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Efficient atom economic approaches towards macrocyclic crownamides via ring closure metathesis

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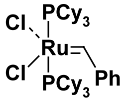
Abstract—RCM of suitable 1,ω-dienes led to efficient atom economic synthetic approaches towards azacrown ether derivatives with eight- to twenty four-membered ring sizes. © 2002 Elsevier Science Ltd. All rights reserved.

Crown compounds and azacrown compounds constitute important macrocyclic groups in supramolecular chemistry. They have been shown to exhibit important applications including selective ion separation and detection, molecular recognition, catalysis, biological applications as well as many other interesting applications in diverse fields of supramolecular chemistry.[1,2] Synthetic approaches towards such macrocycles usually suffer from low yields, losses of considerable amounts of the starting precursors during the macrocyclization step due to polymer formation in addition to the need for high dilution conditions and template effect.[1] We have been investigating several synthetic approaches towards macrocyclic azacrown compounds; some of them showed useful applications in ion selective electrodes and as spectrophotometric reagents.[2] In the present investigation we wish to report an interesting efficient synthetic approach towards azacrown compounds using ring closure metathesis as the key macrocyclization step.

Ring closure metathesis (RCM), a versatile technique used for the formation of cyclic olefins has witnessed an explosive growth in applications over the last decade. It has been mainly applied for the formation of five- to seven-membered carbocycles and heterocycles.[3–7] Some examples of macrocycle synthesis via RCM have been reported.[7–16] Several reviews dealing with RCM and illustrating its wide range of applications have recently been published.[17] Molybdenum alkylidene (Schrock catalysts)[18] and ruthenium alkylidene (Grubbs' catalysts)[16,19] have shown the best catalytic activity in the area of RCM. The commercial availability and ease of handling of some of the Grubbs' catalysts (e.g. **I**) in addition to their good tolerance of normal reaction conditions and to a wide range of functional groups attracted our attention for possible utility in the synthesis of crown and azacrown macrocycles.



Grubbs' catalyst (I)

In the present work we report our initial investigations on the application of RCM with catalyst **I** as the key macrocyclization step in the synthesis of some diaza and azacrown macrocyclic ethers. We have also investigated the photo RCM technique recently reported by Fürstner and Ackermann[20] using $[(p\text{-cymene})RuCl_2]_2$ and PCy_3 in the presence of normal laboratory neon tubes for initiating this photo RCM. Table 1 illustrates our results of the RCM reactions using these two catalytic RCM techniques. Our results indicated that whereas all attempts to conduct the catalytic RCM with catalyst **I** were successful, the photo catalysis gave only moderate yields of RCM products in two cases (runs 1 and 4, conditions b). Moreover, attempts to convert **3** into **15** (run 3) using photo RCM conditions[20] gave less than 10% conversion, yielding a mixture of products including **15**. Therefore, we applied in all other cases catalyst **I** which showed excellent conversion yields (Table 1).

Keywords: ring closure metathesis; 1,ω-dienes; diazacycloalkenes; diazadioxacycloalkenes; benzoazaoxacycloalkenes; dibenzoazadioxacycloalkenes; dibenzodiazadioxacycloalkenes; tribenzoazatrioxacycloalkenes; tetrabenzodiazatetraoxacycloalkenes.

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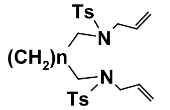
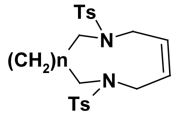
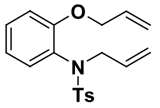
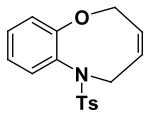
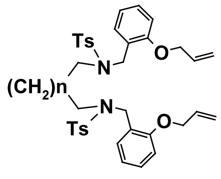
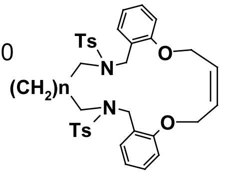
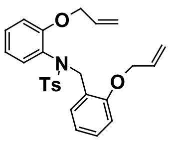
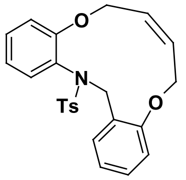
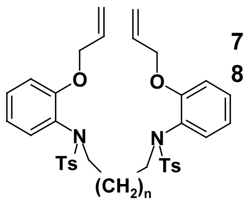
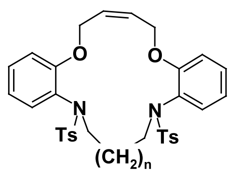
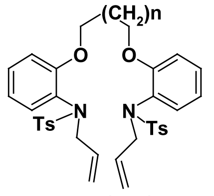
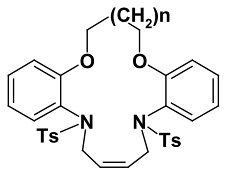
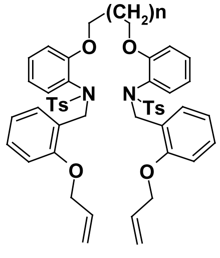
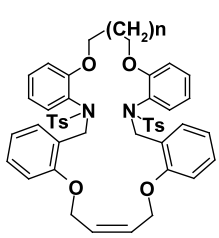
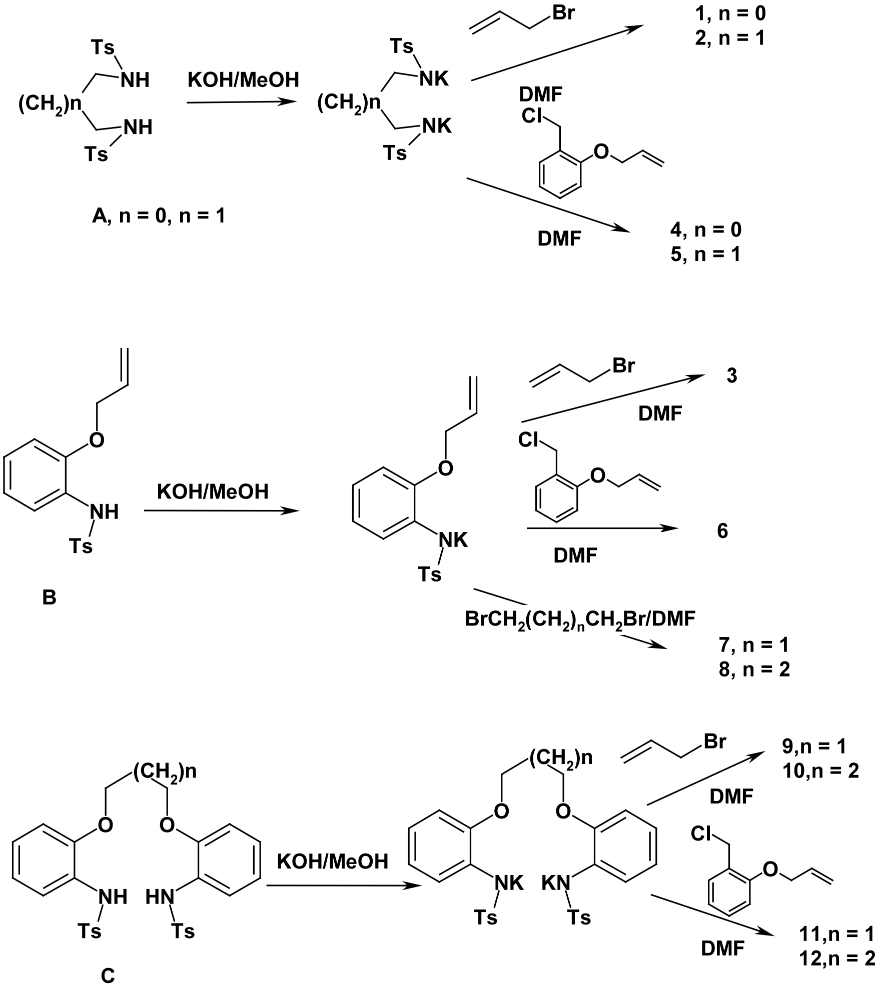
Table 1.

Run	Substrate (d)		Conditions/yield(%) (e)	Product (d)		*Z*:*E* ratio
1		**1** n = 0	a/92, b/60		**13** n = 0	1:0
2		**2** n = 1	a/85		**14** n = 1	2:1
3		**3**	a/88, b/10		**15**	2:1 c
4		**4** n = 0	a/90, b/60		**16** n = 0	7:1
5		**5** n = 1	a/95		**17** n = 1	3:1
6		**6**	a/95		**18**	c
7		**7** n = 1	a/76		**19** n = 1	1:1
8		**8** n = 2	a/100		**20** n = 2	1:2
9		**9** n = 1	a/100		**21** n = 1	1:0
10		**10** n = 2	a/100		**22** n = 2	2:1
11		**11** n = 1	a/85		**23** n = 1	1:2.5
12		**12** n = 2	a/95		**24** n = 2	c

a)Substrate (0.01 M), Grubbs' catalyst **I** (2.5 mol%); CH_2Cl_2,reflux 2 h, b)Substrate (0.01 M), $[(p\text{-cymene})RuCl_2]_2$ (2.5 mol%), PCy_3 (5.5 mol%), CH_2Cl_2, Neon light, Ar atmosphere, reflux 16 h; c)E/Z ratio could not be determined, d)All substrates and products were analyzed by ^1H, ^{13}C NMR, GC-MS, and gave satisfactory elemental analyses, e)yield was determined by 400 MHz ^1H NMR.

Scheme 1 illustrates our synthetic routes starting from the appropriate readily available bistosylamides **A** and **C** or tosylamide **B**, which were converted via their potassium salts into the corresponding 1,ω-dienes. RCM of these dienes proceeded under mild conditions using 2.5 mol% of **I** in CH_2Cl_2 to give excellent yields of the corresponding macrocyclic products (Table 1).

In summary, the present work demonstrates the efficient application of RCM techniques for the atom economic synthesis of macrocyclic crown compounds with potentially diverse applications in supramolecular chemistry. Examples of RCM presented here offer one of the best known macrocyclization reaction techniques known for the synthesis of crown compounds. Applica-



Scheme 1.

tions of this method to the synthesis of other functional derivatives of crown compounds are currently under active investigation in our laboratory. Also, the macrocylic products of these RCM reactions are good starting materials for other functional derivatives of macrocycles through further transformation of the newly formed double bond. We believe that removal of the tosyl group will be possible using one of several reported methods including $LiAlH_4$ (under mild conditions in THF, at 50°C) or by heating in KOH (in DMSO at 80°C).[1e,21]

Acknowledgements

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