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Ring Expansion via Olefin Metathesis

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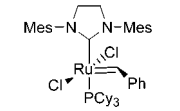
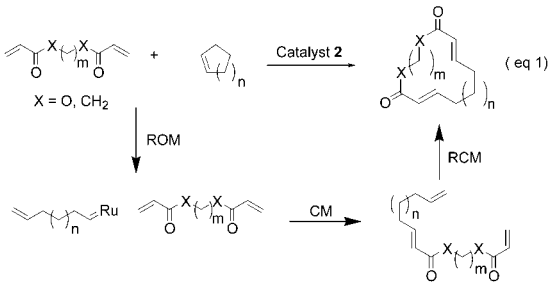
Olefin metathesis is an efficient reaction for the formation of carbon−carbon bonds.[1] Catalyst **1**, $Cl_2(PCy_3)_2Ru{=}CHPh$, helped to open the metathesis to the organic community due to its functional group tolerance and stability to air and moisture.[2] The recent development of the more active and more stable catalyst **2** 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.[3]



Mes= C_6H_2-2,4,6-$(CH_3)_3$

2

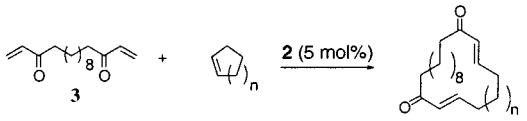
Ring-closing metathesis has provided a new approach to the challenging problem of macrocyclization.[4,5] The efficiency of this process has been improved by the higher activity of catalyst **2**; not only in improved yields but also by reducing the catalyst loading and more importantly, in improved stereoselectivity of the newly formed olefins.[5a,6] This provides an efficient and mild route for the synthesis of macrocycles, especially carbocycles, which is considered harder than macrolactonization or lactamization. Herein, we report a novel method of formation of macrocycles by a ring expansion reaction in which three types of olefin metathesis (ring-opening, cross, and ring-closing) reactions occur sequentially to yield macrocycles (eq 1).



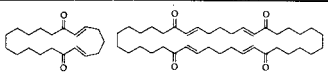
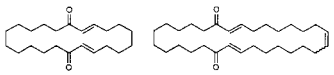
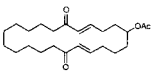
For a successful ring expansion, several conditions must be satisfied. The cycloalkenes must be able to undergo the ring-opening reaction. Once opened, they must react selectively with the acyclic diene for CM and RCM to minimize side products. In addition, the acyclic diene should not undergo reactions with itself such as cyclization or cross metathesis.

To test this idea, we chose bis-acrylates and bis-vinyl ketones systems because they are known to react selectively with terminal olefins in excellent yields and less favorably with themselves.[3c] Catalyst **2** (5 mol %) was added to a solution of bis-vinyl ketone (compound **3**,[7] Table 1) and cyclopentene (5 equiv) in CH_2Cl_2 (5 mM in **3**). After refluxing for 12 h, several products were obtained. The major products were the (1 + 1) fashion (**3** and cycloalkene) ring-expanded product **4** and the double ring-expanded product **5** in ratio of 1.3/1 (entry 1, Table 1). As anticipated, increasing the concentration to 25 mM decreased the product ratio of **4**/**5** to 1/2.3 (entry 2).[8] Since cyclooctene polymerizes by ring-opening metathesis much faster than cyclopentene due to its higher ring strain, the relationship of concentration of cyclooctene and product distribution was explored (entries 3 to 5, Table 1).[9] With 5 equiv of cyclooctene (5 mM), a 1:1 ratio of the desired product **6** (23% yield) and cyclooctene double inserted product **7** was obtained. Decreasing the equivalence of cyclooctene to 2 increased the ratio to 1.2/1, and finally the best yield of 53% for the desired product **6** was isolated with 1.1 equivalence of cyclooctene. Functionalized cyclooctenes are also viable substrates for ring expansion (entry 6).

Table 1. Ring-Expansion Reactions with Bis-vinyl Ketone **3**[a]



3

Ent	Ring size[b] (Eq.)	Conc. (mM)	Ring products[c] (% Yield[d])
1	5 (5.0)	5	 **4** (43) **5** (34)
2	5 (5.0)	25	**4** (13) : **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. [d] Isolated yields. No starting material remained.

Bis-acrylate systems are also useful for ring expansion (Table 2). Substrates **9** and **12** gave 18- to 26-membered macrocycles with moderate yields (entries 1−4). The best yields for ring expansion with cycloalkenes were obtained when bis-acylate **15** was used (entries 5−9). Even though substrate **12** and **15** have the same

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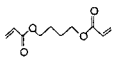
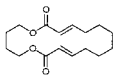
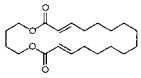
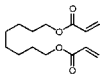
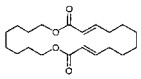
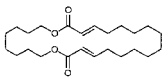
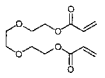
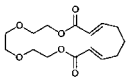
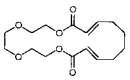
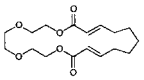
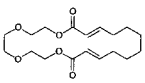
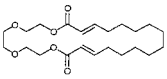
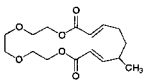
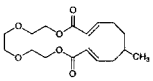
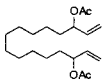
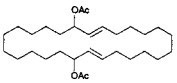
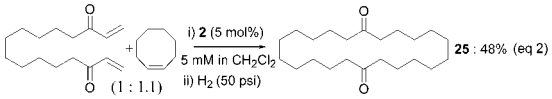
Table 2. Extended Scope of Ring Expansion[a]

Ent	Sub.	Ring size[b] (Eq.)	Ring products[c]	Yield[d] (%)
1	 **9**	8 (1.1)		**10** (45)
2	**9**	12 (1.1)		**11** (54)
3	 **12**	8 (1.1)		**13** (47)
4	**12**	12 (1.1)		**14** (42)
5	 **15**	5 (5.0)		**16** (52)
6	**15**	6 (5.0)		**17** (39)
7	**15**	7 (5.0)		**18** (63)
8	**15**	8 (1.1)		**19** (59)
9	**15**	12 (1.1)		**20** (55)
10	**15**	 (5.0)		**21** (50)
11	**15**	 (5.0)		**22** (37)
12	 **23**	12 (1.1)		**24** (59)

[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 ^{1}H NMR. [d] Isolated yields. No starting material remained except entries 6 and 11 (see text).

number of linker units, the presence of less conformationally constraining oxygen atoms in **15** favors the formation of the desired monomeric products.[5c,e,10] With the best substrate identified, various cycloalkenes were screened to create a family of macrocycles (entries 5−11). For cyclopentene and cycloheptene, 5 equiv of cycloalkenes was used since the rates of the ring opening were slower than for cyclooctene. Higher concentrations of cyclopenetene and cycloheptene resulted in significant side reactions and did not increase the yields of the desired product. The reaction with cyclohexene gave the poorest yield even though one might have expected a yield comparable if not better than for cyclopentene. However, cyclohexene requires a different mode of the ring expansion. 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 can ring-open cyclohexene.[11] Since the enoic carbene is less stable than **2**, fewer catalytic turnovers are expected (entry 6). Substituted cycloalkenes reacted in a similar way to produce substituted macrocycles (entries 10 and 11).

Other acyclic dienes that undergo selective cross metathesis should also serve as partners in this expansion reaction. One such substrate, bis-allylic acetate compound **23** yielded a 59% of the product **24** under conditions similar to the acrylate reactions (entry 12). Although bis-allylic acetate **23** can undergo self-metathesis, the reaction with ring-opened cyclododecene is more favored. In this case, two potentially polymerizable substrates react to form the ring-expansion product.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 **25** was obtained in 48% isolated yield over two reactions in one pot (eq 2).[12]



In summary, we demonstrated the synthesis of various macrocycles by a ring-expansion method using catalyst **2**, where varying the concentration and the stoichiometry of cycloalkenes controlled the product distribution. 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 adjusted by using readily available cyclic olefins.

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Supporting Information Available: Full experimental details and spectral data for products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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