirring. After 15 min at room temperature, the appropriate alcohol or amine (1.2 equiv.) was added, and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1 for **6**; hexane/EtOAc, 7:1 for **9** and **10**).

6: Colorless oil (50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 7.7 Hz, 1 H), 7.26 (dt, *J* = 7.7 Hz, 2 H), 7.04 (d, *J* = 7.9 Hz, 1 H), 6.76 (dd, *J* = 11.0, 17.7 Hz, 1 H), 5.83 (m, 1 H), 5.76 (d, *J* = 17.7 Hz, 1 H), 5.33 (d, *J* = 11.0 Hz, 1 H), 5.01 (d, *J* = 17.4 Hz, 1 H), 4.95 (d, *J* = 10.5 Hz, 1 H), 2.60 (t, *J* = 7.6 Hz, 2 H), 2.06 (q, *J* = 7.4 Hz, 2 H), 1.79 (m, 2 H), 1.48–1.27 (br. m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.3, 148.2, 139.4, 130.6, 130.4, 128.9, 126.6, 126.3, 122.8, 116.5, 114.4, 34.5, 34.0, 29.9, 29.5, 29.4, 29.3, 29.2, 29.1, 26.6, 25.2 ppm.

9: White microcrystalline solid (70%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.76 (d, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H),

7.27 (t, J = 7.7 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.09 (br. s, N*H*), 6.81 (dd, J = 10.9, 17.3 Hz, 1 H), 5.82 (m, 1 H), 5.69 (d, J = 17.3 Hz, 1 H), 5.41 (d, J = 10.9 Hz, 1 H), 4.98 (d, J = 17.1 Hz, 1 H), 4.92 (d, J = 10.2 Hz, 1 H), 2.35 (t, J = 7.3 Hz, 2 H), 2.04 (q, J = 6.9 Hz, 2 H), 1.70 (m, 2 H), 1.43–1.24 (m, 10 H) ppm. ^{13}C NMR (250 MHz, CD_2Cl_2): δ = 171.9, 139.9, 135.3, 132.7, 131.2, 128.8, 127.2, 125.8, 124.5, 118.0, 114.4, 38.0, 34.4, 29.9, 29.6, 29.5, 26.2 ppm.

10: White microcrystalline solid (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, J = 8.8 Hz, 1 H), 6.97 (d, J = 2.9 Hz, 1 H), 6.95 (s, N*H*), 6.84 (dd, J = 2.9, 8.9 Hz, 1 H), 6.75 (dd, J = 10.9, 17.6 Hz, 1 H), 5.87–5.75 (m, 1 H), 5.67 (d, J = 17.5 Hz, 1 H), 5.38 (d, J = 10.9 Hz, 1 H), 4.98 (d, J = 17.3 Hz, 1 H), 4.92 (d, J = 10.2 Hz, 1 H), 3.81 (s, 3 H), 2.36 (t, J = 7.5 Hz, 2 H), 2.07–1.98 (m, 2 H), 1.77–1.68 (m, 2 H), 1.43–1.23 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.8, 157.5, 139.4, 132.9, 132.5, 127.7, 126.4, 117.9, 114.4, 114.2, 111.8, 55.7, 37.6, 34.0, 29.5, 29.3, 29.1, 26.0 ppm.

Representative Procedure for the Synthesis of Macrocyclic Compounds 11–16:[24] A 100-mL three-necked round-bottomed flask was fitted with a condenser and two additional funnels. Solutions of the ruthenium carbene (6.0 μmol) and the diene (120 μmol), each in CH_2Cl_2 (10 mL), were independently added dropwise to refluxing CH_2Cl_2 (10 mL) over a period of 15 min under a nitrogen atmosphere. Aliquots were removed periodically for GC analysis, and GC retention times and integration were confirmed with samples of authentic material. After 24 h, the solvent was removed in vacuo, and the residue was purified by flash chromatography (hexane/ethyl acetate, 10:1 for **12**; hexane/ethyl acetate, 6:4 for **15**, hexane/ethyl acetate, 5:2 for **16**) to afford analytically pure compounds.

12: *E* isomer was obtained as a colorless oil (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.7 Hz, 1 H), 7.31–7.19 (m, 2 H), 7.08 (d, J = 7.7 Hz, 1 H), 6.59 (d, J = 15.9 Hz, 1 H), 6.11 (dt, J = 6.7, 16.0 Hz, 1 H), 2.64 (m, 2 H), 2.31 (q, J = 6.17 Hz, 2 H), 1.84 (br. m, 2 H), 1.61–1.28 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.1, 147.5, 132.9, 131.0, 127.7, 126.7, 126.2, 124.1, 123.0, 35.1, 30.6, 27.4, 26.1, 25.9, 25.3, 25.0, 24.0 ppm. $C_{17}H_{22}O_2$ (258.36): calcd. C 79.03, H 8.58; found C 79.02, H 8.56.

15: *E* isomer was obtained as an off-white microcrystalline powder (85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.9 Hz, 1 H), 7.34 (d, J = 7.4 Hz, 1 H), 7.25 (t, J = 7.9 Hz, 1 H), 7.13 (t, J = 7.4 Hz, 1 H), 6.49 (d, J = 15.7 Hz, 1 H), 5.97 (dt, J = 6.9, 15.7 Hz, 1 H), 2.47 (m, 2 H), 2.20 (q, J = 6.23 Hz, 2 H), 1.80–1.26 (m, 12 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 171.6, 135.5, 134.2, 131.6, 127.9, 127.3, 125.8, 125.7, 124.2, 37.7, 31.0, 27.5, 26.7, 26.1, 25.6, 25.0 ppm. $C_{17}H_{23}NO$ (257.37): calcd. C 79.33, H 9.01, N 5.44; found C 79.33, H 9.03, N 5.42.

16: *E* isomer was obtained as an off-white solid (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, J = 8.7 Hz, 1 H), 7.08 (br. s, 1 H, N*H*), 6.93 (d, J = 2.9 Hz, 1 H), 6.80 (dd, J = 2.9, 8.8 Hz, 1 H), 6.48 (d, J = 15.8 Hz, 1 H), 6.03 (dt, J = 6.6, 15.7 Hz, 1 H), 3.82 (s, 3 H), 2.48–2.40 (m, 2 H), 2.29 (q, J = 6.2 Hz, 2 H), 1.85–1.18 (m, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.0, 157.8, 134.6, 134.3, 127.1, 127.0, 125.7, 113.2, 111.9, 55.6, 37.5, 30.8, 27.4, 26.7, 25.9, 25.8, 25.7, 24.8 ppm. $C_{18}H_{25}NO_2$ (287.40): calcd. C 75.22, H 8.77, N 4.87; found C 75.20, H 8.76, N 4.87.

Computational Details: Density functional calculations were performed on all the systems with the Gaussian09 set of programs.[25] BP86 was used as a functional and gradient corrections were taken from the work of Becke and Perdew.[26–28] The electronic configuration of the molecular systems was described by the split-valence basis set with polarization functions of Ahlirchs and co-worker (standard SVP basis set in Gaussian09), for H, C, N, and O.[29] Minimum free-energy structures were characterized by the presence of zero imaginary frequency. Solvent effects were estimated in calculations based on the polarizable continuous solvation model PCM. CH_2Cl_2 was chosen as model solvent.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization of all new compounds as well as Cartesian coordinates and internal energies of calculated structures.

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