Chapter 3:

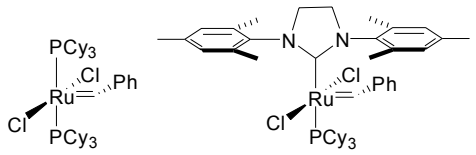
Tandem Ring-Closing Metathesis Reactions with Ruthenium Catalyst Containing N-Heterocyclic Carbene Ligand

Abstract

Catalyst **1**, $Cl_2(PCy_3)_2Ru=CHPh$ has popularized ring-closing metathesis (RCM) over the past seven years. However, the activity of **1** was limited to simple alkenes for RCM. With the development of more active catalyst **2**, $Cl_2(PCy_3)(IMesH_2)Ru=CHPh$, more challenging functionalized olefins were successfully ring-closed in high yields. In this chapter, catalyst **2** was used to synthesize complex molecules with functionalized olefins by tandem cyclization reactions. In the first part of the chapter, tandem ring-opening/ring-closing and tandem enyne ring-closing metathesis strategies are applied in the synthesis of bicyclic compounds. In the second half, synthesis of macrocycles are demonstrated by tandem ring-opening/cross/ring-closing metathesis also known as ring expansion metathesis (REM).

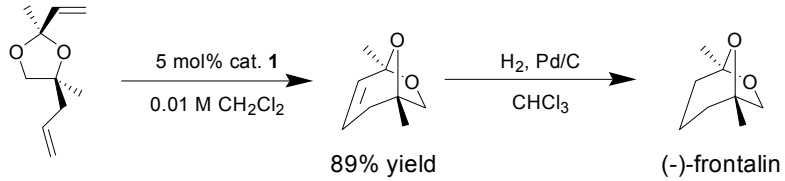
Background

Ring-closing metathesis (RCM) is the most frequently used reaction among the olefin metathesis processes in organic synthesis.[1] Typically 5- or 6-membered rings are produced by the facile intramolecular ring-closure of 1,7- or 1,8-dienes.[2] The equilibrium of RCM is heavily favored to the ring-closed product since thermodynamically stable five- or six-membered rings are formed with entropic gain by loss of ethylene gas. This reaction was further popularized with the development of the functional group tolerant ruthenium-based catalysts.[3] Even though Ru catalysts were less active than early transition metal based catalysts, mainly Mo catalysts, their high tolerance to many functional groups allowed chemists to perform RCM on the highly functionalized substrates. The versatility of RCM was demonstrated by $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**)



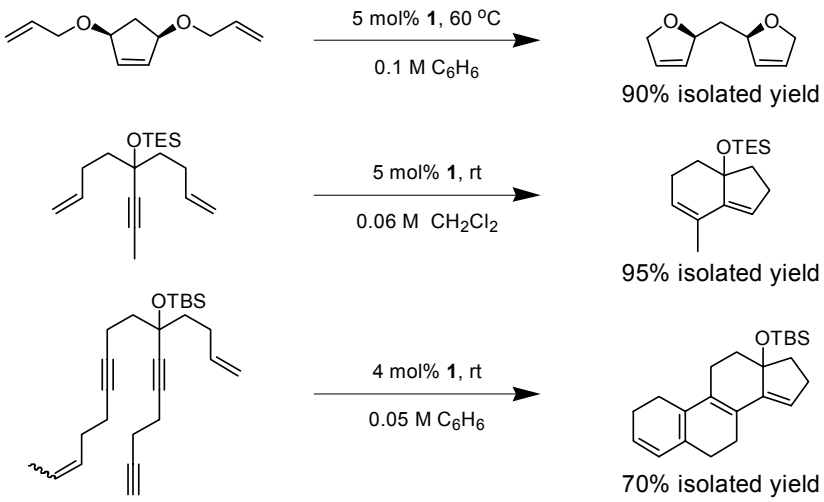
1 **2**

in the total synthesis of many natural products and drugs, in which the RCM was involved in the late stages as a key step for the completion of the syntheses.[4] As an example, our group reported an efficient RCM to provide a concise total synthesis of (-)-frontalin (Scheme 1).[5]



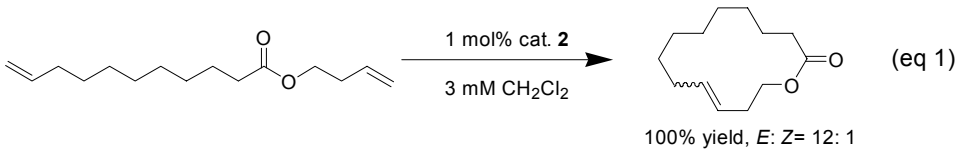
Scheme 1. Synthesis of (-)-frontalin by RCM

A recent advance in RCM includes tandem RCM to prepare complex molecules such as fused bicycles and polycycles (Scheme 2).[6] In these tandem events, cycloalkenes and alkynes were used to promote domino metathesis relay. The power of tandem RCM was demonstrated when the steroid-like skeleton was successfully synthesized in one tandem event (Scheme 1, the last example).[6c]



Scheme 2. Tandem RCM by catalyst **1**

With the development of a highly active and functional group tolerant catalyst **2** bearing N-heterocyclic carbene,[7] more challenging substrates such as acrylates and *gem*-disubstituted olefins were successfully incorporated into the ring system.[8] Also catalyst **2** allows efficient macrocyclization with high stereoselectivity on the newly formed olefins (eq 1).[9] Therefore highly active catalyst **2** opens up the possibility of preparing various ring systems with new functionalities. This chapter demonstrates the efforts to prepare complex bicyclic compounds and macrocycles by tandem RCM strategies.[10]



(eq 1)

Part I. Tandem RCM to Synthesize Bicyclic Compounds

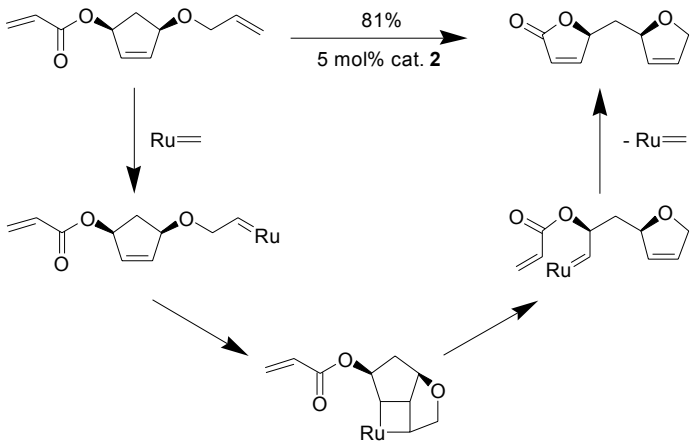
Introduction

Tandem cyclization reactions build up molecular complexity rapidly from relatively simple starting substrates.[11] Complicated molecules have been synthesized in a single step by carbanion,[12] carbocation,[13] free radical,[14] cycloaddtion[15] and Pd coupling reactions[16] whose novelty and efficiency were demonstrated by total syntheses of many natural products.[17] Olefin

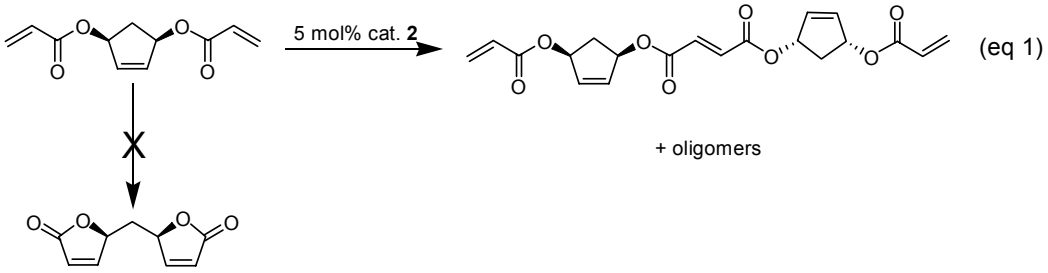
metathesis has become a useful reaction in organic synthesis,[1] and our group has recently demonstrated the viability of tandem ring closing metathesis reactions using catalyst **1**.[6] Unfortunately, catalyst **1** could not incorporate more synthetically valuable functionalized olefins such as α,β-unsaturated carbonyl compounds. However, with the development of the more active catalyst **2**,[7] containing an N-heterocyclic ligand, functionalized olefins could participate in RCM and cross metathesis reactions.[8] Herein, we report tandem RCM reactions, using catalyst **2,** to make synthetically useful α,β-unsaturated lactones and enones.

Results and Discussion

Various substrates containing different olefin arrays were examined for the tandem cyclization, and Table 1 demonstrates the viability of tandem ring-opening/ring-closing metathesis. In entry 1, catalyst **2** reacts with the more reactive terminal olefin, and the resulting alkylidene opens the 5-membered ring (Scheme 3). The sequence of the tandem events is completed by ring-closing onto the α, β-unsaturated carbonyl. It is likely that ring-opening of the substituted cyclopentene ring is not the initial metathesis event because the substrate shown in Scheme 4 did not yield any desired bicyclic compound, instead the products were dimer and other oligomers, which were formed by the enoic carbine intermediate (Chapter 2).[18] In addition 1,4-bisacetoxycyclopentene is not able to undergo ring-opening metathesis polymerization (ROMP).[19] It is believed that bis-allylic substituents on cyclopentene rings greatly suppress the ring-opening reaction. The substrate in entry 2 of Table 1 undergoes a similar domino cyclization as shown to the one Scheme 3 because the acyclic 2, 3-disubstituted olefin in this case is more reactive than the acrylates and the cyclopentene ring. Fused 5,5,7- and 7,5,7-tricyclic compounds were synthesized from highly strained norbornene moiety, but the yields were lower due to competing norbornene polymerization by ROMP (Entries 3 and 4).



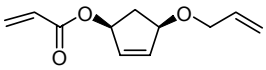
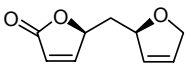
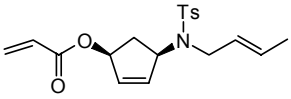
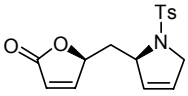
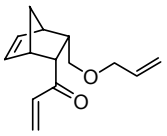
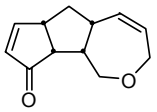
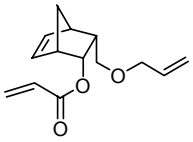
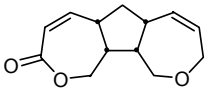
Scheme 3. Ring-opening / ring-closing tandem RCM



(eq 1)

Scheme 4. Undesired dimerization of diacrylate

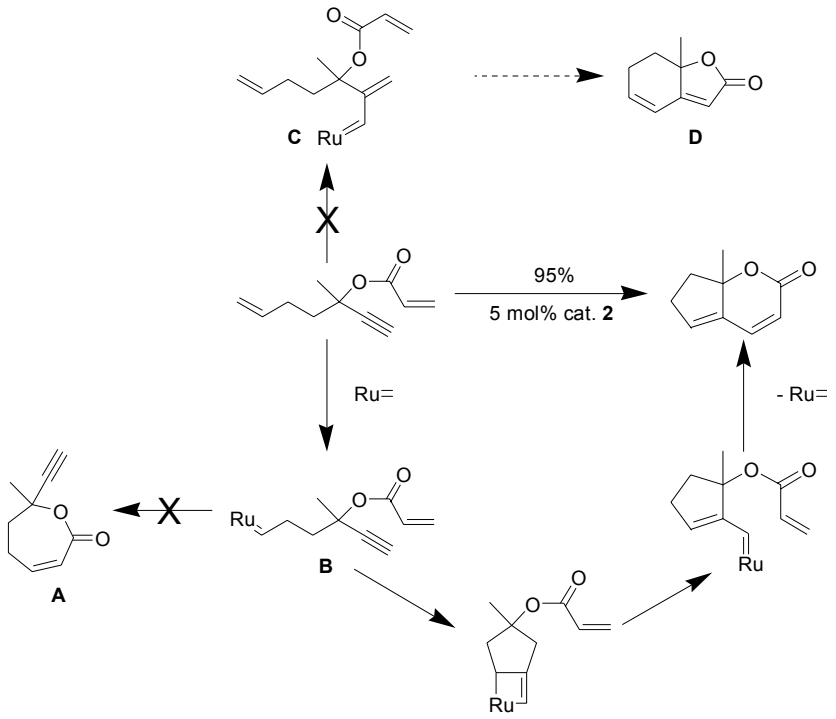
Table 1. Tandem ring-opening/closing metathesis to install functionalized olefins[a]

entry	substrate	concentration [M]	product	yield [%]
1		0.05		81
2		0.05		89
3		0.005		45
4		0.005		47

[a] 5 mol% catalyst **2** at 40 °C in CH_2Cl_2 for 6-12 hrs.

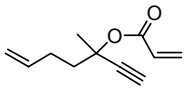
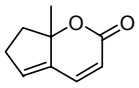
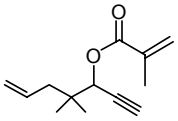
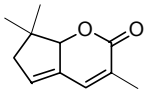
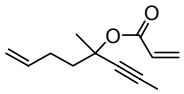
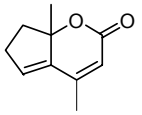
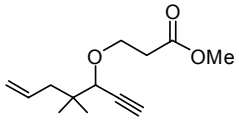
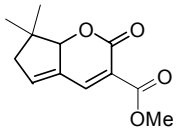
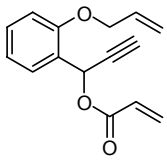
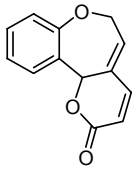
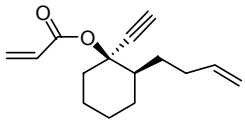
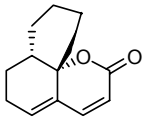
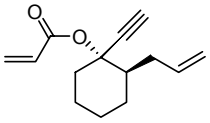
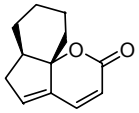
Another type of tandem RCM reaction is demonstrated by tandem enyne ring closing metathesis to form fused bicyclic ring systems (Table 2). Like the previous examples, catalyst **2**

reacts with the terminal olefins preferentially, and undergoes rapid intermolecular enyne metathesis to form the first ring, then reacts with the α,β-unsaturated carbonyl olefin to form the final ring (Scheme 5). The fact that 7-membered lactone **A** is never observed implies that prior to the first RCM event, the newly formed alkylidene **B** exclusively reacts with alkynes over acrylates. Blechert and co-workers have suggested a different mechanism where alkynes reacted first with the catalyst.[20] If such a mechanism is operative in this case, then the resultant intermediate **C** should lead to the product **D**. We do not believe that this mechanism is operative in our cases because compound **D** was not observed. More challenging trisubstituted α,β-unsaturated carbonyl olefins were also successfully cyclized using this methodology (Table 2, entries 2-4) and 7,6-fused bicyclic compound were synthesized in moderate yield (Entry 5). Lastly, tandem RCM to make 6,5,6- and 6,6,6-fused tricyclic compounds are shown in entries 6 and 7, which demonstrate, that this methodology has potential applications in the synthesis of complex natural products.



Scheme 5. Enyne Tandem RCM

Table 2. Tandem enyne ring-closing metathesis to install functionalized olefins[a]

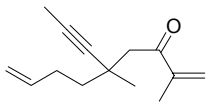
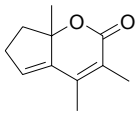
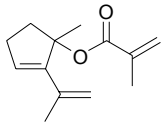
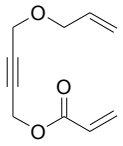
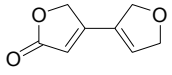
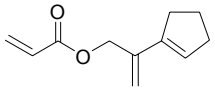
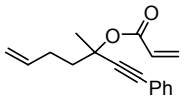
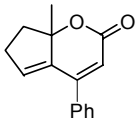
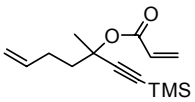
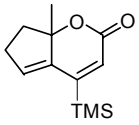
entry	substrate	concentration [M]	product	yield [%]
1		0.03		95
2		0.03		86
3		0.03		72
4		0.03		95
5		0.03		58
6		0.03		100
7		0.06		74

[a] 5-7 mol% catalyst **2** at 40 ^{o} C in CH_2Cl_2 for 6-12 hrs.

Tandem RCM reactions have some limitations, which are illustrated in Table 3. An attempt to make tetrasubstituted α,β-unsaturated carbonyl compound was less than satisfactory, yielding only 10% of desired product and the major product being the half-closed product (Table 3, entry 1). The second ring-closure to make the tetrasubstituted olefin seems to be very slow, so the resulting disubstituted alkylidene of the initial RCM event reacts faster with the terminal olefin of another molecule, yielding the half-closed product as a major product. Entry 2 shows a failed tandem RCM reaction because disubstituted alkylidene from the first ring-closure and the

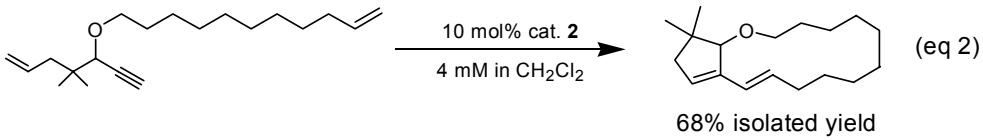
acrylate were likely in conformation unfavored for the final RCM. Bulky substituents on alkynes, such as TMS or phenyl, do not promote even the first enyne RCM (entries 3 and 4).

Table 3. Unsuccessful tandem enyne RCM reactions[a]

entry	substrate	desired product	yield [%]	major product[b]
1			10	
2			0	
3			0	starting material
4			0	starting material

[a] 5 mol% catalyst **2** at 40 °C for 12 hrs. [b] The major products were obtained in greater than 50% yield.

This methodology was further applied to tandem enyne macrocyclization where a small 5-membered ring and a 14-membered macrocyle were formed in one pot (eq 2). Higher catalyst loading (10 mol%) and high dilution (4 mM) were required to produce the bicyclic macrocycle in a moderate yield. Only *E*-isomer product was observed by ^{1}H NMR.



(eq 2)

Conclusion

The highly active catalyst **2** was used in tandem RCM reactions to make molecules possessing various ring systems. The ability to incorporate α,β-unsaturated carbonyl olefins into

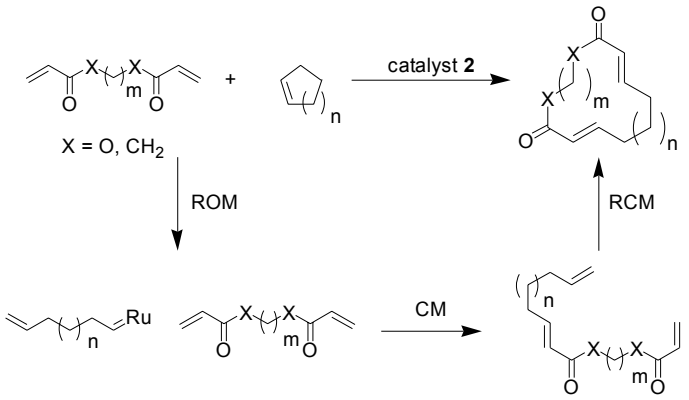
these products makes tandem RCM reactions synthetically more valuable since further manipulation is possible.

Part II. Ring Expansion Metathesis (REM)

Introduction

Olefin metathesis is an efficient reaction for the formation of C=C bonds.[1] Catalyst **1**, $Cl_2(PCy_3)_2Ru=CHPh$, greatly helped to open metathesis to the organic community due to its functional group tolerance and stability to air and moisture.[3] The recent development of the highly active and highly stable catalyst **2**[7] has broadened the utility of olefin metathesis for organic synthesis, as shown by the successful ring-closing and cross metathesis reactions of the functionalized olefins such as α,β-unsaturated carbonyl compounds.[8, 21]

Ring-closing metathesis has provided a new approach to the challenging problem of macrocyclization.[10, 22, 23] The efficiency of this process has been improved by the higher activity of catalyst **2**; not only in improved yields but also by reducing the catalyst loading and in improved stereoselectivity of the newly formed olefins.[10a, 23] Thus metathesis provides an efficient and mild route for the synthesis of macrocycles, especially carbocycles whose formation is considered harder than macrolactonization or lactamization. Herein, we report a novel method of macrocycle formation by a ring expansion metathesis (REM) reaction in which all three types of olefin metathesis (ring-opening, cross, and ring-closing) reactions occur sequentially to yield macrocycles (Scheme 6).



Scheme 6. Proposed route of ring expansion metathesis

Results and Discussion

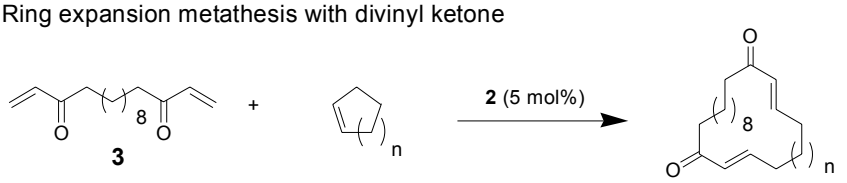
As shown in Scheme 6, the ring expansion is envisioned to occur between cycloalkenes and acyclic dienes. For a successful ring expansion, several conditions must be satisfied. First, cycloalkenes must be able to undergo the ring-opening reaction. Once opened, they must react selectively with the acyclic diene for both CM and RCM to minimize side-products. Finally, acyclic diene should not undergo metathesis reactions with itself, such as cyclization or dimerization and oligomerization by cross metathesis.

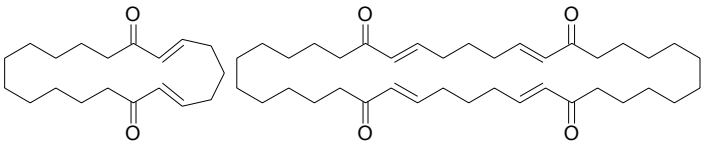
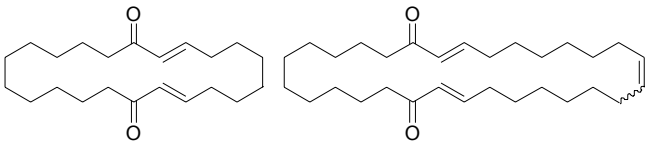
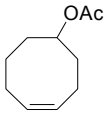
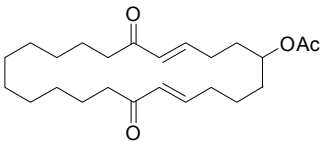
To test this idea, we chose diacrylates and divinyl ketones as acyclic dienes (or linkers) because they are known to react selectively with terminal olefins in excellent yields and less favorably with themselves.[8b] Catalyst **2** (5 mol%) was added to a solution of divinyl ketone (compound **3**, Table 4) and cyclopentene (5 equiv.) in CH_2Cl_2 (5 mM in **3**). After refluxing for 12 hours, several products were obtained with the complete consumption of **3**. The major products were the desired (1 + 1) fashion (**3** and cyclopentene) ring expanded product **4** with *E*-isomer in 43% isolated yield and the (2+ 2) double ring expanded product **5** in ratio of 1.3/1 (entry 1, Table 4). As anticipated, increasing the concentration to 25 mM decreased the product ratio of **4**/**5** to 1/2.3 (entry 2), because at higher concentration, competing oligomerization became more favorable.

Next, more readily ring-opening cyclooctene was tested for REM. Due to its higher ring strain favoring ROMP process, the relationship of concentration between cyclooctene and the product distribution was initially explored (Table 1, entries 3 to 5).[24] With 5 equiv. of cyclooctene (effectively 25 mM in cyclooctene), a low yield of 1:1 ratio of the desired (1+ 1) product **6** (23% yield) and (1+ 2) cyclooctene double inserted product **7** was obtained. The rest were higher oligomers of larger macrocycles. Decreasing the equivalents of cyclooctene to 2 (effectively 10 mM in cyclooctene) increased the yield to 34% with **6**/**7** ratio of 1.2/1, and finally the optimal yield of 53% for the desired product **6** was isolated with 1.1 equivalents of cyclooctene (entry 5). Functionalized cyclooctenes are also viable substrates for ring expansion (entry 6). We believe that the rate of ROMP of cyclooctene is greatly reduced at such low concentration (5 mM) yielding satisfactory amounts of desired ring expanded products.

With good conditions for REM in hand, we investigated other acyclic dienes and found diacrylates were also successful in ring expansion reactions (Table 5). 1,4-Butanediol diacrylate and 1,6-hexanediol diacrylate underwent ring expansion metathesis with cyclooctene to give 18 and 22-membered macrocycles with moderate yields (entries 1 and 2). The best yields for ring expansion with cyclooctene were obtained when diacrylate **9** was used (entry 3). Even though 1,6-hexanediol diacrylate and **9** have the same number of atomic linker units, the presence of less conformationally constraining oxygen atoms in **9** favors the formation of the desired REM products.[23c, e, 25] With the best diene identified, various cycloalkenes were screened to create a family of macrocycles (entries 3 – 9). For cyclopentene and cycloheptene, 5 equiv. of cycloalkenes could be used to give reasonable yields since their rates of ROMP were slow, unlike cyclooctene, which can easily polymerize under the same conditions. A medium ring cyclododecene also underwent REM to give a 26-membered macrocycle with 53% yield.

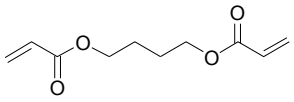
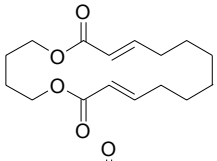
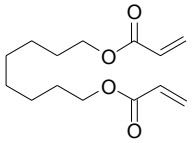
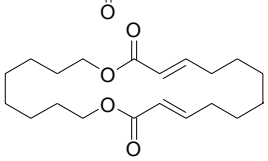
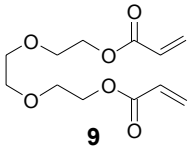
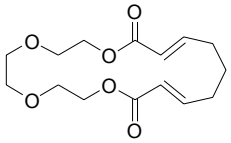
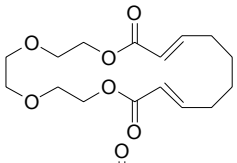
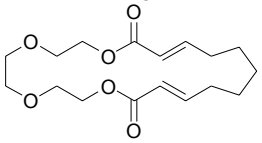
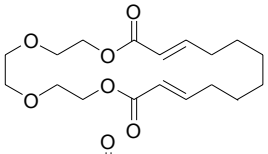
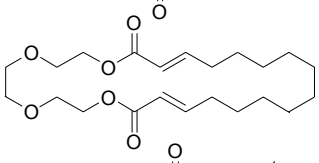
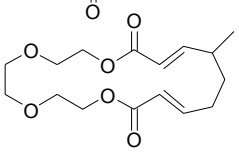
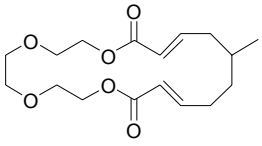
Table 4. Ring expansion metathesis with divinyl ketone



entry	ring sizeb (eq)	conc. [mM]	products[c] [%]
1	5 (5.0)	5	 **4** (43) **5** (34)
2	5 (5.0)	25	**4** (15); **5** (30)
3	8 (5.0)	5	 **6** (23) **7** (23)
4	8 (2.0)	5	**6** (34); **7** (28)
5	8 (1.1)	5	**6** (53)
6	 (1.1)	5	 **8** (43)

[a] Reactions were performed in refluxing CH_2Cl_2 under an atmosphere of argon. [b] Ring size : 5: cyclopentene; 8: cyclooctene. [c] Only (*E*)-isomers were observed by ^1H NMR.

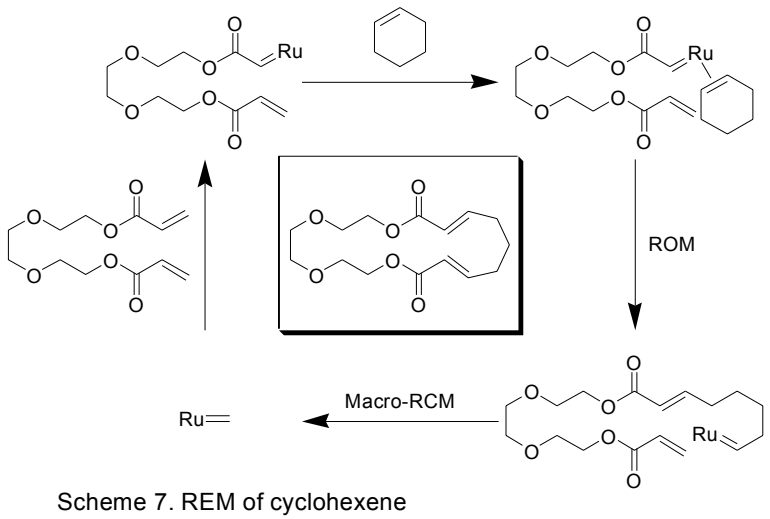
Table 5. Extended Scope of REM

entry	acyclic diene	ring size (eq)	product	yield [%]
1		8 (1.1)		45
2		8 (1.1)		47
3	 **9**	5 (5.0)		52
4		6 (5.0)		39
5		7 (5.0)		63
6		8 (1.1)		59
7		12 (1.1)		53
8	 (5.0)			50
9	 (5.0)			37

[a] Reactions were performed using catalyst **2** (5 mol%) in refluxing CH_2Cl_2 (5 mM) under an atmosphere of argon.
[b] Ring size of cycloalkenes: 5: cyclopentene; 6: cyclohexene; 7: cycloheptene; 8: cyclooctene; 12: cyclododecene.
[c] Only (*E*)-isomers were observed by ^1H NMR.

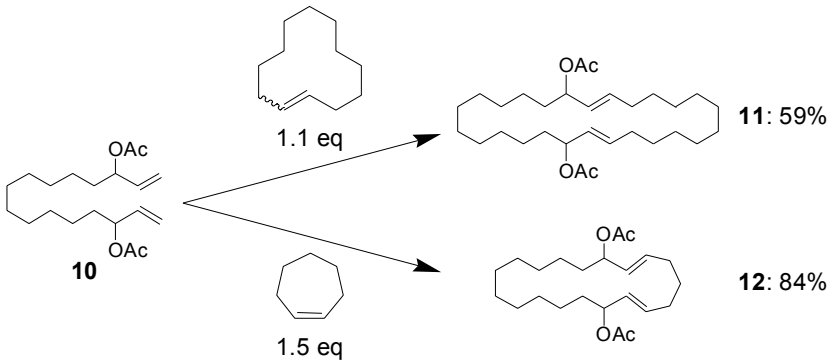
The REM reaction with cyclohexene gave the poorest yield (Table 5, entry 4) even though one might have expected a yield comparable to that for cyclopentene if not better. However, cyclohexene is a unique cycloalkene that does not produce ROMP polymers,[26] so a different mode of ring expansion is required. Since cyclohexene will not undergo olefin

metathesis reactions with catalyst **2**, the initial step is the formation of the enoic carbene, [Ru=CO_2R] in situ, which then can ring-open cyclohexene successfully (Chapter 2) and macrocyclize to give a 20-membered ring (Scheme 7).[18, 27] Since the enoic carbene is less stable than catalyst **2** and its other catalytic intermediates, fewer catalytic turnovers thus lower yields are expected (entry 4). The remaining unreacted **9** can be recovered as a starting material for the next reaction. Methyl substituted cycloalkenes reacted in a similar way to produce methyl substituted macrocycles (entries 8 and 9).



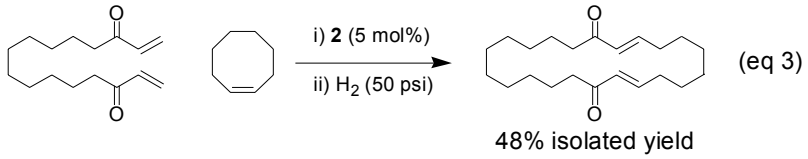
Scheme 7. REM of cyclohexene

Other acyclic dienes that undergo selective cross metathesis should also undergo REM reaction (Scheme 7). One such substrate, bis-allylic acetate compound **10,** yielded 59% of the macrocyle under conditions similar to the acrylate reactions. However, a higher catalyst loading of **2** (7 mol%) was required to completely consume **10,** which seemed to be less reactive than acrylates and vinyl ketones. Protected secondary allylic alcohols are also Type II olefins like acrylates and vinyl ketones (Chapter 2),[29] so the dimerization or cyclization of **10** by itself should be slower than cross metathesis with ring-opened cycloalkenes and subsequent macrocyclization. Especially, REM with cycloheptene gave an excellent yield to produce 19-membered ring (compound **12**).



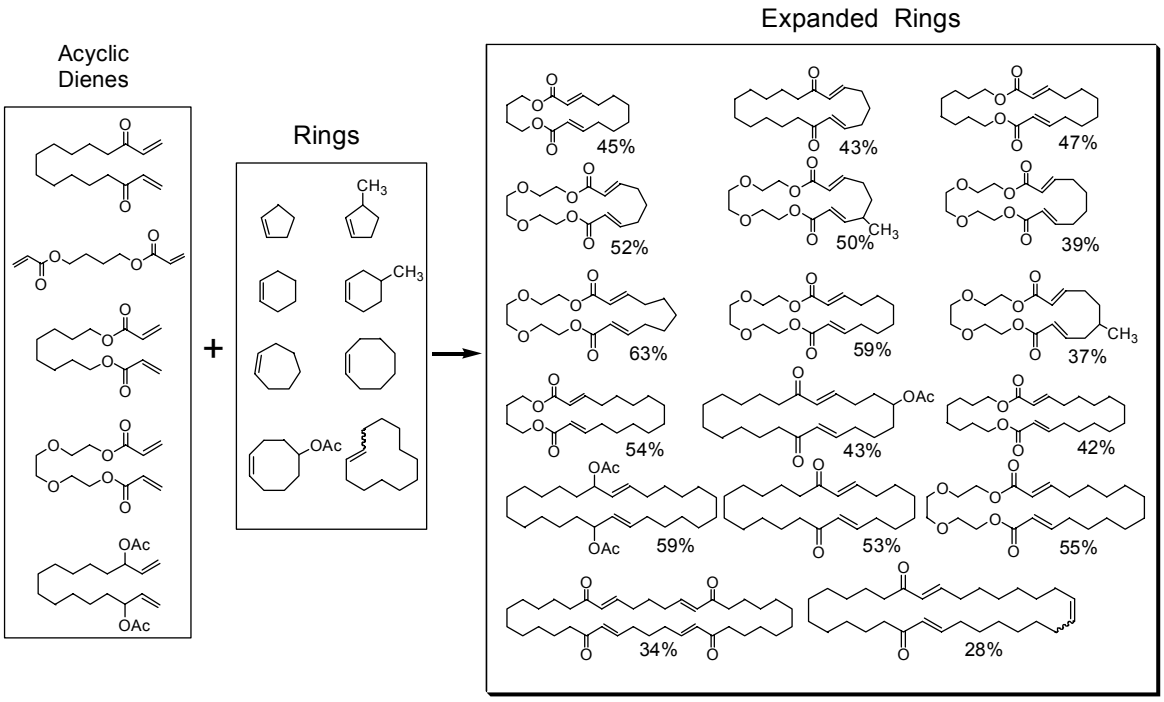
Scheme 7. REM with bis-allylic acetate

This methodology can be extended to the synthesis of macrocyclic ketones in a one-pot process. Using the tandem catalysis recently developed in our group, 22-membered cyclic dione was obtained in 48% isolated yield over two reactions in one pot (eq 3).[28]



Conclusion

In summary, we have demonstrated the synthesis of various macrocycles by ring expansion metathesis using catalyst **2**, where varying the concentration and the stoichiometry of cycloalkenes controlled the product distribution (Scheme 8). Although the yields of the ring expansion products are moderate, this methodology provides an easy access to a variety of macrocycles whose ring sizes can be simply adjusted by using readily available cyclic olefins. REM demonstrates the unique mechanism of olefin metathesis, reversible and thermodynamically controlled process.



Scheme 8. Library of macrocycles synthesized by REM

Acknowledgement: I would like to thank the NIH for generous support of this research, and Dr. C. W. Lee, Dr. H. M. Kim, Dr. A. K. Chatterjee, Dr. M. Scholl, J. P. Morgan, and Dr. S. D. Goldberg for helpful discussions.

Experimental Section

General Experimental Section. NMR spectra were recorded on Varian Mercury-300 NMR (300 MHz for ^{1}H and 74.5 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. High-

resolution mass spectra (EI and FAB) were provided by the UCLA Mass Spectrometry Facility (University of California, Los Angeles).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.

General procedure for RCM:

To a flask charged with substrate olefin (1.0 eq) in CH_2Cl_2, catalyst **2** (0.05 eq) in CH_2Cl_2 was added by cannulation. The flask was fitted with a condenser and refluxed under argon for 6 to 12 hours. The reaction was monitored by TLC. After the solvent was evaporated, the product was purified directly by a silica gel chromatography

Compound in Table 1, entry 1. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 28.7 mg of the product in 81% yield was obtained (R_f= 0.3 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.53 (1H, d, *J*= 6.0 Hz), 6.10 (1H, dd, *J*= 2.0, 6.0 Hz), 5.95 (1H, m), 5.82 (1H, m), 5.14 (1H, m), 4.94 (1H, m), 4.64 (2H, m), 2.02 (2H, m).

Compound in Table 1, entry 2. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 39.3 mg of the product in 89% yield was obtained (R_f= 0.2 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.69 (2H, d, *J*= 9.6 Hz), 7.60 (1H, d, *J*= 6.0 Hz), 7.32 (2H, d, *J*= 9.6 Hz), 6.13 (1H, dd, *J*= 2.4, 5.0 Hz), 5.64 (2H, m), 5.26 (1H, m), 4.04- 4.19 (2H, m), 2.41 (3H, s), 2.08-2.33 (2H, m).

Compound in Table 1, entry 3. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 21 mg of the product in 45% yield

was obtained (R_f= 0.4 in 1: 2 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.58 (1H, dd, *J*= 4.0, 4.0Hz), 5.96 (1H, dd, *J*= 4.0, 8.0Hz), 5.20- 5.40 (2H, m), 4.00- 4.30 (3H, m), 3.62 (1H, dd, *J*= 12.8, 16.0 Hz), 3.40 (1H, m), 3.15 (1H, m), 2.80 (2H, m), 2.0-2.1 (1H, m), 1.5-1.6 (1H, m).

Compound in Table 1, entry 4. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 20.3 mg of the product in 47 % yield was obtained (R_f= 0.2 in 1: 3 = EA: Hx, solid). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.35 (1H, dd, *J*= 2.4, 12 Hz), 5.89 (1H, dd, *J*= 2.0, 14.0Hz), 5.60 (1H, m), 5.42 (1H, m), 4.20- 4.35 (2H, m), 4.18 (2H, m), 3.82 (1H, dd, *J*= 4.0, 8.8 Hz), 3.70 (1H, dd, *J*= 6.0, 12.8 Hz), 2.80- 3.00 (2H, m), 2.66 (1H, m), 2.31 (1H, m.), 1.56 (1H, m).

Compound in Table 2, entry 1. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 25.5 mg of the product in 95 % yield was obtained (R_f= 0.1 in 1: 10 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.08 (1H, d, *J*= 9.6 Hz), 6.02 (1H, t, *J*= 2.7 Hz), 5.90 (1H, d, *J*= 9.6 Hz), 2.4- 2.6 (2H, m), 2.2 (2H, m), 1.40 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 164.5, 138.5, 136.3, 133.1, 119.8, 90.2, 39.5, 30.6, 24.4.

Compound in Table 2, entry 2. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 30.0 mg of the product in 86% yield was obtained (R_f= 0.3 in 1: 5 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.89 (1H, s), 5.83 (1H, d, *J*= 2.7 Hz), 4.99 (1H, d, *J*= 2.4 Hz), 2,28 (2H, m), 1.94 (3H, s), 1.26 (3H, s), 1.00 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.0, 133.8, 133.6, 129.4, 127.5, 90.2, 46.9, 45.0, 26.3, 22.6, 18.2.

Compound in Table 2, entry 3. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 24.4 mg of the product in 72 % yield was obtained (R_f= 0.3 in 1: 3 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.05

(1H, t, *J*= 2.7 Hz), 5.73 (1H. s), 2.3- 2.6 (2H, m), 2.15 (2H, m), 2.02 (3H, s), 1.36 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 164.9, 146.7, 141.2, 130.6, 116.6, 89.9, 39.5, 30.0, 24.6, 18.5.

Compound in Table 2, entry 4. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 39.8 mg of the product in 96 % yield was obtained (R_f= 0.5 in 1: 5 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.30 (1H, d, *J*= 1.5 Hz), 5.86 (1H. s), 4.63 (1H, d, *J*= 17.1 Hz), 4.33 (1H, m), 4.04 (1H, s), 3.72 (3H, s), 2.20 (2H, m), 1.22 (3H, s), 0.91 (3H, s), ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.1, 136.5, 131.1, 130.5, 129.3, 87.3, 66.0, 52.0, 47.3, 43.2, 27.1, 22.2. HRMS (EI) calcd. for $C_{12}H_{16}O_3$, 208.1099, found, 208.1089.

Compound in Table 2, entry 5. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 2 = ethyl acetate: hexane. 26.4 mg of the product in 58 % yield was obtained (R_f= 0.3 in 1: 2 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.52 (1H, d, *J*= 7.8 Hz), 7.24 (2H, m), 7.11 (1H, d, *J*= 7.8 Hz), 7.00 (1H, m), 6.83 (1H, d, *J*= 9.9 Hz), 5.89 (1H,d, *J*= 9.6 Hz), 5.70 (1H, m), 4.99 (1H, m), 4.50 (1H, m), ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 162.1, 154.9, 143.9, 136.6, 132.6, 130.6, 129.5, 125.3, 124.3, 121.5, 116.0, 77.3, 76.9, 75.7, 71.4. HRMS (EI) calcd. for $C_{13}H_{10}O_3$, 214.0630, found, 214.0631.

Compound in Table 2, entry 6. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 5 = ethyl acetate: hexane. 36 mg of the product in 100 % yield was obtained (R_f= 0.3 in 1: 10 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.00 (1H, d, *J*= 9.3 Hz), 6.15 (1H, m), 5.80 (1H, dd, *J*= 0.6, 9.3 Hz), 2.37 (2H, d, *J*= 12.9 Hz), 1.1-2.2 (11H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.2, 142.8, 135.6, 135.1, 118.9, 80.0, 45.1, 35.5, 27.5, 26.5, 26.3, 25.6, 22.0.

Compound in Table 2, entry 7. See **General Procedure. 7** mol**%** catalyst **2** was used for the reaction. The product was purified directly on a silica gel column, eluting with 1: 4 = ethyl acetate: hexane. 14 mg of the product in 74% yield was obtained (R_f= 0.3 in 1: 3 = EA: Hx, white

solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.05 (1H, d, *J*= 9.6 Hz), 5.98 (1H, t, *J*= 2.4 Hz), 5.89 (1H, dt, *J*= 0.6, 9.6 Hz), 1.2- 2.6 (11H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 164.8, 140.7, 136.3, 131.4, 119.6, 88.1, 46.2, 34.67, 34.5, 23.7, 21.7, 19.9**.**

Compound in Eq 2. See **General Procedure.** 10 mol% catalyst **2** in 4 mM CH_2Cl_2 was used to complete the reaction. The product was purified directly on a silica gel column, eluting with 1: 35 = ethyl acetate: hexane. 21 mg of the product in 68 % yield was obtained (R_f= 0.5 in 1: 20 = EA: Hx, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.10 (1H, d, *J*= 15.3 Hz), 5.75 (1H, m), 5.65 (1H, m), 3.98 (1H, s), 3.70 (1H, m), 3.30 (1H, dt, *J*= 3.0, 9.0 Hz), 2.35 (1H, s), 2.29 (1H, s), 2.00 (2H, m), 1.35 (14H, m), 1.12 (3H, s), 1.03 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 140.6, 132.0, 130.3, 126.8, 91.2, 68.6, 47.0, 42.4, 32.3, 30.4, 29.7, 26.9, 26.0, 25.9, 25.8, 24.8, 24.3, 23.2. HRMS (EI) calcd. for $C_{18}H_{30}O$, 262.2297, found, 262.2288.

General Procedure for REM:

To a flask charged with catalyst **2** (0.05 equiv in 0.005 to 0.006 M CH_2Cl_2), α,β-unsaturated carbonyl compounds, and cycloalkenes were added via syringe. The flask was fitted with a condenser and refluxed under argon for 12 hours. The reaction was monitored by TLC. After the solvent was evaporated, the product was purified directly on a silica gel column.

Compound 4 and 5. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 4 = ethyl acetate: hexane. 10.0 mg of the product **4** in 43 % yield was obtained (R_f= 0.4 in 1: 2 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.80 (2H, dt, *J*= 6.9, 15.9 Hz), 6.15 (2H, dt, *J*= 1.5, 15.9 Hz), 2.49 (4H, t, *J*= 6.9 Hz), 2.29 (4H, dq, *J*= 1.2, 6.9 Hz), 1.70 (6H, m), 1.29 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 202.2, 146.8, 131.2, 40.0, 31.4, 28.6, 28.5, 28.3, 26.7, 25.7. HRMS (EI) calcd. for $C_{19}H_{30}O_2$, 290.2246, found, 290.2241.

8.0 mg of the product **5** in 34 % yield was obtained (R_f= 0.3 in 1: 2 = EA: Hx, white solid).). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.79 (4H, dt, *J*= 6.9, 15.9 Hz), 6.10 (4H, dt, *J*= 1.5, 15.9 Hz), 2.52 (8H, t, *J*= 7.2 Hz), 2.24 (8H, q, *J*= 6.6 Hz), 1.67 (12H, m), 1.27 (24H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 201.0, 145.2, 131.1, 40.4, 31.9, 29.6, 29.4, 29.3, 26.8, 24.5. HRMS (EI) calcd. for $C_{38}H_{60}O_4$, 580.4492, found, 580.4486.

Compound 6 and 7. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 9 = ethyl acetate: hexane. 10.0 mg of the product **7** in 23 % yield was obtained (R_f= 0.6 in 1: 2 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.80 (2H, m), 6.07 (2H, d, *J*= 15.6 Hz), 5.37 (2H, m), 2.51 (4H, t, *J*= 6.9 Hz), 2.20 (4H, m), 2.00 (4H, m), 1.6- 1.27 (24H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 201.5, 147.8, 130.8, 130.7, 130.5, 40.0, 32.7, 32.6, 28.1-29.8 (m), 24.7. HRMS (EI) calcd for $C_{22}H_{36}O_2$: 332.2715, found, 332.2712. 9.0 mg of the product **6** in 23 % yield was obtained (R_f= 0.5 in 1: 2 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.78 (2H, dt, *J*= 7.2, 15.9 Hz), 6.09 (2H, dt, *J*= 1.5, 15.9 Hz), 2.49 (4H, t, *J*= 6.9 Hz), 2.22(4H, dq, *J*= 1.5, 6.9 Hz), 1.63(4H, m), 1.47 (4H, m), 1.24 (16H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 202.2, 148.0, 131.1, 39.8, 32.3, 29.2, 29.0, 28.8, 28.5, 28.1, 25.8. HRMS (EI) calcd. for $C_{30}H_{50}O_2$:442.3811, found, 442.3806.

Compound 8. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 13.0 mg of the product in 43 % yield was obtained (R_f= 0.4 in 1: 2 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.78 (2H, m), 6.12 (2H, d, *J*= 16.2 Hz), 4.87 (1H, m), 2.50 (4H, m), 2.22 (4H, m), 2.06 (3H, s), 1.6- 1.25 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 201.6, 170.8, 146.8, 146.1, 131.2, 131.1, 72.7, 40.2, 40.1, 33.5, 32.9, 32.0, 29.1, 28.9, 28.8, 28.5, 25.7, 25.6, 24.1, 21.6. HRMS (EI) calcd. for $C_{24}H_{38}O_4$: 390.2770, found, 390.2770.

Compound in Table 5, entry 1. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 13.3 mg of the product in 45 % yield

was obtained (R_f = 0.3 in 1: 5 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.86 (2H, dt, *J*= 6.9, 15.6 Hz), 5.73 (2H, dt, *J*= 1.5, 15.6 Hz), 4.21 (4H, m), 2.20 (4H, m), 1.81 (4H, m), 1.50 (4H, m), 1.23 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 149.8, 121.9, 64.0, 31.1, 27.7, 27.1, 26.3. HRMS (EI) calcd. for $C_{16}H_{24}O_4$: 280.1675, found 280.1680.

Compound in Tabel 5, entry 2. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 15 = ethyl acetate: hexane. 25.7 mg of the product was obtained in 47% yield (R_f = 0.4 in 1: 10 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.93 (2H, dt, *J*= 6.9, 15.6 Hz), 5.82 (2H, dt, *J*= 1.8, 15.6 Hz), 4.14 (4H, t, *J*= 5.7 Hz), 2.20 (4H, m),1.63 (4H, m), 1.5- 1.3 (16H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.9, 149.2, 121.7, 64.9, 31.4, 29.5, 29.0, 27.5, 27.1, 26.6. HRMS (EI) calcd. for $C_{20}H_{32}O_4$: 336.2301, found 336.2298.

Compound in Tabel 5, entry 3. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 9.0 mg of the product was obtained in 52 % yield (R_f= 0.3 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.85 (2H, dt, *J*= 7.2, 15.6 Hz), 5.84 (2H, dt, *J*= 1.5, 15.6 Hz), 4.26 (4H, m), 3.72 (4H, m), 3.67 (4H, s), 2.29 (4H, m), 1.77 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.4, 148.1, 123.2, 70.7, 69.3, 63.9, 31.7, 24.6. HRMS (EI) calcd. for $C_{15}H_{22}O_6$: 298.1416, found 298.1416.

Compound in Tabel 5, entry 4. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 7.0 mg of the product was obtained in 39 % yield (R_f= 0.35 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.85 (2H, dt, *J*= 7.2, 15.6 Hz), 5.84 (2H, dt, *J*= 1.5, 15.6 Hz), 4.26 (4H, m), 3.75 (4H, m), 3.67 (4H, s), 2.23 (4H, m), 1.45 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.5, 149.2, 122.1, 71.0, 69.4, 64.0, 31.2, 26.3. HRMS (EI) calcd. for $C_{16}H_{24}O_6$: 312.1573, found 312.1584.

Compound in Tabel 5, entry 5. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 12.0 mg of the product was obtained

in 63 % yield (R_f= 0.35 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.92 (2H, dt, *J*= 7.2, 15.6 Hz), 5.83 (2H, dt, *J*= 1.5, 15.6 Hz), 4.28 (4H, m), 3.73 (4H, m), 3.66 (4H, s), 2.24 (4H, m), 1.48 (4H, m), 1.24 (2H, m).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 149.4, 121.9, 71.2, 69.5, 64.1, 32.2, 27.8, 27.7. HRMS (EI) calcd. for $C_{17}H_{26}O_6$: 326.1729, found 326.1732.

Compound in Tabel 5, entry 6. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 29.4 mg of the product was obtained in 59 % yield (R_f= 0.40 in 1: 1 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.98 (2H, dt, *J*= 6.9, 15.6 Hz), 5.84 (2H, dt, *J*= 1.5, 15.6 Hz), 4.29 (4H, m), 3.74 (4H, m), 3.68 (4H, s), 2.21 (4H, dq, *J*= 1.5, 6.6 Hz), 1.50 (4H, m), 1.29 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 149.8, 121.5, 71.2, 69.6, 64.0, 31.2, 27.3, 26.9. HRMS (EI) calcd. for $C_{18}H_{28}O_6$: 340.1886, found 340.1893.

Compound in Tabel 5, entry 7. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 2 = ethyl acetate: hexane. 31.3 mg of the product was isolated in 55 % yield. (R_f= 0.55 in 1: 1 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.95 (2H, dt, *J*= 7.2, 15.6 Hz), 5.81 (2H, dt, *J*= 1.5, 15.6 Hz), 4.26 (4H, m), 3.70 (4H, m), 3.65 (4H, s), 2.20 (4H, m), 1.44 (4H, m), 1.23 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.8, 150.2, 121.4, 71.1, 69.8, 64.0, 32.2, 29.1, 28.9, 28.4, 27.7. HRMS (EI) calcd. for $C_{22}H_{36}O_6$: 396.2512, found 396.2507.

Compound in Tabel 5, entry 8. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 9.0 mg of the product was isolated in 50 % yield. (R_f= 0.35 in 1: 1 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.83 (1H, dt, *J*= 6.9, 15.6 Hz), 6.71 (1H, dd, *J*= 9.6, 15.6 Hz), 5.81 (2H, dt, *J*= 1.5, 15.6 Hz), 4.36 (2H, m), 4.13 (2H, m), 3.73 (4H, m), 3.67 (4H, s), 2.35 (1H, m), 2.25 (2H, m), 1.79 (1H, m), 1.50 (1H, m), 1.04 (3H, d, *J*= 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 166.5, 153.0,

148.4, 123.0, 121.6, 70.7, 70.5, 69.2, 69.2, 63.8, 63.8, 37.2, 33.1, 30.7, 21.1. HRMS (EI) calcd for $C_{16}H_{24}O_6$: 312.1573, found 312.1581.

Compound in Tabel 5, entry 9. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 7.0 mg of the product was isolated in 37 % yield. (R_f= 0.35 in 1: 1 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.91 (2H, m), 5.81 (2H, d, *J*= 15.6 Hz), 4.20 (4H, m), 3.72 (4H, m), 3.67 (4H, s), 2.20 (4H, m), 1.5- 1.3 (3H, m), 0.95 (3H, d, *J*= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.5, 149.3, 148.3, 122.8, 121.9, 71.1, 70.1, 69.4, 69.3, 64.1, 39.2, 33.5, 31.3, 29.1, 20.6. HRMS (EI) calcd. for $C_{17}H_{26}O_6$ 326.1729, found 326.1728.

Compound 11. See **General Procedure**. This time 8 mol% of catalyst **2** was used. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 25.4 mg of the product was isolated in 59 % yield. (R_f= 0.5 in 1: 5 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.60 (2H, m), 5.33 (2H, dd, *J*= 8.1, 15.9 Hz), 5.13 (2H, m) 2.10 (2H, m), 2.00 (6H, s), 1.60 (2H, m), 1.50 (2H, m), 1.40 (2H, m), 1.2 (24H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 170.5, 134.8, 128.9, 75.5, 34.4, 32.1, 29.8, 29.6, 29.2, 29.1, 28.6, 28.2, 24.9, 21.8. HRMS (EI) calcd. for $C_{26}H_{44}O_4$: 420.3240, found 420.3247.

Compound 12. See **General Procedure**. This time 7 mol% of catalyst **2** was used. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 28 mg of the product was isolated in 84 % yield. (R_f= 0.5 in 1: 5 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.62 (2H, m), 5.32 (2H, dd, *J*= 15.3, 7.5 Hz), 5.13 (2H, m), 2.20 (2H, m), 2.00 (6H, s), 1.60 (4H, m), 1.20- 1.40 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 170.3, 135.7, 135.3, 128.7, 128.6, 75.8, 75.6, 34.1, 34.0, 32.6, 32.4, 29.5, 29.4, 29.0, 28.8, 28.7, 28.0, 27.8, 23.9, 21.9. HRMS (EI) calcd. for $C_{21}H_{34}O_4$: 350.2457, found 350.2453.

Compound in Eq 3. See **General Procedure**. After metathesis reaction was done, the pot was pressured up with 50 psi hydrogen gas, and ran for overnight. The product was purified directly

on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 13.0 mg of the product was isolated in 48 % yield. (R_f= 0.45 in 1: 4 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.39 (8H, t, *J*= 6.9 Hz), 1.58 (8H, m), 1.23 (24H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 212.5, 41.6, 29.1, 29.0, 28.8, 24.1. HRMS (EI) calcd. for $C_{22}H_{40}O_2$: 336.3028, found 336.3024.

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