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Efficient atom economic approaches towards macrocyclic crown diamides via ring-closing metathesis

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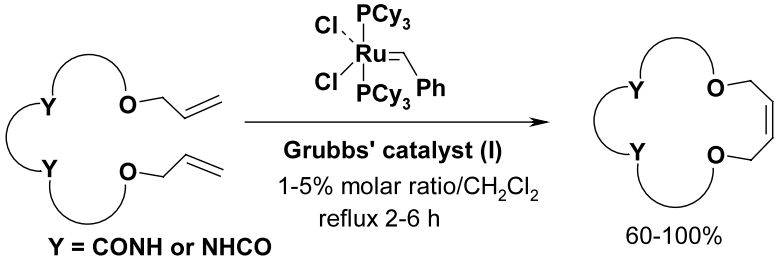
Abstract—RCM of suitable diamides containing 1,ω-dienes led to efficient atom economic synthetic approaches towards macrocylic polyoxadiamides with 15–25-membered ring sizes.

The development of neutral ionophores useful in measurements of intracellular as well as extracelluar cation concentrations is a subject of considerable current interest.[1] In general, 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.[2,3] Of particular interest are crown ethers incorporating amide groups, since such groups modify the binding properties of the crown compounds with respect to alkali metal ions.[1,3] Moreover, the number of ether oxygen, amide carbonyl groups, ring size, lipophilic groups as well as other structural features control the selectivity towards different ions.[1,3] Synthetic approaches towards such macrocycles usually suffer from low yields, the loss 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 effects.[2] We and others reported several moderate-to-good yielding synthetic approaches towards macrocyclic crown-amides some of which showed useful applications in ion selective electrodes.[3] However, previous synthetic approaches suffer from a considerable decrease in yields as the ring size increases, in favor of polymer formation.[3f] In the present investigation we report an efficient synthetic approach towards crown diamides with ring sizes extending from 15–25, using ring-closing metathesis as the key macrocyclization step.

Recently, ring-closing metathesis (RCM) has been widely used as a versatile technique for the formation of cyclic olefins. It has been mainly applied for the formation of five- to seven-membered carbocycles and heterocycles.[4–8] Some examples of macrocycle synthesis via RCM have been reported.[8–17] Several reviews dealing with RCM and illustrating its wide range of applications have recently been published.[18] Molybdenum alkylidene (Schrock catalysts)[19] and ruthenium alkyli-



Keywords: ring-closing metathesis; 1,ω-dienes; bis-*o*-allyloxybenzamides; bis-*o*-allyloxyanilides; dibenzodioxadiazacycloalkenediones; tribenzodioxadiazacycloalkenediones; tetrabenzodiazatetraoxacycloalkenediones; pentabenzodiazatetraoxacycloalkenediones.

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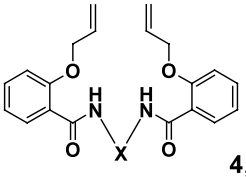
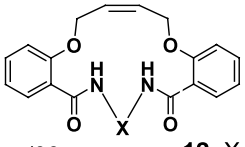
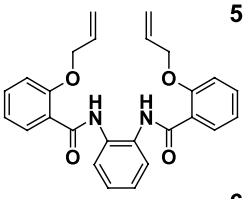
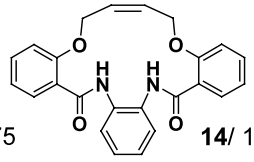
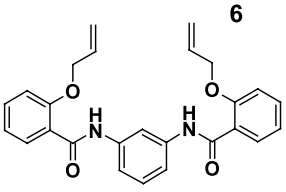
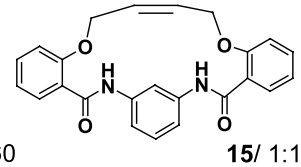
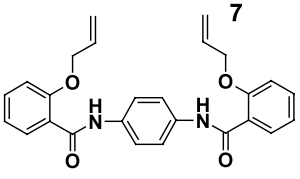
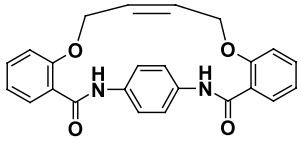
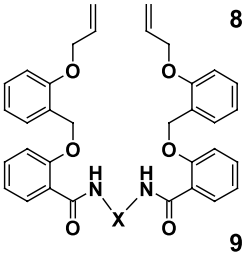
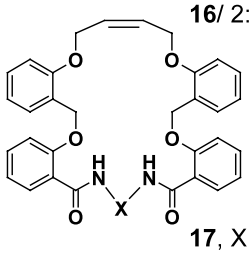
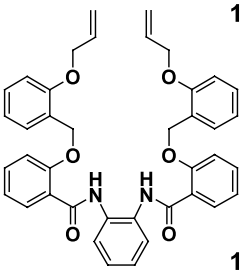
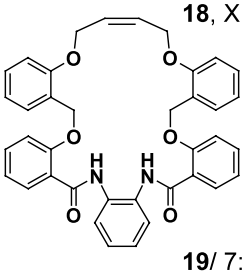
dene (Grubbs' catalysts)[17,20] have shown the best catalytic activity in the area of RCM. The commercial availability and ease of handling of some of the Grubbs' catalysts (e.g. **I**) in addition to their good tolerance of normal reaction conditions and to a wide range of functional groups attracted our attention for possible utility in the synthesis of crown and azacrown macrocycles. In a recent publication we demonstrated the versatile application of this technique for the efficient atom economic synthesis of a number of azacrown cyclic olefinic compounds with 8–24 ring sizes.[21] Recently, isophthaloyl benzylic amide macrocycles possessing an internal olefin were prepared and shown to spontaneously self-assemble via interlocking to give [2]catenanes in >95% yield.[22]

Table 1.

Entry	Substrate (e)	Conditions/yield(%) (f)	Product (e) /*E*:*Z* ratio
1	 **4**, X = $(CH_2)_2$	a/60, b/100, c/60	 **12**, X = $(CH_2)_2$/ 8.5:1.5
2	**5**, X = $(CH_2)_3$	a/40, b/60	**13**, X = $(CH_2)_3$/ 2:1
3	 **6**	c/100, d/75	 **14**/ 1.1:1
4	 **7**	a/5, b/60	 **15**/ 1:1
5	 **8**	a/10, b/70	 **16**/ 2:1
6	 **9**, X = $(CH_2)_2$	a/100	 **17**, X = $(CH_2)_2$/ 7:1
7	**10**, X = $(CH_2)_3$	a/80	**18**, X = $(CH_2)_3$/ 3:1
8	 **11**	a/80	 **19**/ 7:3

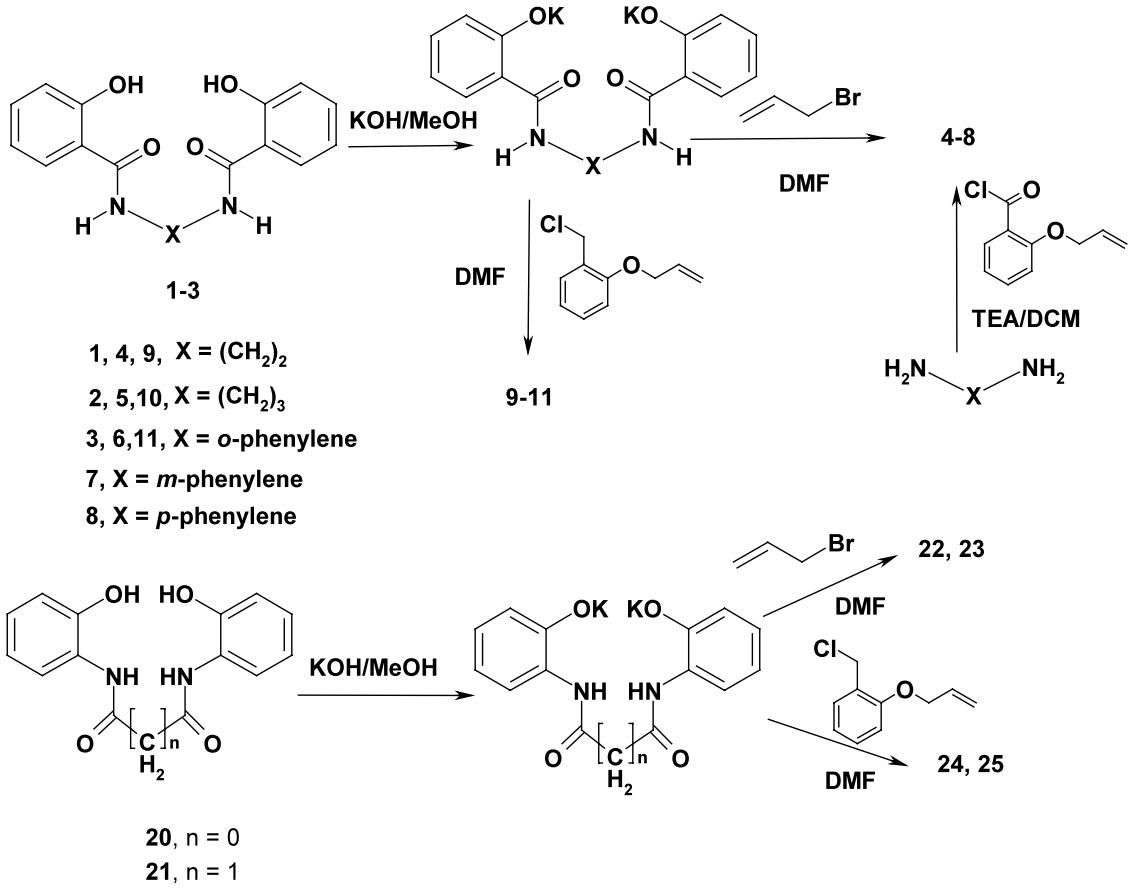
a) Substrate (0.01 M), Grubbs' catalyst **I** (2.5 mol%); CH_2Cl_2, reflux 2 h, b) Substrate (0.01 M), Grubbs' catalyst **I** (5 mol%); CH_2Cl_2, reflux 2 h, c) Substrate (0.01 M), Grubbs' catalyst **I** (1.25 mol%); CH_2Cl_2, reflux 6 h, d) Substrate (0.01 M), Grubbs' catalyst **I** (1 mol%); CH_2Cl_2, reflux 6 h, e) All substrates and products were analyzed by ^1H, ^{13}C NMR, GC-MS, and gave satisfactory elemental analyses, f) The yields were determined by 400 MHz ^1H NMR.[24]

In the present work we report our investigations on the application of RCM with catalyst **I** as the key macrocyclization step in the synthesis of macrocyclic polyethers containing amide groups in the macrocyclic ring. Results obtained in this work (Table 1) provide an efficient atom economic synthetic approach towards macrocylic polyoxadiamides with 15–25-membered ring sizes.

Scheme 1 illustrates our synthetic routes starting from the appropriate readily available bis-(*o*-hydroxyphenyl)amides **1**–**3**, **20** and **21** which were, converted via their potassium salts into the corresponding 1,ω-dienes **4**–**11**, **22**–**25**. Some 1,ω-diene derivatives were also readily obtained by reacting the appropriate diamine with *o*-allyloxybenzoyl chloride. RCM of these dienes (Tables 1 and 2) proceeded under mild conditions using 1–5 mol% of **I** in refluxing CH_2Cl_2 to give excellent yields of the corresponding macrocyclic products.

Table 1 shows that the RCM reactions proceeded in high yield in most cases by heating the substrate in dichloromethane with 2.5–5 mol% of **I**. It is also remarkable that the formation of the 16-membered ring (entries 1, 3) led to 100% macrocyclization by this technique. Moreover, only 1.25% molar ratio of the catalyst was needed for the full RCM macrocyclization of **6**; however, using 1% molar ratio of **I** led to only 75% macrocyclization where 25% of the starting compound **6** was recovered unreacted (entry 3). On increasing the ring size to 17, (entries 2, 4, 5) the RCM reaction could only be accomplished in reasonably good yields by increasing the catalyst to 5% molar ratio. However, by increasing the ring size even more to 24 and 25 (entries 6, 7, 8) macrocyclization yields of 80–100% were achieved with only 2.5% molar ratio of the catalyst **I**.

The *E*:*Z* isomers of the olefinic crown diamides were readily assigned and their ratios were determined from the ^1H and ^{13}C NMR spectra. Full proton and carbon signal assignment of *E* and *Z* **14** was made using ^1H NMR, NOE-difference spectra, H,H-COSY, HMQC and HMBC NMR techniques. By irradiation of the OCH_2 the *ortho* aromatic protons were enhanced, thus identified and used in the COSY experiment to assign all the other aromatic protons. The latter were then used to assign the different carbon signals from the 2D HMQC and HMBC experiments.



Scheme 1.

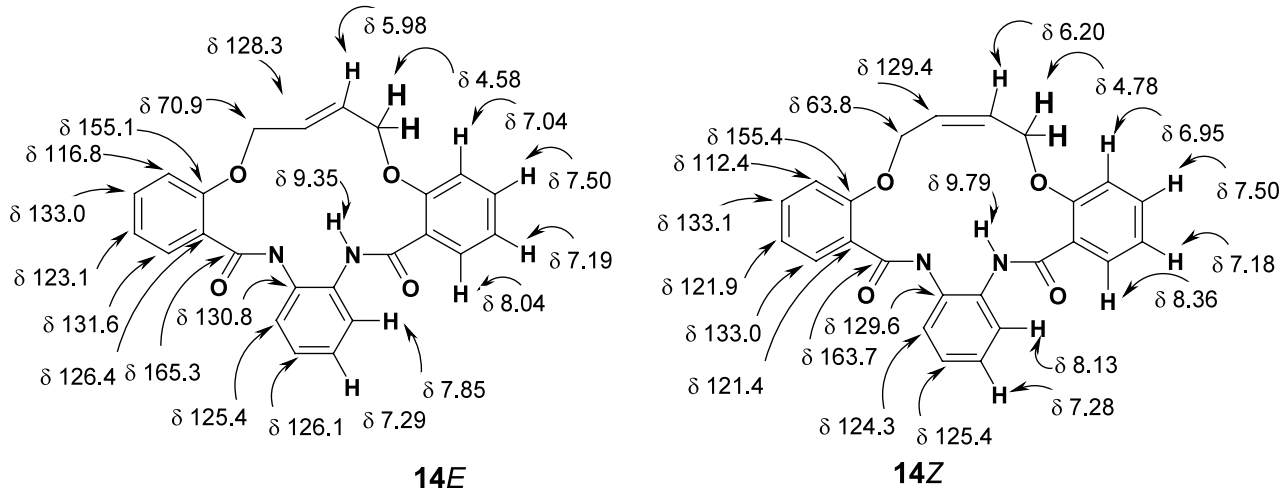
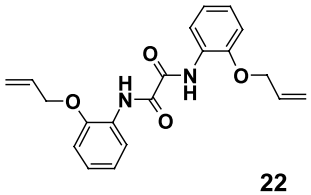
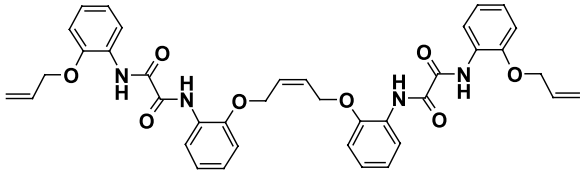
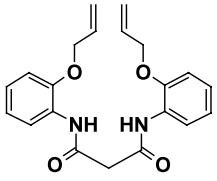
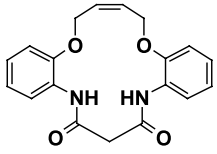
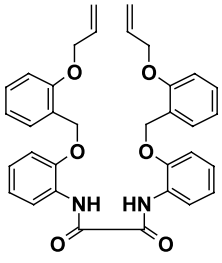
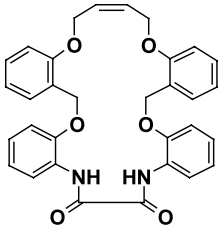
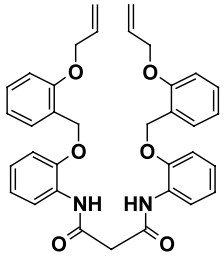
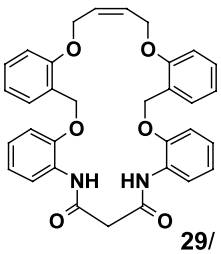


Table 2.

Entry	Substrate (c)	Conditions/yield(%) (d)	Product (c) / *E:Z* ratio
1	 **22**	a/100, b)60	 **26**/ undetermined
2	 **23**	a,b/100	 **27**/ 1:1
3	 **24**	a/100	 **28**/ 1:1
4	 **25**	a/70	 **29**/ 1:1

a) Substrate (0.01 M), Grubbs' catalyst **I** (2.5 mol%); CH_2Cl_2, reflux 2 h, b) Substrate (0.01 M), Grubbs' catalyst **I** (1 mol%); CH_2Cl_2, reflux 6 h, c) All substrates and products were analyzed by ^1H, ^{13}C NMR, GC-MS, and gave satisfactory elemental analyses, d) The yields were determined by 400 MHz ^1H NMR.[24]

The major products in all other RCM reactions **12**, **13**, **16**–**19** were shown to be the *E* isomers [(**15** is 1:1 (*E*:*Z*)] with the characteristic ^{13}C signal of the OCH_2 (of the $OCH_2CH{=}CHCH_2O$) in the range of $\delta = 66.6$–70.9. On the other hand the ^{13}C signal of the OCH_2 of the *Z* isomers appeared upfield at around $\delta = 63$–64. As another representative example, the ^1H and ^{13}C NMR of compound **12** *E* and *Z* are given.[23]

Application of RCM techniques using catalyst **I** to the oxalic diamides **22** and **23** and bis-malonamides **24** and **25** was also, investigated. All attempts to metathesize compound **22** led only to precipitation of the dimeric ring open structure **26**. Most probably this is due to the presence of **22** in the *trans* conformation around the oxamide group. Furthermore, attempts to cyclize compound **26** in different solvents using Grubbs' catalyst **I** failed and gave unchanged **26**. On the other hand the application of RCM techniques to the malonic diamide **23** led to 100% formation of the macrocyle **27**. Likewise compounds **24** and **25** underwent RCM reactions with **I** to give the corresponding macrocycles **28** and **29**, respectively.

The present work demonstrates the efficient application of RCM techniques for the atom economic synthesis of macrocyclic crown diamide derivatives with potential diverse applications in supramolecular chemistry and as starting compounds for further synthetic transformations. The examples of RCM presented here represent one of the best macrocyclization reaction techniques for the synthesis of crown compounds. It also, expands the utility of RCM methodology and its application to the synthesis of cyclic olefins of large ring sizes with different functional groups. Applications of this method to the synthesis of other functional derivatives of crown compounds are currently under active investigation in our laboratory.

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References

1. Goodall, M.; Kelly, P. M.; Parker, D.; Gloe, K.; Stephan, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 59–69 and references cited therein.
2. (a) *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Elsevier Science, 1996; Vol. 1; (b) *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Elsevier Science, 1996; Vol. 2; (c) Weber, E. *Kontakte (Merck)* **1983**, p. 38; **1984**, p. 26; (d) Sutherland, I. O. *Chem. Soc. Rev.* **1986**, *15*, 63; (e) Fujita, T.; Lehn, J. M. *Tetrahedron Lett.* **1988**, *29*, 1709–1712; (f) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112; (g) Hamilton, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press, 1984; Vol. 7, pp. 731–761; (h) Gokel, G. W.; Freder, M. F. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press, 1996; Vol. 9, pp. 863–892; (i) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.* **1989**, *89*, 929–972.
3. (a) Ibrahim, Y. A.; Elwahy, A. H. M. *Synthesis* **1993**, 503–508; (b) Ibrahim, Y. A.; Elwahy, A. H. M. *J. Chem. Res. (S)*, **1993**, 252; *(M)*, 1684–1695; (c) Ibrahim, Y. A.; Elwahy, A. H. M.; Elkareish, G. M. M. *J. Chem. Res. (S)*, **1994**, 414–415; *(M)*, 2321–2331; (d) Ibrahim, Y. A.; Elwahy, A. H. M; Elkareish, G. M. M. *Heteroatom Chem.* **1995**, *6*, 183–187; (e) Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A.; Kassab, R. M. *J. Chem. Res. (S)*, **1999**, 522–523; *(M)*, 2201–2217; (f) Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A. *J. Chem. Res. (S)*, **1998**, 548–549; *(M)*, 2501–2531; (g) Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A. *Tetrahedron* **1994**, *50*, 11489–11498; (h) Ibrahim, Y. A.; Elwahy, A. H. M.; Barsoum, B. N.; Abbas, A. A.; Khella, S. K. *Talanta* **1998**, *47*, 1199–1213; (i) Barsoum, B. N.; Khella, S. K.; Elwahy, A. H. M.; Abbas, A. A.; Ibrahim, Y. A. *Talanta* **1998**, *47*, 1215–1222; (j) Ibrahim, Y. A.; Barsoum, B. N.; Elwahy, A. H. M.; Khella, S. K. *Supramolecular Chem.* **1998**, *9*, 5–12; (k) Attiyat, A. S.; Kadry, A. M.; Hanna, H. R.; Ibrahim, Y. A.; Christian, G. D. *Anal. Sci.* **1990**, *6*, 233–237 and references cited therein; (l) Attiyat, A. S.; Ibrahim, Y. A.; Kadry, A. M.; Xie, R. Y.; Christian, G. D. Z. *Anal. Chem.* **1987**, *329*, 12–17 and references cited therein; (m) Sharghi, H.; Eshghi, H. *Tetrahedron Lett.* **1995**, *51*, 913–922 and references cited therein.
4. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427.
5. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.
6. Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
7. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800–3801.
8. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–552 and references cited therein.
9. Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoyveda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926–10927.
10. Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123–126.
11. Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942–3943.
12. König, B.; Horn, C. *Synlett.* **1996**, 1013–1014.
13. Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614.
14. Meng, D. S.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorenson, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.
15. Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2399–2401.
16. Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.
17. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
18. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043 and references cited therein; (c) Arm-

strong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388; (d) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007; (e) Ivin, K. *J. Mol. Catal. A-Chem.* **1998**, *133*, 1–16; (f) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A-Chem.* **1998**, *133*, 29–40.

19. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.
20. Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
21. Ibrahim, Y. A.; Behbehani, H.; Ibrahim, M. R. *Tetrahedron Lett.* **2002**, *43*, 4207–4210.
22. Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600.
23. Compound **12** (*trans*): ^{1}H NMR ($CDCl_3$) δ 3.79 (m, 4H, CH_2N), 4.70 (m, 4H, OCH_2), 6.33 (m, 2H, CH=), 7.01 (d, 2H, $J=8.2$ Hz), 7.14 (t, 2H, $J=8.0$ Hz), 7.40 (dt, 2H, $J=1.6$, 8.0 Hz), 8.24, (dd, 2H, $J=1.6$, 8.2 Hz), 8.17 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 40.6 (CH_2N), 68.4 (OCH_2), 113.3 (CH), 122.1 (CH), 122.4 (C), 130.3 (CH), 132.4 (CH), 132.9 (CH), 156.4 (C), 165.6 (C=O). Compound **12** (*cis*): ^{1}H NMR ($CDCl_3$) δ 3.72 (m, 4H, CH_2N), 4.80 (d, 4H, $J=6$ Hz, OCH_2), 6.20 (t, 2H, $J=6$ Hz, CH=), 7.05 (d, 2H, $J=8.2$ Hz), 7.14 (t, 2H, $J=8.0$ Hz), 7.40 (dt, 2H, $J=1.6$, 8.0 Hz), 8.24 (dd, 2H, $J=1.6$, 8.2 Hz), 8.17 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 39.5 (CH_2N), 63.2 (OCH_2), 112.9 (CH), 122.1 (CH), 122.5 (C), 129.7 (CH), 132.3 (CH), 132.8 (CH), 156.1 (C), 165.4 (C=O). Compound **14***E*: ^{1}H NMR ($CDCl_3$) δ 4.58 (d, 4H, $J=3.2$ Hz, OCH_2), 5.98 (t, 2H, $J=3.2$ Hz, CH=), 7.04 (d, 2H, $J=8.2$ Hz), 7.19 (t, 2H, $J=7.5$ Hz), 7.29 (m, 2H), 7.50 (dt, 2H, $J=1.6$, 8.2 Hz), 7.85 (m, 2H), 8.04 (dd, 2H, $J=1.6$, 7.5 Hz), 9.35 (s, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 70.9 (OCH_2), 116.8 (C), 123.1 (CH), 125.4 (CH), 126.1 (CH), 126.4 (C), 128.3 (CH), 130.8 (C), 131.6 (CH), 133.0 (CH), 155.1 (C), 165.3 (C=O); Compound **14***Z*: ^{1}H NMR ($CDCl_3$) δ 4.78 (d, 4H, $J=4.1$ Hz, OCH_2), 6.20 (t, 2H, $J=4.1$ Hz, CH=), 6.95 (d, 2H, $J=8.2$ Hz), 7.18 (t, 2H, $J=7.6$ Hz), 7.28 (m, 2H), 7.50 (dt, 2H, $J=1.6$, 8.2 Hz), 8.13 (m, 2H), 8.36 (dd, 2H, $J=1.7$, 7.6 Hz), 9.79 (s, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 63.8 (OCH_2), 112.4 (CH), 121.4 (C), 121.9 (CH), 124.3 (CH), 125.4 (CH), 129.4 (CH), 129.6 (C), 133.0 (CH), 133.1 (CH), 155.4 (C), 163.7 (C=O).
24. The yield was determined after the reaction by first removal of the reaction solvent, dissolving in $CDCl_3$ taking the ^{1}H NMR, then adding an accurately weighed amount of CH_2Cl_2 and comparing the integration of the OCH_2 group of the starting, products with that of CH_2Cl_2 at δ 5.3 and hence getting the molar ratio which can then be converted into percent based on the original molar amount of the starting materials.