DOI: 10.1002/adsc.200600444

Synthesis of Oxygen-Containing Medium and Large Rings using One-Pot Combinations of Sequential Alkene, Enyne and Alkyne Metathesis Reactions

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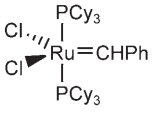
Received: August 29, 2006

Abstract: The first and second generation Grubbs' catalysts are shown to convert cyclohexane and cyclohexene bis-allyl and allyl propargyl ethers into 6,8-fused bicyclic derivatives by alkene and enyne metathesis reactions, respectively. The corresponding cyclohexane and cyclohexene bis-propargyl ethers are converted into 6,8-fused bicyclic trienes by enyne metathesis when treated with the second generation Grubbs' catalyst. Cyclohexene and norbornene esters bearing two alkyne units undergo alkyne metathesis when treated with molybdenum hexacarbonyl and 2-fluorophenol to give 12-membered ring containing alkynes which subsequently undergo alkene and enyne metathesis reactions when treated with first or second generation Grubbs' catalysts. Both Grubbs' catalysts are shown to be compatible with the reagents and conditions used for the molybdenum alkyne metathesis catalyst, thus allowing the two catalysts to be used in a one-pot process involving alkyne, enyne and alkene metathesis transformations.

Keywords: alkenes; alkynes; macrocycles; medium-ring compounds; metathesis; oxygen heterocycles

In recent work,[1] we have reported the use of a cascade of alkene and enyne metathesis reactions initiated by first **1** and second **2** generation Grubbs' catalysts[2,3] to convert readily available norbornene derivatives into highly functionalized polycyclic oxygenated heterocycles in a single synthetic transformation. The driving force for these reactions was initially assumed to be the release of the strain inherent in the norbornene ring system. However, during the course of this work it became apparent that in the presence of ethene, the norbornene units first underwent ring-opening alkene metathesis to give unstrained cyclopentane derivatives which subsequently underwent a cascade of ring-closing enyne and alkene metatheses to give the final products. Thus it appeared that a strained starting material was not needed for this chemistry and this prompted us to investigate the possibility of carrying out related alkene, enyne and alkyne metatheses on unstrained systems. In this manuscript, we first describe alkene and enyne metatheses of suitably substituted cyclohexane and cyclohexene derivatives,[4] before demonstrating the sequential use of ring-closing alkyne metathesis and alkene/enyne metathesis with two different catalyst systems in a one-pot process.



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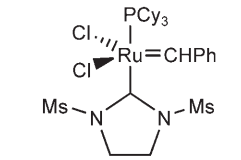

Ms = 2,4,6-trimethylphenyl

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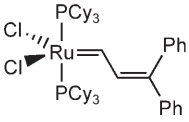

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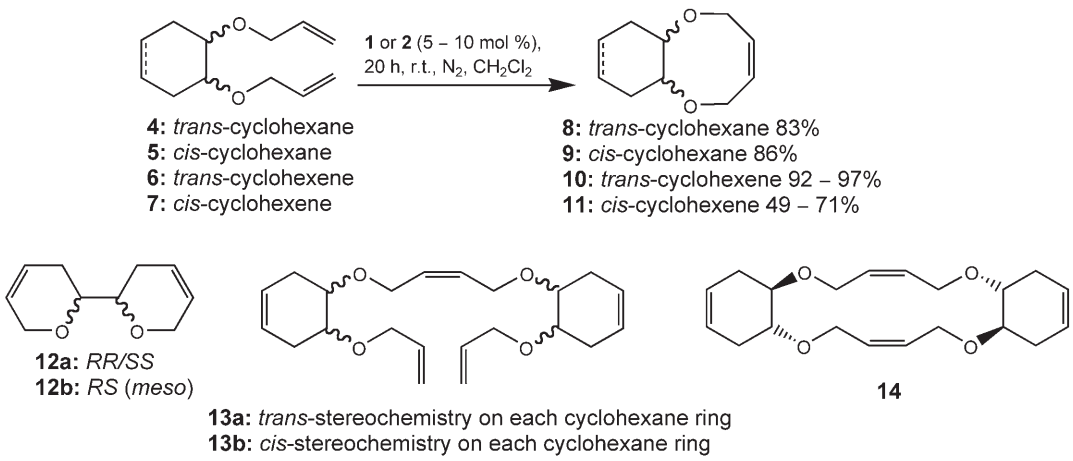
Grubbs and co-workers have previously investigated the ring closing metathesis of cyclohexane derivatives **4** and **5** using metathesis initiator **3**.[5] Using 8 mol% of catalyst **3** at 55°C, it was found that whilst the *trans*-cyclohexane derivative **4** was cyclized to the corresponding 8-membered ring-containing product **8** in 60% yield, the corresponding *cis*-isomer **5** gave bicyclic product **9** in just 20% yield. This difference was attributed to the relative strain energies of the bicyclic products. We decided to start our study by reinvestigating this system using the first generation Grubbs' catalyst **1**. With catalyst **1**, both compounds **4** and **5** could be converted into the corresponding 6,8-fused bicylic compounds **8** and **9** in greater than 80% yield after an overnight reaction at room temperature (Scheme 1). The *cis*-isomer **5** was again found to be



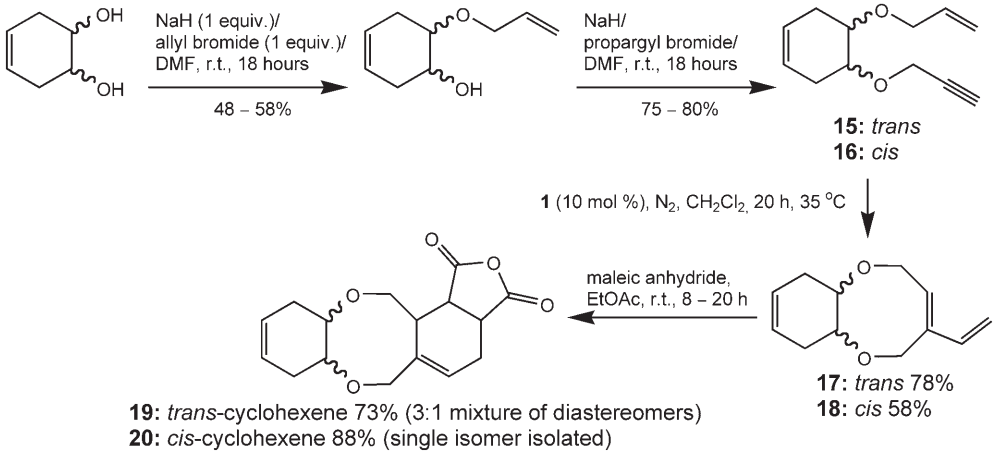
Scheme 1.

less reactive than *trans*-isomer **4** and required 10 mol% of catalyst **1** to drive the cyclization to completion, whilst only 5 mol% of catalyst **1** was required in the case of *trans*-isomer **4**.

Encouraged by these results, the metathesis of the corresponding cyclohexene derivatives **6** and **7** was investigated.[6] For these compounds, the metathesis reaction could proceed in two ways. Firstly, a single ring-closing metathesis could take place to give the 6,8-fused bicyclic systems **10** and **11**, or the initial metathesis could occur between the terminal alkene and the cyclohexene unit *via* a ROM/RCM pathway, leading to bis-dihydropyran derivatives **12a,b**. The latter would be expected to be thermodynamically more stable; and it has previously been reported that treatment of compound **6** (or the corresponding acyclic tetra-alkene: racemic 4,5-diallyloxy-octa-1,7-diene) with catalyst **1** leads exclusively to compound **12a**.[7] However, to our surprise when compounds **6** and **7** were treated with catalyst **1** under the conditions shown in Scheme 1, no evidence for the formation of compounds **12a,b** was obtained and the 6,8-fused bicyclic compounds **10** and **11** were isolated. The *trans*-isomer **6** was again more reactive than *cis*-isomer **7** since 5 mol% of catalyst **1** converted compound **6** into product **10** in 92% yield, the remaining mass being 6% of dimer **13a** and 2% of macrocycle **14**. In contrast, under the same conditions, the *cis*-product **11** was only isolated in 49% yield along with 5% of dimer **13b**. In each case, compounds **13** and **14** appeared to be a single isomer by ^{1}H and ^{13}C NMR spectroscopic analysis. The ^{1}H and ^{13}C NMR spectra of compound **10** were significantly different to those reported[7] for compound **12a**, and for both compounds **10** and **11** all of the spectral data (including COSY and NOESY spectra) were consistent with the 6,8-fused bicyclic structure. Use of second generation Grubbs' catalyst **2** under otherwise identical reaction conditions increased the yields of compounds **10** and **11** to 97% and 71% respectively.

Since alkene metathesis to form 8-membered rings in cyclohexyl fused systems occurred in high yield, the corresponding enyne metatheses[3,8] were investigated.[9] Thus, cyclization precursors **15** and **16** were prepared in two steps from the corresponding diols[10] as shown in Scheme 2. In both cases, the metathesis precursor underwent ring-closing enyne metathesis on treatment with first generation Grubbs' catalyst **1** at 35°C to give the corresponding 8-membered ring dienes **17** and **18**. Once again, the *trans*-isomer **15** was the more reactive substrate giving product **17** in 78% yield (along with 16% recovered starting material), whilst the *cis*-isomer **16** gave only 58% of product **18**. In both cases, higher yields for the enyne metathesis were obtained when the reaction was carried out under a nitrogen atmosphere than when it was carried out under an ethene atmosphere. This is in contrast to the general trend for enyne metatheses,[11] although a similar effect has been noted before.[9] In this case, the detrimental effect of ethene is probably due to it facilitating competitive cross-metathesis reactions leading to a mixture of products. The first generation Grubbs' catalyst **1** was also significantly more effective than the second generation catalyst **2** in effecting these transformations as the latter catalyst gave yields of only 15–30%. Both metathesis products readily underwent Diels–Alder reactions with maleic anhydride to form tetracyclic products **19** and **20** in good yield. Anhydride **19** was obtained as a 3:1 ratio of diastereomers whilst anhydride **20** was isolated as a single stereoisomer.

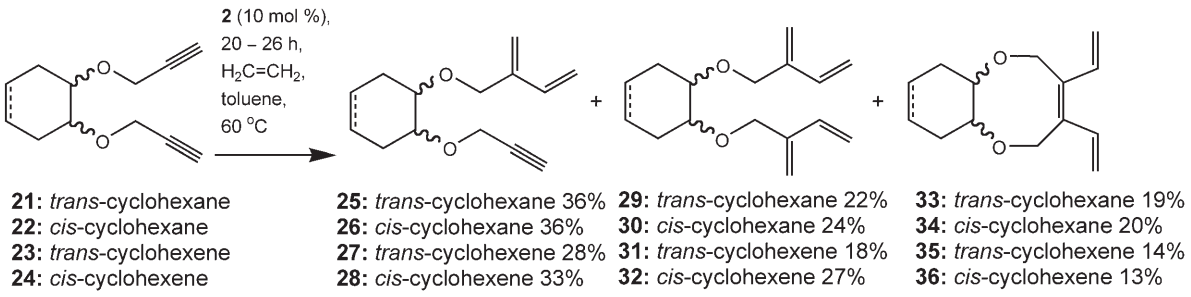
To further explore enyne metathesis reactions in these unstrained systems, diynes **21**–**24** were prepared. These substrates failed to react with first generation Grubbs' catalyst, but did react with the second generation catalyst **2** at 60°C in the presence of ethene



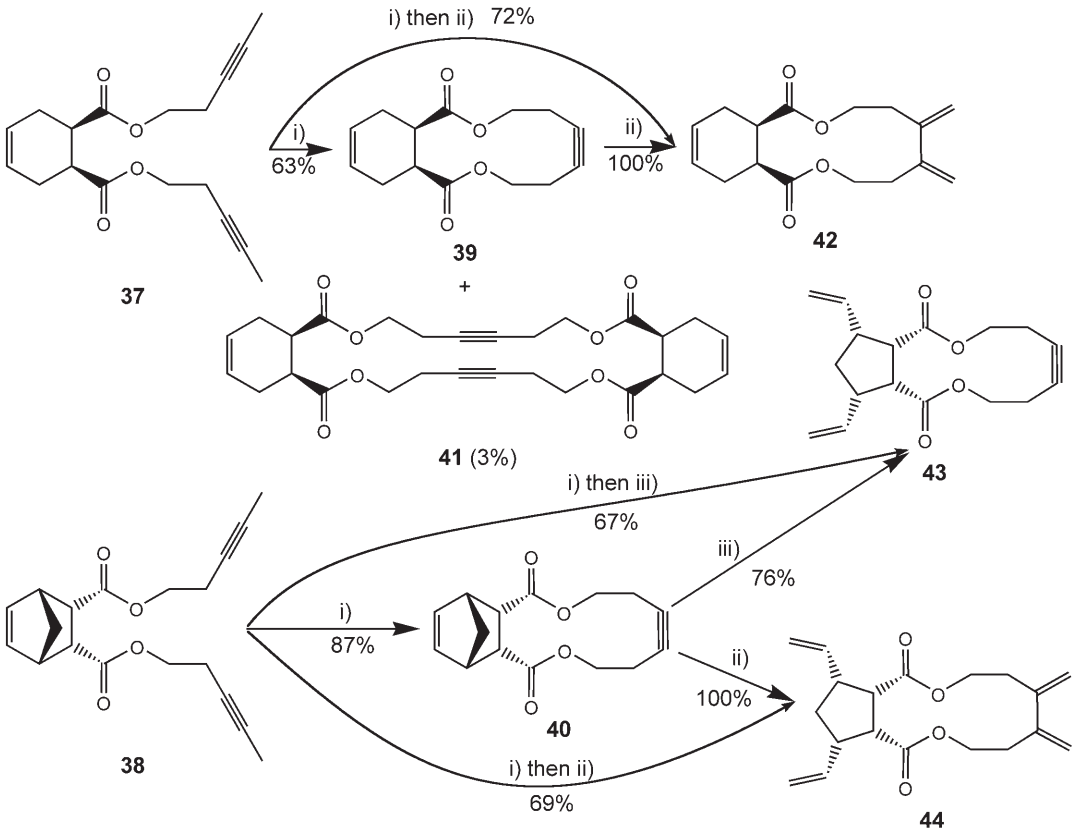
Scheme 2.

(Scheme 3). In each case, a mixture of three products was obtained consisting of dienes **25**–**28** formed from an enyne cross-metathesis between one of the alkyne units and ethene,[12] bis-dienes **29**–**32** formed from an enyne cross-metathesis between both alkyne units and ethene, and 8-membered ring trienes **33**–**36** in which the alkylidene formed during the initial cross-metathesis underwent ring-closing enyne metathesis followed by trapping with ethene.[13] No conditions could be found under which just one of the three cross-metathesis products formed predominantly or exclusively.

Alkynes can also undergo a different type of metathesis reaction; namely alkyne metathesis[3,14,15] and it was of interest to investigate the use of substrates related to compounds **21**–**24** in sequential metathesis processes initiated by a ring-closing alkyne metathesis.[16] We elected to use the molybdenum hexacarbonyl/2-fluorophenol-based catalyst system of Grela[17] and preliminary experiments revealed that terminal alkynes were not metathesized under these conditions. In addition, ring-closing alkyne metathesis is only possible if the ring being made contains at least twelve atoms,[3,12,13] so we chose compounds **37** and **38** as potential substrates. These compounds are readily available by esterification of the corresponding commercially available diacids with pent-3-yn-1-ol, and both substrates underwent ring-closing alkyne metathesis to give the corresponding 12-membered ring compounds **39** and **40** respectively when treated with the Grela catalyst system (Scheme 4). In the case of cyclohexene derivative **37**, 3% of the macrocyclic dimer **41** was also isolated. It is notable that no enyne metathesis occurred under these conditions, and that the strained alkene unit in substrate **38** was totally unaffected.[18] Compound **39** subsequently underwent enyne cross-metathesis with ethene to give diene **42** in quantitative yield when treated with second generation Grubbs' catalyst **2** and this could also be carried out as a one-pot process by sequential addition of the molybdenum and ruthenium catalysts to a solution of diyne **37** in chlorobenzene. Similarly, compound **40** reacted with first generation Grubbs' catalyst **1** in the presence of ethene to give cyclopentane **43** resulting from ring-opening metathesis of the strained norbornene unit. No enyne metathesis occurred under these conditions. In contrast, treatment of compound **40** with second generation Grubbs' catalyst in the presence of ethene gave product **44** resulting from both ring-opening metathesis and enyne metathesis. Both of these processes could also be carried out as 'one-pot reactions' and for the conversion of **38** into **44**



Scheme 3.



Scheme 4. Reagents; i) $Mo(CO)_6$ (5 mol%)/2-FC_6H_4OH/ClC_6H_5, 6 h, reflux; ii) 2 (5 mol%), ethene, 60°C, 20 h; iii) 1 (5 mol%), ethene, room temperature, 20 h.

this involved the sequential occurrence of all three types of metathesis reaction: alkyne, enyne and alkene metatheses in a single one-pot reaction.

The conversion of alkynes **39** and **40** into dienes by enyne metathesis opens up new possibilities for alkyne metathesis in synthesis as previously alkyne metathesis has only been combined with reduction processes[12] leading to stereochemically pure *E*- or *Z*-alkenes or with furan formation.[19] This work also demonstrates the compatibility of Grubbs' alkene and enyne metathesis catalysts **1** and **2** with the reagents and conditions required for the ill-defined molybdenum-based alkyne metathesis catalyst of Grela. This opens up new potential for sequential and cascade metathesis processes involving multiple catalysts and reaction types.

Experimental Section

All metathesis reactions were carried out at least twice to ensure reproducibility. All yields reported in this manuscript correspond to isolated, pure materials and all new compounds were fully characterized by appropriate spectroscopic methods including high resolution mass spectra and 2D NMR techniques where appropriate.

General Procedure for Ring-Closing Alkene and Enyne Metatheses using First Generation Grubbs' Catalyst

To a stirring solution of substrate **4–7, 15, 16** (0.51 mmol) in dry dichloromethane (46 mL) was added a solution of catalyst **1** (0.021 g, 0.026 mmol, 5 mol%) in dry dichloromethane (5 mL). The reaction mixture was stirred for 20 h at room temperature under a nitrogen atmosphere. The solvent was removed under vacuum and the residue was purified by column chromatography (hexane/EtOAc, 90:10) to give 6,8-fused bicyclic products **8–11, 17, 18** as transparent oils.

General Procedure for Ring-Closing Enyne Metatheses using Second Generation Grubbs' Catalyst

Diyne **21–24** (0.53 mmol) was dissolved in dry toluene (48 mL) and ethene was passed through the stirred solution for 20 min. A solution of catalyst **2** (0.045 g, 0.053 mmol, 10 mol%) in dry toluene (5 mL) was added and the reaction mixture was stirred at 60°C for 24 h under an ethene atmosphere. The solvent was then removed under vacuum and the residue subjected to column chromatography (hexane/EtOAc 90:10) to afford mono cross-metathesis products **25–28**, bis-cross-metathesis products **29–32** and ring-closed products **33–36**.

General Procedure for Ring-Closing Alkyne Metathesis

A solution of compound **37** or **38** (1.0 mmol), $Mo(CO)_6$ (0.013 g, 0.05 mmol, 5 mol%) and 2-fluorophenol (0.112 g, 1.0 mmol) in chlorobenzene (20 mL) was refluxed for 6 h. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography (cyclohexane/EtOAc 80:20) to give product **39** or **40** as a white solid.

General Procedure for One-Pot Sequential Metatheses

A solution of substrate **39** or **40** (0.10 g, 0.32 mmol), $Mo(CO)_6$ (0.004 g, 0.016 mmol, 5 mol%) and 2-fluorophenol (0.036 g, 0.318 mmol) in chlorobenzene (5 mL) was refluxed for 20 h. The reaction mixture was allowed to cool to room temperature and ethene was passed through the stirred solution for 10 min. A solution of catalyst **1** or **2** (5 mol%) in chlorobenzene (2 mL) was then added and the mixture was stirred at room temperature or 60 °C for 20 h under an ethene atmosphere. The solvent was then removed under vacuum and the residue was purified by column chromatography (CH_2Cl_2/EtOAc, 95:5) to give products **42**–**44**.

Acknowledgements

Mass spectra were recorded by the EPSRC national mass spectrometry service at the University of Wales, Swansea, and use of the EPSRC's Chemical Database Service at Daresbury is also gratefully acknowledged.

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